SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

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NOTE

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ANNEX F

Radiation carcinogenesis in man

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Introduction

1. Carcinogenesis is the main late-stage somatic effect of ionizing radiation. The malignancies induced by irradiations are indistinguishable from those occurring from many other causes. Therefore, the observations of these effects in man have been limited to study populations who were more highly exposed in various ways and for various reasons. These results form the primary basis for assessments by UNSCEAR of the risks of ionizing radiation.

2. Previous UNSCEAR Reports on radiation carcinogenesis in man [U2, U3] have adopted a site-specific approach, focusing on cancers of the breast, lung, thyroid and on leukaemia. This was inherent in the basic descriptive epidemiological results available. There has always been a desire to interpret results from the standpoint of an understanding of the mechanisms of carcinogenesis. While there have been some developments, particularly in the field of molecular biology, that are relevant and are reviewed here, the updated and revised epidemiological results continue to serve as the primary basis for the risk assessment. This Annex, however, attempts a more analytical approach to risk evaluation, especially for projection of risks beyond observational experience.

3. It is particularly propitious that risk assessments be made now, in light of the revised dosimetric evaluations of the Japanese survivors of the atomic bombings, the most important study population. This re-evaluation, completed in 1986 and known as the dosimetry system 1986 (DS86), replaces the previous estimates of 1965 (T65). Not all of the revisions could be taken into account in analysing cancer incidence frequencies, but the latest values are used in the Committee's analytical evaluation of risk coefficients for mortality.

4. Of all of the factors that affect the carcinogenesis process, age at exposure is particularly significant. Susceptibility of tissues to radiation effects is related to proliferative activity of cells, and periods of active growth and development can be expected to be periods of greater sensitivity. There are difficulties, however, in accounting for age differences. Many study populations involve individuals of particular predispositions exposed under special circumstances. Data from individuals who were youngest at the time of the atomic bombings are incomplete, as they are just now entering the important stage in their late adult lives when cancer prevalence increases.

5. There are many reasons for uncertainties in the risk assessments. A main concern that cannot be adequately resolved is how to relate the results obtained at high doses and dose rates to the low levels of exposure that may be expected in environmental and routine occupational settings. The difficulties and developments in the field of radiation carcinogenesis are discussed in this Annex. The risk evaluations provided by the Committee reflect the current best knowledge and approaches and are put forward to serve as background information for consideration of international and national bodies of radiation protection.

I. GENERAL CONSIDERATIONS

A. TERMS, APPROACHES AND CONCEPTS

1. Terms and units of radiation exposure

6. A variety of units are or have been used for the quantities needed in assessments of exposures to ionizing radiation. However, it having been decided to adopt the modern metric system, the Système International (SI); throughout this Annex, SI units will be used wherever practicable. A detailed account of the correspondence between the older units and the SI units is found in [N3]. For the reader unfamiliar with these units, it is sufficient to note that 1 rad, the old unit for absorbed dose, equals 0.01 gray (Gy); 1 rem, the old unit for dose equivalent, equals 0.01 sievert (Sv); and, finally, the curie (Ci), the old unit for activity, equals $3.7 \cdot 10^{10}$ becquerel (Bq).

7. The subjective expressions "low", "intermediate", "high" and "very or ultra-high" as applied to absorbed doses of sparsely ionizing radiation are arbitrarily defined here, following the convention established in the UNSCEAR 1986 Report [U1], as 0-0.2, 0.2-2.0, 2.0-10.0, and above 10 Gy, respectively. For other

types of radiation the corresponding dose equivalent ranges are the same, but with units of sievert. This correspondence does not necessarily reflect RBE, but rather assigned quality factor values. Following the same convention, "low" dose rates for all radiations are those below 0.05 mSv/min; "high" dose rates are those above 0.05 Sv/min; and "intermediate" dose rates fall between the two figures quoted.

8. Exposure of the lung to alpha particles from radon daughter products is customarily expressed in terms of working level (WL) or working level months (WLM). The WL is any combination of radon and its daughter products in a litre of air that will result in the emission of $1.3 \ 10^5$ MeV of potential alpha energy; the WLM is the exposure resulting from the inhalation of air with a concentration of 1 WL of radon daughters for 170 (working) hours.

2. Concepts of risk

9. Conventionally, the risk associated with exposure to radiation, either sparsely or densely ionizing, has been expressed in absolute or relative terms. Absolute risk is usually taken to mean the absolute increase in the frequency of cancer, mutation, or the like, and the absolute risk coefficient is the increase per unit exposure per unit time of risk after adjustment for confounding variables. Commonly, it is defined as the excess deaths or incident cases per gray (or rad) per ten thousand (or million) person-years and is estimated by regressing the difference between the observed number of events and the expected number, based on a suitable comparison group or population, as a function of dose (see, e.g., [K7] or [W5]). Relative risk is the ratio of the number of cases observed in an exposed population to the number of cases expected in a non-exposed, but otherwise comparable, population.

(a) Dose-response pattern

10. One objective of risk assessment is to estimate the relationship between the dose administered and the response elicited, specific to exposed individuals of differing ages, sex, or other biological characteristics. This relationship is called the dose-response relationship, and is an expression of the form

$$r = f(D)$$

where r is a defined measure of response, e.g., a risk quantity, usually an excess absolute or excess relative risk, and f(D) is a function of absorbed dose. The function f(D) commonly takes one of the following forms: (a) linear, i.e., $a + bD$; (b) linear, non-threshold, better called proportional, i.e., bD; (c) quadratic, i.e., $a + bD + cD^2$; (d) pure quadratic, i.e., cD^2; (e) proper order polynomials. In addition, any of these forms may be modified by multiplying by an exponential term with the exponent containing negative terms in D and D^2. A quadratic term in the dose-response function is usually included when the effects at low doses are less than would be predicted by a strictly linear response to dose at intermediate doses. For dose-response relationships going through a maximum at intermediate doses, it is assumed that cells exposed

to high doses may be prevented from dividing by the sterilizing (or cell-killing or inactivation) effects of irradiation. These matters have been thoroughly discussed in Annex B of the UNSCEAR 1986 Report.

11. The age, sex and other characteristics of the exposed individual may or may not be specified in assessing the dose-response pattern. Similarly, the age, the time since exposure and the end-point used to assess the response may vary from one application to another. In practice, all data from the time of exposure to the time of analysis are often pooled, and the cumulative excess risk in the exposed population, commonly expressed as excess deaths or incident cases, is related to the dose received. However, in principle, there may be significant differences in the dose-response relationships between different groups of people, e.g., between exposed children and adults. These might be reflected as host-factor effects on the shape of the dose-response function.

(b) Risk measures and projection

12. A second objective of assessing risk is to follow individuals after exposure has begun, or after it is complete, and to quantify the excess cancers during the lifetime of groups of such individuals. Since the individuals may vary in other respects than simply their ages, different assessments may be made for each sex, age at exposure, exposure to other risk factors and so on. It may also be important to be able to predict future risk in exposed cohorts, even to ages beyond those for which current estimates exist.

13. In this Annex, the assessment of events after exposure and beyond the period of observation will be referred to as the projection of risk. When the risk in the exposed individuals exceeds the spontaneous (non-exposed) risk level by the same amount at all ages, the effect of exposure will be termed additive (often the term absolute has been used in this context, since at all ages the excess risk is constant). When the risk to the exposed is some constant fraction greater than the spontaneous risk, this will be termed a multiplicative effect (often the term relative has been used, in the sense that at all ages after exposure the relative risk, or risk ratio, is constant). Actual effects may fit neither of these simplified models, or they may fit some combination of them.

14. When the risk experiences of several age (or other) strata are combined into a single summary measure, one must be aware of the nature of the exposure experiences over which the single value is computed. If no method is specified in the naming of such a measure, then no assumptions can be made about the way in which aggregate data were used to compute the expected risk. When the measures are single values derived from the cumulative experience of an exposed cohort, this will be referred to as the total relative or absolute risk.

15. The excess risk is usually computed from the risk in a comparable group, either the population at large or a control group. When using an unexposed control group matched by age and sex, the number of cases in

that control group is considered to be the baseline number. Often, however, the control group is the entire population of which the exposed are a part. The risk schedule in that population, say r(x), is the annual incidence (or mortality) per person at age x per year; this can also be made specific to sex and historical time period. In a cohort of exposed persons, over the course of the investigation, a certain number of person-years of experience at age x will arise: this is the sum of all years spent by exposed cohort members at age x. Let this number be c(x). Then the expected number of cancers in the cohort, E, can be approximated by

$$E = \sum_r c(x) r(x)$$

and the excess number of cases is the observed number, O, minus the expected number, O-E. The number of person-year-grays (PYGy) of exposure to which this excess applies is the sum over all exposed individuals of the product of the dose to the i-th individual, d_i, times the number of years that individual was followed in the study (up to the point of manifesting the cancer of interest) y_i. That is, summing over the n individuals in the cohort,

$$N = \sum_i d_i y_i$$

The desired summary measure is then (O-E)/N excess cases per 10^4 PYGy. Note that this measure aggregates the experience of different ages and that it is possible to obtain the same value for N by including exposed cohorts of different age distributions, followed for differing lengths of time, to a different distribution of doses. Life-table methods can make the computation of expected numbers of cases somewhat more precise by accounting for the fraction of the exposed cohort expected to die from causes of mortality other than the cancer of interest.

16. The relative risk is usually computed simply as O/E, again aggregating the experience of individuals at different doses and of different ages. When the irradiated population is actually a subset of the comparison population under scrutiny, this ratio is not strictly the relative risk of exposure compared to non-exposure, and in this case 100 times (O/E), should be referred to as the standardized mortality (or morbidity) ratio (SMR); however, because of its nearly universal use in radiation epidemiology, the term relative risk (RR) will be used, in general, for the ratio of the observed to the comparison group.

17. In addition to depending on the details of the age pattern of cases since exposure, relative to age at exposure and dose, both of these measures also depend on the background, or baseline, risk in the population [r(x)], so that it may be difficult to apply excess deaths (cases) or relative risk estimates to populations epidemiologically different from the exposed population.

18. In the latest reports on the survivors of Hiroshima and Nagasaki [P15, S48, S49], excess relative risk, at 1 Gy of exposure, has been computed. This is the excess relative risk value (i.e., RR-1) over all age, sex and other strata in the data. This measure combines aspects of the other measures, but is still a single, cumulative measure of effect. Relative or absolute risks can always be calculated in this manner. For example, they can be computed after any number of

years of observation or by pooling individuals with different ages at exposure or pooling both sexes. Such measures are dependent on these pooling or aggregating procedures and may not be comparable between studies. Computation of an absolute risk in this way does not imply that the projection effect (on post-exposure age-specific risks) is additive, nor does computing relative risk mean that the projection effect is itself multiplicative.

19. For these reasons, it is necessary to distinguish between the projection effect (additive or multiplicative) and the measure of risk based on observational data (absolute risk, that is, excess deaths or cases, relative risk, attributable risk [see paragraph 22]). This distinction is not always clear in the literature, where the same terms are often used in both circumstances. To make it quite clear, when projection effects are referred to in this Annex, the terms multiplicative or additive will be used; when measures in data are referred to, the terms absolute or relative risk will be used.

3. Assignment of causation

20. An increasingly frequent question addressed to radiation biologists is whether a specific cancer could have been radiation-induced. This question may arise in litigation, in the adjudication of occupational compensation or in the legislative process or it may arise through simple curiosity. Rarely, if ever, is it possible to state categorically that a specific cancer was or was not due to radiation exposure. At present, there is typically no radiation-specific tumour pathobiology, and radiation-related tumours appear similar to spontaneous tumours at the same site. Inasmuch as some tumours that are extremely rare in the general population are much more common after radiation, it may be that radiation alone is able to produce a tumour. In general, however, radiation exposure only increases the frequency of an already prevalent tumour.

21. Despite these conceptual problems, it is possible to consider causation in a probabilistic manner [B17]. Briefly, if an outcome, A, can occur only when one of a series of exhaustive and mutually exclusive events occurs, and if the a priori probabilities of these latter events are known, then it is possible to compute the conditional probability that A is due to a specific one of the series of events. This latter, conditional probability is sometimes described as the a posteriori probability of the event. In the present context, the probability of causation, P, or, more formally (given the occurrence of a cancer in an exposed individual), the probability that it is due to radiation (one of a series of presumably mutually exclusive causes of cancer) is simply the ratio of the additional risk imposed by the radiation dose D to the total risk; the latter is, of course, the sum of the baseline risk and the radiation risk. It can be written as

$$P = [D \times R]/[B + (D \times R)]$$

where R is the absolute annual site-specific risk per gray and B is the baseline cancer rate, specific for site, age, sex and other pertinent concomitants.

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22. A related, commonly employed epidemiological notion is that of attributable risk. The latter is the proportion of a health disorder that can be attributed to a causal factor. Epidemiologists use a variety of mathematical definitions of attributable risk. One is derived by subtracting the incidence of the disorder among persons not exposed to the factor, e.g., ionizing radiation, from the incidence among persons who were exposed. Thus, in the present context, it is merely

$$\text{Attributable risk} = \frac{\text{observed} - \text{expected cases}}{\text{person/years at risk}}$$

4. The analytic approach to radiation carcinogenesis

23. There are a number of factors that influence the risk of cancer in individuals exposed to radiation. These include the nature of the individual receiving the dose, often known as the host (genetic background, general health, specific health problems, sex etc.); the nature of the dose received (high or low, acute or chronic, radiation quality); other factors that may interact with radiation or affect the susceptibility of the host (e.g., smoking, diet, weight, exposures to chemicals, other diseases and medical treatments); and the nature of the carcinogenic process itself. Because of the existence of these factors, there is no single way in which effects should be assessed. Actually, several approaches have been taken.

24. The first is to examine the relationship between biological models of carcinogenesis and the effect of different exposures or host conditions. There have been many different attempts to model radiation carcinogenesis. Generally, the parameters of the process are estimated using epidemiological data on exposed individuals to infer the action of radiation and to estimate the relative importance of different components of the process. Those components usually include mutation, mutation-repair, growth stimulation and cell sterilization. Specifically, various multi-stage processes have been applied to the age-onset distribution of cancers following irradiation in an attempt to determine the consistency of such processes with the action of ionizing radiation and to infer which part of the process is affected by exposure. These investigations do not provide risk estimates for a given dose, but they do suggest aspects of risk, such as vulnerable ages, and whether the effects of exposure can be expected to be long lasting or not.

25. Another approach is to analyse dose-response and risk-projection relationships. Much effort has been devoted to assess the response of various tissues to differing exposure levels or durations, and numerous studies have sought to estimate the cancer risk at various dose levels. Interest has been particularly great in extrapolating risks from high-dose data to low doses and from high dose rates to low ones. It is assumed that most controllable exposures, such as occupational ones, will involve much lower doses (and generally lower dose rates) than those experienced by the studied populations. One goal has been to provide risk estimates so that individual exposures, such as those experienced for medical or occupational reasons,

can be controlled in an informed way. Another goal has been to use the limited epidemiological data to infer the risks that attend other conditions of exposure.

26. A continuing objective has been to determine, for given exposures and tissue sites, whether there is a linear or non-linear (specifically, quadratic) dose-response relationship at low doses. This issue has been studied, without resolution, in animals and in man, for decades. There is still no unambiguous answer, but in many cases newer data have contributed to the ability to infer the existence or non-existence of risk thresholds or the likely forms of the dose-response relationships, a subject treated at length in Annex B of the UNSCEAR 1986 Report [U1].

27. A different approach to the dose-response relationship has also been taken [F6]. Species-specific parameters for a theoretical model of cancer have been fitted to experimental data and used to estimate low-dose response rates. While the theory seems to work for cellular effects in vitro, it is not obvious that it applies in vivo, where species-, individual- and tissue-specificities, as well as differences in the nature of the radiation action, are not controllable and often cannot be measured accurately. However, a theoretical approach is necessary when actual observational data do not exist.

28. Finally, there have been direct regression approaches to risk assessments. Recently, multiple regression theory has been extended to the evaluation of risk factors in a complex disease (exposure) phenomenon. This has been very useful in chronic disease epidemiology and, given the nature of the data, seems appropriate to assessing the risk of radiation carcinogenesis. Several applications of these methods, generally those called proportional hazards models (see, e.g., [K12]), have been made in this context and will be reviewed.

29. Since the carcinogenic effects of very low doses cannot be shown directly with existing data (see, for example, [U5]) nor reliably extrapolated from high-dose data (for a discussion of some of the problems associated with extrapolation, see [D25]), the shape of dose-response relationships at low doses of ionizing radiation remains conjectural. An understanding of these relationships will involve a knowledge of carcinogenesis as a biological process and the relation of radiation to this process (e.g., [F5, F6]).

B. SOURCES OF DATA

30. Data on radiation carcinogenesis in man can be derived from a limited number of sources. The main types of human exposures that have occurred and the study populations available are listed in Table 1. These include the survivors of the atomic bombings of Hiroshima and Nagasaki; observers of nuclear tests and those exposed to fallout; patients irradiated therapeutically to treat cancers or other disease conditions; workers in nuclear installations, miners and radiologists; individuals exposed at home to elevated levels of background radiation; and indivi-

duals involved in nuclear accidents. The exposure conditions have included single, multiple and chronic irradiation from external and internal sources. The main categories of exposure are reviewed below.

1. Special exposed cohorts

31. Much of the knowledge about radiation carcinogenesis still comes from the study of the Japanese populations exposed during the atomic bombings at Hiroshima and Nagasaki and from data on Marshall Islanders exposed to substantial doses of fallout during the testing of nuclear weapons. The accident at the Chernobyl nuclear reactor in the USSR has also exposed a sizeable number of people to non-trivial doses, and their experience may become a valuable source of information. These exposures have contributed importantly, and will undoubtedly continue to do so, to the limited data on the lifetime risks, with regard to all cancer sites and all ages and doses, associated with acute radiation, to an ostensibly healthy and unselected population.

2. Patients treated with therapeutic radiation

32. Numerous cohorts of individuals have been identified to whom substantial doses of radiation were administered for various therapeutic purposes. The doses were typically given over a short period of time and usually administered locally. Individuals in these groups were exposed, for example. to radiotherapy for cancer or for ankylosing spondylitis or to radiation to the thymus and thyroid for various reasons, to the head for tinea capitis or various parts of the body for haemangiomas, to treat Hodgkin's disease or to suppress the immune system to prevent the rejection of tissue transplants. Although many of these exposures no longer occur, other forms of radiation therapy continue to increase. The Patterns of Care Study sponsored by the American College of Radiology has shown that in the United States over the 10 years from the first of its surveys, in 1973, to the fifth, in 1982, the number of new radiation therapy patients per thousand population per year has grown over 17%, from 1.46 to 1.71, or from 304,020 to 401,263 individuals [K10]. The improved survival of many cancer patients means that there will be an increasing amount of data on the risk of second cancers among these people, especially those treated in childhood. Such risks will have an impact on the management of selected diseases and thereby on the structure and process of clinical care and outcome [D6, H3, H4, K9]. It is worth noting that the beams in the newer radiological techniques are more sharply edged than in the older techniques. and exposures can be more readily restricted to the tumour itself.

3. Individuals receiving diagnostic examinations

33. Millions of individuals have been exposed to low doses of radiation for the diagnosis of a great variety of conditions or for the monitoring of treatment. With the continued improvement of roentgenographic and other diagnostic techniques and equipment, the doses per examination are being reduced and the exposures becoming more focused. The availability of ultrasound and magnetic resonance imaging techniques is also diminishing the frequency with which ionizing radiation is used. However, the development of computerized tomographic methods, including positron emission tomography, and the various uses of radioisotopes for diagnostic purposes may have increased the doses received and frequency of irradiations. While the individuals exposed to moderate doses may be few, diagnostic radiation, in general, is likely to continue to be an important source of exposure. Since these exposures usually occur where serious disease is present, risk-benefit analysis will be particularly valuable in justifying and optimizing them (see Annex C, "Exposures from medical uses of radiation").

4. Occupational groups

34. Several earlier groups of people have been exposed to substantial doses of ionizing radiation over long periods of time, commonly because the dangers of such exposure were unrecognized. These groups include radium dial painters, radiologists, radiology technicians and industrial radiographers, all of whom were exposed earlier in this century, and miners who worked for many years in environments with high levels of radon. The exposures have generally been in the intermediate-to-high (0.2-10 Gy) dose range.

5. Populations receiving chronic exposures

35. Many individuals are chronically exposed to low doses (below 0.2 Gy) of radiation, but few have been studied as well-defined cohorts. Commonly they have been exposed because of the place in which they live, or because of their occupations, or because of various medical or other exposures (e.g., those that involve radioisotopes with long half-lives), or because of radioactive fallout. In many countries, radon in homes may be the largest single source of chronic exposure to low doses of ionizing radiation that the average person confronts [C13]. Populations in all countries are exposed, but the distributions of individual exposures are largely unknown. Instances have been recorded of persons residing in houses where the exposure to radon amounted to as much as 30 WLM, that is, almost eight times the limit set for uranium miners. These persons are usually unaware of the risk they face, for their homes are not necessarily built on or in the vicinity of mine tailings, but rather on rock containing high levels of natural radioactive substances. Water sources may also contain radon that is released to air in the houses. While inhaled radon is not chemically bound in body tissues nor is its solubility in tissues high, the simultaneously inhaled radon daughter products are deposited in the respiratory tract. and these, notably the shorter-lived ones, decay, exposing the bronchial epithelium. This is discussed in Annex A, "Exposures from natural sources of radiation". As yet, there have been few epidemiological studies of populations exposed in

their homes to radon and its daughter products that enable reliable quantification of the risk of cancer of the bronchial tree.

6. Accident victims

36. There will continue to be isolated cases of high exposures due to accidents of various sorts. Heretofore, these cases have provided little insight into the long-term consequences of exposure to ionizing radiation, but with the establishment of a world-wide Registry of Radiation Accidents at Oak Ridge in the United States, they may become more informative [D7, F4]. At present the Registry lists more than 230 accidents; by far the largest number were the result of either a mishandling of industrial, sealed radio-isotope sources or an inadvertent exposure to x rays used for quality control [S25]. Often the accidents involved unsuspecting individuals, not a few of them children, who picked up a metal object and carried it home, where they and other household members became exposed, unknowingly, to the radiation emitted by what was a metal-encapsulated source. No fewer than 1,100 individuals are enumerated, 38 of whom died, presumably as a direct consequence of their exposure; about half of those who died received significant exposures of 0.25 Sv or more to the whole body or of 6 Sv locally to the skin, or of 0.75 Sv or more to a critical organ. The accident at Ciudad Juarez in Mexico is typical of the accidents that involved general populations. There, a cobalt-60 source, improperly disposed of, resulted in the exposure of 300-500 individuals, some of whom received doses of 0.5-1.0 Gy. A similar but more recent accident at Goiania, Brazil, involved some 244 individuals, 54 of whom were subsequently hospitalized and 4 of whom have died; exposure in that instance was to ^{137}Cs. Accidents have also occurred when fuel rods were being inserted or removed from reactors [see, e.g., W7, W8, W9]. In these latter instances, the subsequent health experience of the exposed individuals is generally being carefully scrutinized by the employing laboratories or utility companies.

37. In the review of radiation carcinogenesis that follows, data from all these sources will be considered. Of necessity, this review will overlap in some particulars with material contained in other UNSCEAR documents, specifically in Annexes A and B of the UNSCEAR 1986 Report [U1]. The reader should consult these for further details and for aspects of radiobiology that do not apply directly to human radiation carcinogenesis. Thus, for example, no effort will be made here to review the data on radiation-induced cancers in experimental animals.

C. TYPES OF STUDIES

38. Of the ways in which radiation carcinogenesis may be studied, two have predominated: (a) cohort studies, in which individuals exposed in some special way and individuals not exposed are compared. The follow-up can be retrospective or prospective, or both; and (b) case-control studies, in which cancer cases

and matched normal individuals are ascertained and their prior exposure histories compared. These types of investigations on available population groups are outlined in Table 2.

1. Cohort studies

(a) Ongoing investigations

39. Most of the investigations in progress in 1977, when UNSCEAR last reported on human radiation carcinogenesis, have continued, and additional results have since been reported. Moreover, the investigations concluded prior to the last Report have received fresh scrutiny and much of the older data has been subjected to further analysis and interpretation. In several instances, the early findings have been improved and joint estimates of dose-response patterns made more precise by combining data from several investigations (see, e.g., [D11] or [T16]). In other instances, previous results have been called into question because, for example, doubts had been cast upon the dose estimates or ascertainment biases or because better, later studies had yielded conflicting observations.

40. There are further data on women who received chest fluoroscopy (to monitor pneumothorax), irradiation for mastitis, or other exposures to the breast in connection with breast cancer [H6]. These results show (a) a higher susceptibility of the young; (b) dose fractionation does not reduce the risk of breast cancer in all studies; and (c) there is uncertainty as to the level of risk at low dose rates. Similarly, much has been added to the literature on the effects of exposing the thyroid to various kinds of irradiation in childhood [R1, S13]. Quantitative estimates of dose-effects have been improved; however, the pattern of radiation-induced thyroid cancer has been extensively reviewed, leading to the suggestion that, while radiation does have an effect at moderate doses, the clinical significance of this in terms of active thyroid cancer, rather than subclinical thyroid changes, is not patent [C6, P4].

41. Studies of cancer following pelvic irradiation for malignancies of the cervix have not discovered the excess of leukaemia that had been expected [B12, B13, W6], although cancers have appeared at other exposed sites and more information should arise as follow-up continues. New studies of cancer resulting from the use of injected radioisotopes, including radium and Thorotrast, have been reported, and substantial re-analysis of the older data has occurred. The dose-response patterns of bone and liver cancer in relation to sources of alpha-particle radiation have been improved, but some concern has been voiced about the meaning of estimates of effective dose to susceptible cells, in the presence of local cell necrosis. Related issues have been advanced in regard to lung, thyroid and cervical cancers. There are additional data on leukaemia subsequent to diagnostic radiation, showing very low frequencies of occurrence, and there is further information on individuals exposed to localized high doses of therapeutic radiation for the treatment of childhood cancers. Data on radium dial painters

have been re-analysed [R10], and there are more estimates of exposure risks in underground miners [M19, M42, R5, R7, S20, S51].

42. Several studies, interpretations, and reinterpretations have appeared since 1977, particularly in connection with occupational exposures (Hanford [e.g., G12, K20]; Portsmouth Naval Shipyard workers [N6, R17, R21, S33]; and plutonium handlers [C21, V2, V3, W18]). The earlier results have often been shown, on closer examination, to have been spurious, and the effects of different ascertainment or reporting biases have been revealed.

43. The Life Span Study in Hiroshima and Nagasaki, continues and three further reports on mortality data, as well as additional incidence data have become available. The consequences have been to improve estimates of dose effects for some tumours, to include others in the list of radiation-induced sites (e.g., colon, ovary and, possibly, multiple myeloma), to confirm the absence of excess cases at some sites (e.g., pancreas, uterus and chronic lymphocytic leukaemia) and to confirm the existence of only marginal risk for some sites (urinary tract and oesophagus) [K7, P15, S48, S49]. The Hanford study, the study in the Marshall Islands and studies in British patients irradiated for ankylosing spondylitis, pneumothorax, mastitis or thymus-related conditions continue. While details of the dose-response curve at low exposure levels remain unclear, much has been added to the high-level data and to the nature of the relative risks. In some series, the time distribution of leukaemia seen in Japan and elsewhere has been further corroborated. Absolute and relative risks continue to increase in Japan for many sites, and further follow-up could reveal elevated risk at other sites, clarify some relationships and add new ones.

44. The large series of 14,000 British ankylosing spondylitis patients has continued to accumulate person-years of observation, and some of the patients have been followed for more than 30 years [D21, S31]. The doses received by the patients have been re-evaluated, although not on an individual basis, and several new patterns have been observed. Most notably, unlike the findings in Japan and elsewhere, adult solid tumour risk appears to diminish more than 30 years after exposure.

(b) Ascertainment of exposed and comparison individuals

45. A few new problems have been identified in the ascertainment of cases and matched controls, or comparison individuals since the UNSCEAR 1977 Report. Mostly, however, there has been continued concern over the nature and level of exposure to individuals. For example, as a result of variation in the calibration of equipment and therapeutic technique, it is uncertain how much radiation was actually delivered to the thyroid in children irradiated for tinea capitis or to different tissues in spondylitic patients. There is also the problem of resolving whether, in some instances, the cases were similar to the general population in regard to other cancer risk factors. In

one study of radiation effects in childhood leukaemogenesis, it has been suggested that children exposed in utero during diagnostic radiation examinations may already have been at risk of leukaemia, because no similar risks had been observed in Japan [K6]. Exposed individuals at the Portsmouth Naval Shipyard seem more likely to have been discovered if they later developed cancer, and a potential ascertainment bias exists in situations where extraordinary efforts were made to detect cancer in individuals or their exposure to irradiation [B6]. This bias may well exist in studies of military servicemen exposed to the testing of nuclear weapons [C16, C17, K21] or of children exposed in Utah to fallout. A "healthy worker" effect, in which employees in a given industry are healthier than the general population, may have led to spurious interpretations in many epidemiological studies and must be accounted for wherever possible. In several studies, the unexposed group disclosed excess cancers at sites that had been associated with elevated risk from radiation exposure; clearly the status of such individuals in regard to other risk factors must be evaluated. Such an evaluation can be especially difficult if the later effects are small (as in low excess risks of late-onset tumours), if the dose estimates are uncertain or if the investigators are so thorough as to perhaps over-define cancer, as may have occurred in regard to thyroid tumours.

46. In population studies such as those in Japan and the Marshall Islands, the exposed individuals are known and the task is to continue reporting the results as the diseases appear. It is clear that even 40 years of surveillance is not sufficient to exhaust all of the effects, so these large studies must be continued throughout the lifetimes of the exposed. Similarly, in smaller special-cohort studies, such as those of uranium mine workers and therapeutically exposed patients, the long-term effects must be continually monitored as the cohorts diminish through attrition.

47. The more challenging ascertainment problems are to determine the actual exposure levels of the individuals and the correct expected cancer risks for them. The exposure levels are reasonably well known in some of the cohorts, but not well known in others. Even when exposure is well known, the amount of radiation delivered to specific tissues or cell types may not be. This has become an important consideration in regard to liver, bone, and lymphatic cancers in patients exposed to internal radium sources and Thorotrast, for example. Furthermore, it is vital to determine the comparability of exposures to other carcinogens to which the individuals in these cohorts may have been subject.

(c) Suitability of comparison group

48. For a number of potentially relevant studies, there is a continuing debate and re-analysis of data to determine whether the control individuals have been appropriate. For example, it is not obvious whether individuals suffering from disorders such as thymus enlargement or tinea capitis, many of whom were economically underprivileged, were normal in all the other health respects that might relate to cancer.

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Similarly, second tumours may arise because of other effects of the treatment for cancer, independently of irradiation: the treatment may debilitate or it may alter hormonal or other physiological states. It is difficult to know the extent to which this may occur, since in the absence of therapy most cancer is fatal, and not much data exist on the subject. If an inappropriate comparison is made, the relative risk applies only to that comparison, not to a more general population. It is essential that the control data, or the population-based expected risks used, do not confound different exposures with other risk factors.

(d) Accurate determination of expected risks

49. One of the most serious problems that has arisen in connection with estimating risks in exposed cohorts is the problem of defining the appropriate expectations for the cohort. The first question is whether the exposed are comparable to the contemporary population from which the expected rates are derived. Specifically, it is critical to determine whether they are similar to the general population in regard to the cancer-related aspects of general health, to socio-economic status as it bears on exposure to other agents, and to other factors that may have affected ascertainment or that may be affected by the subject's awareness of his continued surveillance. In the Life Span Study in Japan this matter of comparability is less likely to be a problem, although it could be serious in the smaller studies in which specific cancers (such as thyroid cancer, following childhood exposure, or leukaemia, following fallout exposure) may have been screened much more carefully, or defined more loosely, than in the general population. In Japan, internal controls have often been applied, whereby those exposed to high doses are compared to those receiving essentially no exposure.

50. In a large series of cervical cancer patients, there is evidence that other risk factors, presumably involving environmental exposures, make the results less representative for more general populations. In a similar way, the results of the ankylosing spondylitis series indicate various causes of death at different rates from the general British population.

(e) Meaning of relative risk in a changing exposure environment

51. Many significant changes in exposure to non-radiation risks are taking place in regard to diet, the use of tobacco, exogenous hormones and other drugs, toxic agents in the work-place, pollutants, and the like. When these interact non-additively with radiation, they may materially alter the lifetime radiogenic risk of cancer. Such changing regimes of exposure to other risk factors may seriously affect the meaning of relative risk and the dose-response patterns for radiation exposure unless these other factors are taken into account. This is clearly important in risk assessment, because for many organ sites the relative risk for a given radiation dose is a function of the general risk for the tumour.

52. The dependence of the cancer risk due to radiation on the general level of risk for that cancer may not be a serious problem at high doses if those effects appear as very unusual tumours, or as tumours in locally irradiated tissues. However, this dependence is more likely to be important in regard to low-dose effects or to late-onset, long-latency tumours that occur naturally with substantial frequency.

(f) Identification of new exposed cohorts

53. Since the UNSCEAR 1977 Report [U2], several additional groups of exposed individuals have come under scrutiny, and others are potentially available. The groups being studied include nuclear workers [B22, C21, D24, R21] and military servicemen from Great Britain [D26] and the United States [C16, C17, R16] exposed to fallout from nuclear weapons testing. The results are equivocal and may remain so even if the cohorts continue to be followed. To date, most claims have been for leukaemias, and the occurrence of new radiogenic cases, if any, should have ceased, based on what is known about radiogenic leukaemias in other exposed cohorts. Another group is composed of children exposed in southern Utah to fallout from nuclear weapons testing [L4]; this study is controversial, and its estimates of risk are not accepted by most critical investigators (see, e.g., [L5]).

54. A more consequential group of individuals now being studied is one that comprises children exposed to therapeutic radiation for childhood cancers. The continuing investigation of these individuals suggests that second primary tumours occur more frequently than in non-irradiated children. Many of these are leukaemias or sarcomas in the irradiated areas, but carcinomas also occur, including those of the thyroid. These subjects may afford risk estimates for second tumours, especially for sarcomas for which little data exist (except for bone); the doses in these cases were large, and they are reasonably accurately known.

55. Another important new group is a series of over 180,000 women, in a number of countries, who have been followed after treatment for cervical cancer. These women received high pelvic doses and moderate to low doses to more distant organs. Since the UNSCEAR 1977 Report was issued, many reports have appeared on this set of patients. The number of person-years of observation has become substantial and excess cancers are appearing [B12, B23, D9].

56. Many disparate groups of individuals have in common the fact that in the course of their lifetimes they have been or will be exposed to atypical amounts of external, low-LET radiation. Among these groups are radiologists and radiographers, nuclear shipyard and atomic energy workers, as well as segments of the general population exposed to high-LET radon daughter products in their homes or to higher-than-usual backgrounds as a result of where their homes are sited. Most receive small to modest amounts of radiation above the average, but some (early radiologists, for example) may have accumulated lifetime exposures of 2-20 Gy. More and more data are becoming available on the cancer risks in these groups [see, e.g., M18, M30]. Data are also accumulating on nuclear laboratory employees who have been exposed

in the course of their occupational lifetimes (e.g., [W7, W8, W9, W20]). For example, causes of death have been examined for employees of the Chalk River Nuclear Laboratories in Canada who received lifetime occupational doses of 0.2 Sv or more. Through 1982, 413 long-term, traceable employees had accumulated exposures of this magnitude (their average lifetime occupational dose was 0.42 Sv). There have been no excess cancer deaths among the 64 members of this cohort who succumbed; indeed, only 12 cancer deaths were observed where 17.6 had been expected [W9].

57. Information should be available shortly from the study of employees of the United States Atomic Energy Commission (and its administrative successors) who have received occupational exposures of 0.05 Sv or more.

2. Case-control studies

58. Case-control studies have been, for several reasons, less valuable than cohort investigations in the present context. The shortcomings of case-control studies are several. First, in most situations the frequency of prior radiation exposure among cancer cases will be low, requiring very large case numbers in order to estimate relative risks accurately. Second, the absolute dose-response relationship cannot be estimated statistically from retrospective designs alone, since the affected and non-affected fractions are specified through the sampling strategy rather than being the observed outcome proportions among exposed and unexposed individuals [B19]. Third, it is often difficult, retrospectively, to select a truly comparable control group whose risk-factor characteristics closely match those of the cases; this is not a problem in some prospective designs. Finally, there are several sources of potential bias in terms of case ascertainment when exposure history must be ascertained long after the fact (such as a more intensive search for a history of exposure among the exposed group than among the ostensibly non-exposed group).

II. ASSESSMENT OF DOSE-RESPONSE AND RISK PROJECTION

A. PROBLEMS ASSOCIATED WITH ASSESSMENT

1. Form of the regression of response on dose

59. One of the central problems in risk estimation continues to be the shape of the dose-response relationship, an issue treated exhaustively in Annex B of the UNSCEAR 1986 Report [U1]. A number of models have been used or advocated; these include a linear model, a linear-quadratic model, and a quadratic model, to each of which a separate term (or terms) may or may not be added for neutron exposures and for cell sterilization (a decline in response at very high doses). Many of these alternatives are special cases of the more general form:

$$R = (a + bD + cD^2) \exp(-fD - gD^2)$$

where R is the response, or increased risk of cancer (such as absolute or excess relative risk), D is the absorbed dose, and a, b, c, f, and g are coefficients to be estimated from the epidemiological data. These coefficients are usually determined by either the method of least squares or the method of maximum likelihood. In many circumstances it is more accurate to express the value of R as a function of variables in addition to dose; for example, age, sex and history of exposure to other carcinogens.

60. The attractiveness of this model resides in its simultaneous provision for the estimation of linear and quadratic effects ascribable to radiation and those competing effects of radiation, such as cell sterilization or killing, that could obscure the carcinogenic effect itself. Commonly, when the absorbed doses are not large, the exponential term is ignored. A still simpler, frequently used model is of the form:

$$R = (a + bD^h) \exp(-fD - gD^2)$$

Its merit rests largely in its incorporation of either a pure linear effect (when h = 1) or a quadratic effect (when h = 2), with or without competing effects (f and g) and in the fact that it approximates a linear-quadratic form when h has a value between 1 and 2. Thus, it can reflect a convexity in the dose-response curve. However, h can also be less than 1, which poses problems, for then the slope becomes infinite at zero dose.

61. Each of these approximations to the true, biological dose-response relationship has its limitations or potential pitfalls. Common to all the approximations is that inferences based on the shape of the dose-response curve are more susceptible to error than inferences based on the overall slope. In addition, there are errors that stem from (a) an inappropriate choice of the reference value; (b) systematic or random mismeasurement of exposure; and (c) inadequate allowance for latency or too short a period of follow-up. Errors in the measurement of exposure are particularly troublesome, for even the inevitable random mismeasurements can introduce a spurious curvilinearity and cause the slope to be underestimated [G13, G15] and the intercept to be overestimated, unless the latter is constrained to its true value, which is, however, rarely, if ever, known.

62. Much of the data that have helped to identify radiogenic tumours have limited applicability to the analysis of the dose-response relationship, for the doses are either too poorly known or too invariant to permit discrimination among different models. The data on the atomic bomb survivors constitute one of the very few bodies of relevant information.

2. Contingency tables and proportional hazard models

63. Past analyses of the Hiroshima and Nagasaki data have leaned heavily on contingency table methods (a full explication of these can be found in Appendix 3 of [B16]). Essentially, the subject population is divided into several categories (by age, sex, exposure level and so on), and the relative risks within given exposure categories are determined among individuals similar in

other characteristics. This identifies category-specific patterns in which risk is elevated and estimates the excess in each such category. More recent analyses have employed proportional hazard models.

64. Proportional hazard models combine features of traditional multivariate analysis and life-table analysis. The latter method allows one to calculate survival rates and cumulative survival rates making use of all of the data, even if the periods of observation of the subjects differ; the former method allows one to estimate, when several factors are associated with a disease, the extent of the association for a specific factor when all of the other factors are considered. All methods entail assumptions about the presence or absence of interaction and about the nature of the relationship of the causal variables to the occurrence of cancer, which assumptions may not obtain.

3. Mortality versus morbidity data

65. Dose-response relationships at Hiroshima and Nagasaki had at one time been based almost exclusively on the results of the continuing mortality surveillance. However, in 1958 tumour registries were established in these two cities under the auspices of the respective City Medical Associations and with the technical support of the Atomic Bomb Casualty Commission (ABCC), predecessor to the present Radiation Effects Research Foundation (RERF). The specific purpose was to develop and maintain a source of information on tumours diagnosed in the two cities. Like most such registries in Japan and elsewhere, they incorporate various kinds of information (clinical, pathological, radiological, etc.); however, because they employ field investigators who visit all large hospitals periodically to collect data, their ascertainment of the occurrence of a tumour and its confirmation is more complete than that of most other registries, which depend upon voluntary reports from participating hospitals. Thus, for example, in the Nagasaki registry, 72% of the tumour cases are confirmed (that is, there is, in addition to the clinical report, autopsy, surgical pathological or surgical operational data on the tumour) and only 7% of cases are ascertained solely through death certificates. This contrasts markedly with the figures obtained from other registries in Japan, where, on average, only 50% of the cases are confirmed and 37% are ascertained through death certificates alone. These superior methods of ascertainment notwithstanding, the utility of the registry data hinges ultimately on the absence of bias. No exposure status bias in data collection has been revealed in the data of either city [W5]. Method of diagnosis of the tumour, reporting hospital and frequency of doubtful cases do not differ as a function of dose.

66. For fatal cancers, the relative risks based on excess incidence cases, rather than excess deaths, and on T65 doses are generally either the same as or slightly higher than the relative risks based on mortality for the same years (1959-1978); however, the absolute risk estimates (excess incidence cases per 10^4 PYGy) are higher. The mortality data suggest an overall average excess risk of death from a solid malignant tumour of about 2 per 10^4 PYGy; registry data from Nagasaki, on the other hand, limited though they are, suggest a morbidity risk six to seven times higher. Thus, for all cancers except leukaemia, the number of excess incidence cases per 10^4 PYGy is 9.6 whereas the number of excess deaths is 1.4. In Hiroshima, similar data suggest a twofold greater absolute risk; the values are 13.6 excess incidence cases and 6.2 excess deaths per 10^4 PYGy. In both cities, a substantial proportion of this difference is of course accounted for by tumours of the breast, prostate and thyroid, which are seldom identified immediately as the causes of death. However, an important contribution is also made by cancers of the digestive organs, notably the stomach.

B. DOSE-RESPONSE PATTERNS

67. The accurate estimation of dose-response patterns for each tumour site and the evaluation of low-dose effects are impeded by several facts: (a) the long average latent period (the continuing increase in absolute risks of cancer among the atomic bomb survivors in Japan suggest this period exceeds 40 years); (b) the relatively small expected additional risk, even at intermediate or high doses; and (c) changes in exposures to other carcinogens, which could interact with radiation exposure and make it difficult to interpret dose-response patterns in terms of the future risks of current exposure levels. It is certain also that the increased accuracy of dose measurements and the increasingly sharp focus of the beams used in therapeutic radiation will cause dose-response estimates to change.

1. Assessment of the effects of low dose

68. As was stated and thoroughly discussed in Annex B of the UNSCEAR 1986 Report [U1], an assessment of the effects of low dose is clouded by the need for large samples, the difficulty of accurately estimating exposure and the growing importance of extraneous sources of variation, including diagnostic and therapeutic exposures that are less compromising when the doses are large. Two of these difficulties warrant special consideration. Precise direct estimation requires impracticably large samples. Estimates of low-dose risks based largely on high-dose data must depend heavily on the assumptions about the shape of the dose-response curve and are, of necessity, no better than the model is applicable. Current data suggest that resolution of these difficulties will not be easy, and it seems likely that there will be many site-specific differences.

69. Many individuals who entered Hiroshima or Nagasaki soon after the bombs (to carry out relief or other activities) are included in the "not-in-city" group of the Life Span Study cohort in these two cities, a group which has not been used in recent analyses of the Life Span Study data. Early entrants, defined as individuals who entered Hiroshima or Nagasaki within one month of the bombs, are represented by 4,512 individuals in the cohort sample

[K13]. Most presumably, they received some exposure to residual radiation from fallout and neutron activation in soil (if they were in the vicinity of the hypocentre). It is difficult to estimate precisely the dose received by these individuals, for it attenuates rapidly with distance from the hypocentre, and the exposure depends upon their proximity to the hypocentre and time spent in a particular location. However, since it is improbable that individual exposures could have been large, as they were for directly (promptly) exposed persons, a remarkable increase in radiation-induced cancers is highly unlikely.

70. Mortality among early entrants has been followed, and some site-specific incidence studies have sought to determine whether they are at increased risk of the specific malignancy. Kato and his colleagues [K13] found no increased incidence of leukaemia and other cancers among the early entrants. However, Rotblat [R8] has described an increased incidence of leukaemia among these subjects, based on a report of Hirose [H9], and maintains that this is an example of a low-dose effect. The latter report is flawed in many ways. First, there is a problem in the estimation of the denominator (the base population) used to calculate the leukaemia incidence. In the studies of Hirose and Rotblat [H9, R8] the number of early entrants residing in Hiroshima and Nagasaki is estimated on the basis of data from two or three cross-sectional surveys conducted from 1950 to 1974 and not on the basis of data from a cohort. Second, migration is not taken into consideration. Estimation of the base population is a particularly serious problem since the authors did not employ a compelling method to examine the dose-response through grading early entrants by time and place of entry. Third, although the leukaemia cases among the early entrants have a distribution by type similar to that seen among atomic bomb survivors, the peak annual incidence does not occur in the early 1950s, as it does among atomic bomb survivors, but in the early 1960s, when leukaemias among the survivors themselves were few in number. Ohkita has called attention to still other difficulties [O4].

71. More recently, as part of a general study of the incidence of thyroid cancer among atomic bomb survivors, Ishimaru and his colleagues looked for, but did not find, excess risk of malignancy among early entrants in Hiroshima and Nagasaki. Indeed, only one case of thyroid cancer was observed in Hiroshima (and none in Nagasaki) among those early entrants who were close to the hypocentre within two days of the bombing. Patently, the number of cases are too few to evaluate the effect of exposure to residual radiation rigorously, but no difference in incidence was seen among early entrants, late entrants and survivors who had received a dose of less than 0.01 Gy in either Hiroshima or Nagasaki.

72. The discussion here focuses on specific studies, namely, those that involve high dose rates (albeit low doses), from which most of our knowledge is derived. However, to the extent possible, it will also consider low-dose, low-dose-rate exposures such as those received occupationally or those received by individuals who live in houses with high radon levels.

Limited though the data may be, they are summarized on a site-specific basis to illustrate differences and to indicate approximately values of relative risks.

2. Assessment of the effects of high dose

73. The mortality experiences of the survivors of Hiroshima and Nagasaki have been, and will undoubtedly continue to be, the most relevant single source of information on the frequency of occurrence of radiation-related cancers. These experiences have not only identified those malignancies that increase in frequency following exposure but also provided insights into the probable dose-response relationships that obtain. These differ by site in biologically consequential ways.

74. Estimates of tissue-absorbed dose for Hiroshima and Nagasaki were published in 1978 [K14] (see also for the foetus [H7]), though they had already been used in the UNSCEAR 1977 Report; these estimates will be discussed later in connection with the reassessment of the individual exposures of the survivors of the atomic bombings. Revised estimates for the Marshall Islanders will soon be available.

75. Re-evaluation of the exposures of the survivors of the atomic bombings of Hiroshima and Nagasaki has disclosed that their estimated neutron doses were substantially lower than had previously been thought [R9, R20]. The findings, particularly those for Hiroshima, are therefore much less informative about the effects of neutrons than heretofore presumed. Differences, albeit not statistically significant ones, exist between the cities, and there remains a need to find alternative explanations for these. It will also be necessary to re-examine carefully the even more limited epidemiological data on the relative biological effectiveness (RBE) of neutrons, if this source of radiation is to figure appropriately in the estimation of risk.

76. Risk assessment from results of the cervical cancer series are complicated by the very different doses delivered to the various organs. In particular, pelvic organs were exposed to doses high enough to make cell sterilization probably quite important (i.e., risk is less than would be expected under linear dose-response assumptions), while other tissues were so little exposed that accurate dose-response information cannot be obtained. Under such circumstances, it is difficult to use the results of this series to determine whole-body risk estimates.

C. RISK PROJECTION

77. From the public health and regulatory points of view, it is important to know as accurately as possible the impact which a given radiation exposure would have on a population, so that criteria for controlling such exposures, or for anticipating the results of accidents, can be developed. An important aspect of such knowledge is the need to estimate the lifetime cancer experience of an exposed cohort of individuals. Lifetime data are rare, even for single-site risks, and

complete lifetime multi-site data are not yet available from the major cohorts that have been under surveillance for the past three or four decades. As a consequence, it is still necessary to project lifetime risks from data based on only portions of the lives of exposed individuals. Such risk projections depend heavily on: (a) the actual risks observed in the available cohorts and (b) the model used to extend the risk beyond the currently available data. Thus, in comparing the results to be discussed below of different projections made at different times, one must recognize not only the changes in the observational data as a result of further follow-up or estimated doses, but also in the projection model that was used. It must also be borne in mind that the projections are invariably least certain for those individuals exposed early in life.

78. Risk projection, generally or site-specifically, requires knowledge of at least the following: (a) the latency time (that is, the time from exposure to the first expression of excess risk) and the plateau period (that is, the time from the first expression of excess risk until the excess risk disappears); (b) the relationship between excess risk and baseline risk, as a function of time since exposure; (c) the age distribution of the exposed population and the baseline pattern of age-specific mortality rates from all causes and from the cancers under consideration; (d) the effect of age at exposure; (e) the effect of sex; (f) a dose-response function; and (g) the effect of environmental exposures. Other factors may also need to be considered, such as the different effects of low- and high-LET exposures, and of low and high dose rates.

79. Knowledge of these factors can only be derived from the experience of a small number of cohorts (the survivors of Hiroshima and Nagasaki, the ankylosing spondylitis patients, and the large international series of cervical cancer patients). The details of these studies and their site-specific risk coefficients will be presented later in this Annex. Most of the other studies serve primarily to confirm these three studies. (These comments pertain mainly to low-LET, high dose rate exposure.) There are as yet no definitive studies from which to estimate lifetime effects of exposure to high-LET radiation (e.g., occupational exposure in mines, radon in homes) or very low-dose and low-dose-rate exposures of either high- or low-LET radiation.

80. There have been several recent attempts to project the long-term post-radiation effects of whole-population exposure. Notable are (a) the BEIR 1980 Report [C4]; (b) a study by the United States Nuclear Regulatory Commission regarding risks in a population from exposures due to a nuclear accident [G11]; and (c) an attempt by the National Institutes of Health of the United States to estimate the probability that a specific cancer was radiation induced at times subsequent to exposure [U4]. These studies have had specific objectives, and all have been applied to the population of the United States.

81. The purpose of the BEIR computations was to estimate as accurately as possible the lifetime risk in a

population of the United States exposed to a given dose of radiation according to two different projection models [C4]. The purpose of the report of the Nuclear Regulatory Commission was to provide estimates of the lifetime additional risk from a whole-population exposure, such as in a reactor accident, based on a range of assumptions that were consistent with the available radiation data. The purpose of the National Institutes of Health study was to assess the probability of causation of a given cancer by radiation exposure as a function of time since exposure; the computations could be useful for assigning compensation to persons in whom radiogenic cancer may have occurred.

82. This section will review the factors that must be known in order to make risk projections. It will also summarize the main studies that have attempted such projections, and will outline the basic concepts employed by the subsequent review of the literature. The same concepts will be used in chapter VII of this Annex, where new lifetime risk projections will be made. Most of the parameters for the risk projections have been estimated from the Japanese data [K7, W5] and the ankylosing spondylitis data [S28, S31]. Both sets of data have undergone major risk estimate revision [e.g., D21, P15, S48, S49] and dose estimate revision [L16, N9, R20]. While these revisions do not alter the number of excess cases from these exposures, they do change the level of risk per unit dose. While the following discussion on risk projections is not based on the most recent dose-estimate data, the methods themselves are appropriate. Chapter VII provides risk projections based on the most recent data.

1. Latency time and the plateau period

83. Epidemiological data cannot distinguish between the first occurrence of a radiogenic tumour and its clinical appearance, so that in this Annex the time until the tumour is clinically detectable is referred to as the "latency time" for a cancer. As will be shown below, different human cancers have clear and characteristic latency times following radiation exposure [L9].

84. For adult exposures, leukaemias and bone cancers have a minimum latency time of 2-5 years, whereas solid tumours have a minimum latency time of approximately 10 years [U1]. For solid tumours, excess tumours commonly occur at ages comparable to those at which spontaneous tumours of the same site occur. The evidence is not clear or consistent as to whether other risk factors, such as smoking in the case of lung cancer, interact with exposure to hasten the onset of radiogenic tumours.

85. The pattern following childhood exposure is somewhat variable. Tumours that typically arise in childhood, such as osteosarcomas, occur in the exposed at ages similar to those at which they occur naturally. Bone cancers and leukaemias have a 2-5 year latency. For carcinomas of typically adult onset, the latency time is 10 years or more, and current evidence suggests that they also arise at their normal ages, late in adult life.

86. The appearance of radiogenic leukaemias and bone cancer commonly follows approximately a log-normal distribution [C4]; as earlier noted, the excess risk appears after about 2 years and reaches a peak by 10 years. Data on other tumours are less clear, and it is usual to assume that after the latency time full excess risk is, approximately, attained [C4]. One report [U4] has fitted a cubic function in order to produce a smooth transition from zero risk to maximum risk over the period from 5 to 10 years after exposure.

87. The plateau periods, or periods of expression of excess risk, observed for specific tumours are generally consistent over a variety of studies, although there are exceptions. For leukaemias and bone cancers, excess risk typically declines with time, but still exceeds that in the controls as much as 40 years later in the case of the atomic bomb survivors and the ankylosing spondylitics, though it has ended after 25-30 years in other studies.

88. The plateau period for adult carcinomas among individuals exposed as adults appears to be open-ended; that is, in almost every instance, once risk has become elevated it remains elevated for the rest of the life of the exposed individual. Most major exposed cohorts are still under investigation, and this finding could change; in one major study, that of the ankylosing spondylitics [D21], the excess risk of adult carcinomas seems to disappear 25 years after exposure. Since this finding with respect to the spondylitics has not generally been seen with respect to adult atomic bomb survivors or the subjects of other studies, it may be unique to that study. However, it should be noted that in Hiroshima and Nagasaki among the two youngest cohorts, i.e., 0-9 and 10-19 years of age at the time of the bombing (ATB), the risk has been declining significantly in the 0-9 year group, also in the 10-19 age group, but not significantly so.

2. Excess and baseline risks as a function of time since exposure

89. As was stated in paragraph 13, there are two basic models for the pattern of expression of risk after exposure (once the latency time has passed). These are often known as projection models. The first is the constant additive projection model, according to which there is a constant number of excess cancers in any given year per unit number of persons exposed per unit dose. That is, the number of excess cancers is fixed, regardless of the baseline risks:

$$R(exposed, t) = A + R(unexposed, t)$$

where A is the absolute excess risk for all $t >$ latency time. The value A is usually estimated in one of two related ways. In the first, the total number of cancers expected in the cohort had they not been exposed (i.e., the baseline risk) is computed, and subtracted from the number observed in the cohort, and divided by the total number of person-year-Gy (PYGy) of observation. In the second, a regression model may be fitted to the time of onset of every cancer; such models express the excess risk and the baseline risk as a

function of age, sex, time since exposure and perhaps other risk factors. If the additive projection model is correct, then at any post-latency time the difference between observed and expected cancers, divided by the total PYGy observed, will be constant. Sometimes a variable excess risk model is used, in which the value of A is estimated from the data by regression methods, specific to sex, age at exposure, time since exposure, and/or other variables.

90. The second basic projection model is known as the multiplicative projection model. According to it, the ratio of incidence or mortality rate in the exposed to that in the unexposed is constant once the latency time has elapsed. That is,

$$R(exposed, t) = RR \times R(unexposed, t)$$

where RR is constant for all $t >$ latency time. The value RR has been estimated in two ways. First, the number of observed cancers at some time t after the latency time is divided by the number of expected cases. Sometimes, the excess relative risk per Gy is computed. If the multiplicative projection model is descriptively correct, there should be an approximately constant relative risk at any post-latency time in an exposed cohort. In some instances, a variable multiplicative risk model is used, in which the value of RR is estimated from the data by regression methods, specific to sex, age at exposure, time since exposure and/or other variables.

3. Age and sex structure of the population and baseline mortality rates

91. To predict future cancers in an exposed cohort, it is important to know the age (and sex) distribution of the cohort. This is so because with either the multiplicative or the additive risk models, since baseline cancer risks change with age and sex, the number of cancers expected depends on how many person-years of experience at different age (and sex) categories occur in the data. In an exposed population of mixed ages the number of expected cases per exposed person of age t is E(t) and a fraction f(t) of the exposed cohort is in that age category, the total number of expected cancers will be

$$\sum_{t=0}^{\infty} f(t) \times E(t)$$

A similar weighted expectation can be computed for each sex. The observed number of cancers can then be compared to this aggregate expectation.

92. The number of expected cancers depends on the number of person-years at risk experienced at each age (after the latency period) and the baseline risk. The number of person-years to be lived between ages y and $y + n$, per person now in age group x to $x + n$, is a standard life-table function which depends solely on the baseline age-specific mortality rates, m(t), for ages $x < t < x + n$. The number of person-years declines each year as mortality occurs (i.e., as survivorship declines). The cause-specific mortality rate for a specified tumour site is a component of the m(t) schedule, and the expected deaths at any given age can

be computed approximately by multiplying the cause-specific rate by the number of person-years. This approach is followed in risk computations for this Annex in chapter VII, and is essentially the method used by the BEIR III, the National Institutes of Health, and the United States Nuclear Regulatory Commission computations referred to earlier [C4, G11, U4].

93. On the assumption that current mortality rates do not change, life-tables may be constructed for an actual or hypothetical exposed cohort to compute the person-years and expected cancers. The excess cancers are determined by multiplying the person-years by a series of coefficients appropriate to a given projection model. For example, with the additive projection model, the number of excess cancers per person-year is the coefficient. With the multiplicative projection model, the baseline rate [m(t, cause)] is multiplied by the relative risk coefficient, RR. This is multiplied by the person-years to determine the number of cancers in the exposed group. Excess cancers are this number minus the number expected in the population in the absence of exposure. Given the assumption of unchanging risk coefficients and baseline mortality rates, it is possible to compute the additional risk to any exposed group of persons in the population for which the baseline risks are applicable.

4. Age at exposure

94. The age at exposure can affect the coefficients of subsequent absolute or relative risk (i.e., the values of A or RR can be specific to age at exposure). Few statistically sound generalizations can be made about this, except (as will be shown later) that for some tumours, notably those of the female breast, exposure in childhood can lead to much greater risks, and exposure after age 50 to lesser risks, than exposure at intermediate ages. Childhood exposures leading to childhood cancers are generally treated separately; other than for leukaemia and bone cancer, there is relatively little data on the details of the projection effects for such exposures because the Japanese exposed to the atomic bombs in childhood (the main source of data) are still too young for the late-age effects to have been expressed.

5. The dose-response function

95. The dose-response function is discussed fully in the UNSCEAR 1986 Report [U1]. For projecting risk, the dose received by each exposed individual must be taken into account. Where a linear dose-response pattern is assumed, the dose is used directly. Where a more complex pattern is assumed, the dose is translated into some selected function of dose via the equation relating risk to dose for that pattern. The risk is then linear relative to this function of dose. The equations used in human studies have essentially all been variants of those described in paragraphs 59 and 60.

96. Usually, in projection, a model of excess deaths (cases) or relative risk per unit dose is determined. If a

non-linear dose-response is desired, the number of excess deaths (cases) or the relative risk per unit dose is multiplied by the appropriate function of the dose (e.g., $a + bD + cD^2$).

6. Other exposure factors

97. Where adequate information is available, the projection of risk may take into account such factors as exposure to smoking or other environmental hazards, other radiation exposures, or the different biological effectiveness of high-LET radiation. As long as one can supply an appropriate dose-response function, a projection model, and an estimate of additive or multiplicative projection coefficients, the same principles should apply.

7. Previous approximations of lifetime risk projection

98. It is useful to summarize the most important recent attempts to estimate lifetime risks, or related measures, from population exposures. As was noted earlier, while these studies attempted to synthesize risk coefficients from the world literature, they relied most heavily on the Japanese and ankylosing spondylitis data; however, the latter studies have since been updated, in terms of both new dose estimates and longer follow-up times, so the specific risk estimates they once provided must now be reconsidered.

99. *The BEIR 1980 Report* [C4]. The BEIR Committee attempted to synthesize the data on radiogenic cancer risk as of approximately 1979. It used a life-table projection approach, employing the 1969-1971 life-tables from the United States, and baseline cancer mortality rates for five-year age groups. A table was devised to convert mortality data to incidence data, based on cancer survival rates, so that estimates could be made for both the commonly fatal and the rarely fatal radiogenic cancers. This is given here as Table 3. A table of risk coefficients, excess cancer incidence per 10^4 PYGy was derived, and estimates of the lifetime risks associated with single exposures and continuous exposures were computed, based on linear and linear-quadratic dose-response functions, for both risk projection models. Estimates were made separately for leukaemia and bone cancer and for all other cancers combined. Representative summary tables from the BEIR III Report are repeated here as Tables 4, 5, 6 and 7 for comparison with the projections presented in chapter VII.

100. *The United States Nuclear Regulatory Commission study.* As part of a study sponsored by the United States Nuclear Regulatory Commission, Gilbert [G11] developed estimates of lifetime risks that would pertain to the population of the United States were it exposed to a nuclear accident. These estimates are for low-LET, single-exposures and are specific to the population of the United States (e.g., baseline cancer rates from the United States were used).

101. Gilbert used (a) the age and sex distribution in the United States; (b) the age, sex, and cause-specific

mortality rates in the United States; (c) a model of the dose-response pattern, latency period, and projection effects; and (d) estimates from past studies of the absolute or relative risk per unit exposure, largely from the BEIR 1980 Report updated by subsequent papers from Japan and the spondylitics. She provided methods for computing the total number of years of life expected to be lost as a result of the exposure incident. The input characteristics used in her study are given in Table 8, which is an adaptation of material from the Nuclear Regulatory Commission study.

102. Gilbert's projection of lifetime effects is based on a linear-quadratic dose-response model, with non-linear effects at intermediate dose rates (<0.05 Gy/day) of low-LET radiation, as might obtain in a nuclear power plant accident. Upper and lower bounds and central estimates for the effects of exposure were computed. These do not have statistical meaning as, for example, mean and confidence limits do; in fact, there is currently no way to provide probability statements on the likelihood that the true effects will take any particular value. Gilbert merely provided what appeared to be reasonable limits for the plausible range of effects.

103. Gilbert used a linear-quadratic dose-response equation to account for the incomplete human data for low-LET radiation [C4], consonant with animal experimental data [N1]. The extent of effect-reduction at low doses and low dose rates is not yet known, but the National Council on Radiation Protection and Measurements of the United States (NCRP) has suggested that the correction coefficient is in the range 2-10 [N1], which is the range used by Gilbert [G11].

104. For comparison with chapter VII, a summary table of Gilbert's results (Table 9), provides her bounds, for various sites, for years of life lost as well as excess cases. Gilbert provided both relative and absolute projection computations. Her absolute risk coefficients were based on empirical data and her relative risk coefficients were those multiplying factors that would produce the same number of excess cases as actually observed.

105. *Probability of causation: the radioepidemiological tables of the National Institutes of Health* [U4]. For some purposes, it is of interest to estimate what fraction of cancers occurring in a given exposed population at a specific time post-exposure may have been caused by the exposure. Even if a specific cancer cannot be said to be radiogenic, it can be estimated by what fraction the baseline risk is elevated. In general epidemiology this would be termed the attributable risk, but in radiation epidemiology it is often referred to as the probability of causation (PC). The probability of causation of a specified cancer by radiation was defined earlier as the excess cases due to radiation divided by the total cases (see paragraph 21).

106. The study of the National Institutes of Health used essentially the same data as Gilbert, with modifications to various components but a comparable life-table approach. The study computed a value, R, defined from PC as follows:

$$PC = [\text{Prob(cancer w exp.)} - \text{Prob(cancer w/o exp.)}]/\text{Prob(cancer w exp.)} = R/(1 + R)$$

where R is the excess relative risk, defined as the increase due to dose D as a proportion of the probability of cancer in the absence of the exposure. These probabilities are specific to a given dose, sex, and age at and since exposure.

107. The National Institutes of Health report defined R in terms of its components as follows:

$$R = F \times T \times K \times W$$

where F is a function of dose, T gives the dependence of R on time since exposure, K is the dependence of R on age at exposure and W is the effect of an additive interaction between radiation and other (known) risk factors. The study described each of these parameters for each tumour site.

108. Qualitatively, the results of this study can be summarized as follows. For leukaemias and bone cancers, the probability of causation rises rapidly with time after the minimum latency time, reaches a peak (whose height depends on dose and which is maintained for 10-20 years) and then falls to zero at the end of the risk period. For other cancers, the probability of causation is roughly constant at all ages after the minimum latency time has passed, but is a function of age at exposure. It is typically highest for young ages at exposure, declines to a minimum (which varies by site) for ages 40-50 at exposure and then may rise slightly or stay roughly constant.

8. Risk coefficients for high-LET radiation

109. Much of the collective dose from high-LET radiation received by human beings comes from exposure to inhaled radon daughters, thorium decay products and the like. The radiation dose in these instances is mainly from alpha emissions. In addition, the exposure is chronic over many years, as, for example, in the cases of underground miners in hard-rock or miners of radioactive ore, and of the many individuals who live where the bedrock or soil provides a source for radon gas entry into homes.

110. Because the doses received under these circumstances are chronic in nature, the models discussed above are not really applicable (they project the risk subsequent to single or short-term exposures.) In chronic exposures, the cancer effects are the results of a dose that continues to build over many years. The most widespread risk is cancer of the lung due to the inhalation of radon daughters.

111. Thomas and McNeill [T11, T16] estimated excess deaths and relative risk of lung cancer from available data on exposures of underground miners to radon and daughters. Their results, which are given in Table 10, are discussed further in chapters III and VII.

112. The risk estimates varied considerably from one study to another in the survey by Thomas and McNeill. This variation may be due to several factors, including the effects of smoking, differing dose rates (i.e., ambient concentrations of radionuclides in the air of the mines), inaccuracies in dose estimation, or other confounding factors. Some of these factors are discussed below. No simple, single risk pattern emerges; there is about a fourfold difference in estimated lifetime risks, per WLM, depending on which exposed cohort is used as the basis for the estimate.

113. The risk coefficients derived from these high-LET exposure data have not been used to project lifetime risks in exposed cohorts. A method for such computations will be suggested later in this Annex.

9. Selection of preferred projection model

114. The BEIR 1980 Report [C4] predicted lifetime risks under a variety of assumptions by projecting risks estimated from observed data into the future, but unobserved, lifetimes of exposed individuals. The number of excess cases estimated using an additive model of risk per 10^4 PYGy was about a factor of three less than the number of excess cases estimated using a multiplicative model. Although they had employed somewhat different assumptions and updated data, Gilbert's results were essentially the same [G11].

115. When the additive and multiplicative projection models provide differing results, it is obviously important for practical applications to determine which, if either, model is to be preferred. In examining this problem and its consequences for risk projection, Muirhead and Darby [M36, M37] developed a generalized statistical model for risk projection and tested its fit, as well as the fits of the additive and multiplicative projection models, which are special cases of the generalized model, to the available data. The authors expressed risk in the exposed, R(d), in relation to the age-specific risk, R(0), in the unexposed, as a function of dose, d. They used the general function

$$R(d) = \{[R(0)]^{\gamma} + [1 + \alpha d \exp(\Sigma \beta_i x_i)]^{\gamma} - 1\}^{1/\gamma}$$

where the x values in the exponential term are covariates and the β values are their regression coefficients, taking into account age at exposure, time since exposure and sex, and Σ implies summation over all such covariates. The parameter γ can be thought of as indicating the model type: if $\gamma = 1$, the additive projection model results; if $\gamma = 0$, the multiplicative model results; other values of γ express intermediate types of model.

116. Muirhead and Darby tested this approach with mortality data on all cancers except leukaemia in Hiroshima up to 1978 between the 0-0.09 Gy and above 1 Gy dose groups. Table 11 shows the results of some of their fitting efforts, and Table 12 the implications of the different models for lifetime risk projection. While this work was not based on the most recent dose estimates, the qualitative nature of their

findings seems unlikely to be changed appreciably with new doses.

117. In the absence of covariates, the best-fitting value of the parameter lies between 0 and 1, but the fit of this model to the data is not good. Adding age at exposure improves the fit, which is even further improved by adding time since exposure. Those models which do fit well are shown in Table 11. What is clear is that none of the simplest models fits the data best, and a variety of models can generate a statistically comparable fit. Yet, as shown in Table 12, (a) these models lead to very different lifetime risk projections; (b) the multiplicative and additive projection models do not necessarily provide upper and lower limits to the risks among this family of models; and (c) the number of years of life lost, which Gilbert's projections had shown to be relatively similar under multiplicative and additive models (compared to the excess number of deaths), are quite variable among the possible models. The latter difference is probably due to Gilbert's using a constant risk coefficient for all ages at exposure.

118. This work shows the importance of knowing the nature of the effects of radiation after exposure, on the projection of lifetime risks, and that it is difficult with present data to determine a clearly best-fitting model. Different data sets would be fitted best by somewhat differing models. Only if the total lifetime effect of radiation is known can a choice of a projection model be made confidently. If, as has recently been found in the spondylitis data, excess risk of solid tumours, in fact, diminishes or disappears after 30 years, then the bulk of tumour expression may have been seen in some of the current cohorts, and projection efforts could be made with relatively less uncertainty. However, the Japanese data do not yet show such a decrease, except at the youngest ages at time of exposure.

119. The major importance of the work by Muirhead and Darby is to suggest that current data cannot yet provide a model by which to project lifetime risk accurately, or even confidently to bracket the range of likely risks. Indeed, even if (with currently available cohorts of data) one projection model fits the data best, this must be taken to be a numerical rather than biological fact; not enough is known about radiation carcinogenesis to construct a single biologically correct projection model, if indeed one exists.

III. BIOLOGICAL ISSUES IN THE ASSESSMENT OF RADIATION CARCINOGENESIS

120. The data available for the assessment of radiation carcinogenesis in man come from several sources, the most important of which have already been cited. A number of different approaches have been used to evaluate the patterns of cancer that occur in irradiated individuals. While some studies have combined several approaches, and the approaches are not incongruent, most have employed only one, or a few.

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A. BIOLOGICAL MODELS OF RADIATION CARCINOGENESIS

1. Multi-stage models and the role of radiation in carcinogenesis

121. At the cellular level, cancer is a clonal, molecular-genetic disease. One way to understand the response of an individual to radiation is to model the process of carcinogenesis itself in terms of the events thought to occur at the cellular level during the transformation of cells from normal to malignant. Generally, such models consider cancer to be a multi-stage process; it is presumed that for a cell to be affected, a series of k events must occur in its lineage; the time, or age, to a tumour is a function of the rate at which these events take place. The k events must occur in a single cell lineage, the last event rendering some single cell cancerous and causing it to become the progenitor of the entire subsequent tumour and its metastases. This has been established biologically for such a wide variety of tumours that it can be accepted as a fact.

122. Numerous multi-stage models have been proposed (see [W1] for a review). One of the motivating factors behind the development of these models has been the observation that many tumours in man and animals exhibit a linear increase in the logarithm of the incidence (or hazard) function, h(t), plotted against the logarithm of age, t; that is,

$$h(t) = At^{(k-1)}$$

where A is a constant of proportionality, usually a function of the transformation rates of the k events, among other things. Empirically, the slope of such a plot on a log-log scale is 4-6 for a wide array of human [C1] and animal [P1] cancers. It should be noted that many non-mutational chronic diseases show similar patterns.

123. Many other variations of multi-stage models have been proposed, but there are problems associated with any purely formal approach to radiation-induced carcinogenesis. Stochastic models of carcinogenesis model the process at the cellular level, yet data on human radiation carcinogenesis used to test those models come from observations on populations of individuals. It may be unrealistic to infer from such data much about the nature of the process itself or of the role of radiation. Additional errors may arise from the heterogeneity of the exposed population, which is not considered by statistical models.

124. Based on the way the multi-stage statistical models were developed, some investigators have interpreted the slope of a log-log plot of cancer incidence data (4-6) as directly reflecting the number of stages involved. For a variety of reasons, it is unlikely that this interpretation, based on population data used to infer cellular processes, is useful for this purpose [W3]. However, it is possible, without specifying the nature or even the number of stages, to express the effect of exposures of varying intensity to carcinogenic agents that affect only one of the required stages. This has been done by Whittemore [W2], by Day [D2] and by Day and Brown [D1]; Whittemore derived a table

of the expected effects on both the absolute and relative risks of constant exposures, single exposures and short-term exposures [W2]. If the first of the necessary transforming events is affected by the exposure, the number of individuals already partially transformed should increase, and even after the specific exposure terminates, they will remain at excess risk, having to await only a smaller number of events in subsequent years. If the last stage is affected, then those cells that have already experienced some events will be quickly transformed, but once the exposure ceases there will be no further excess risk in the exposed cohort relative to the unexposed cohort. If an intermediate event is affected by the exposure, the fraction of the cohort in a more highly prepared state (and, hence, the rate of occurrence of disease) should increase, as with an early stage event. However, after some time has passed, the remainder of the cohort will also gradually accumulate these stages, and the excess risk in the exposed cohort will diminish.

125. These predictions have been applied to age-onset data in exposed cohorts of individuals to infer what event may be affected by radiation in the generation of cancer in various organs; the results are summarized in Table 13. The bases for these inferences are the relationship between age at exposure, the relative risk, and time since exposure. A major point is that if a late stage is affected, then individuals who have already experienced all prior stages will quickly manifest a cancer; because a higher fraction of older individuals are presumably in such a condition, late age of exposure should, according to this model, manifest more, and quicker, excess cancers than in younger individuals. On the other hand, if an early event is affected by radiation, there will be a long time until those affected will manifest their excess tumours. Further, the effect of radiation would be less at later ages, since more of the older population would already have experienced these early stage events. The logic of the interpretation is given in [C22], and several applications can be found in [W2].

126. As Table 13 shows, these ideas may have merit, but they have not yet led to easily understood conclusions. In leukaemia and other tumours, there are no simple or clear patterns of relationship of latent period with age at exposure, or latency itself. Therefore, epidemiological evidence alone cannot be used to make reliable inferences about the nature of the carcinogenic process either in terms of the number of stages involved, or which of those stages is affected by radiation.

127. To account for smaller numbers of events, or for the differential growth of tumours relative to normal tissue, several models have been proposed [W1]. One is a three-stage model that includes dose-dependent cell killing (or sterilizing) effects, originally proposed by Neyman and Scott [N2]. It is consistent with data on radiogenic osteosarcomas in dogs and humans caused by ^{226}Ra (half-life: 1,600 years) in showing that a response is proportional to the square of the dose at low doses; that incidence is not dependent on time and dose at high doses; and that radiogenic tumours may appear at a much later time

after exposure than simply the tumour growth period [M3, W1, W4]. The first two events are assumed to be affected by the radiation directly, perhaps as mutations with effect proportional to dose, while the third is a bone growth phenomenon related to bone remodelling and the eventual stimulus for transformed cells to grow.

128. This result is somewhat different from the result observed in individuals, both children and adults, who had been given ^{224}Ra, which has a shorter half-life and a very different skeletal dosimetry. In those individuals, excess cancers occur a few years after exposure but no longer occur about 25 years after exposure. The Marshall-Groer model calls for a cell-division effect, which should lead to different results in children, whose bones are more actively growing, and adults; however, this has not been observed [M22].

129. In an attempt to generalize the carcinogenic process, taking into account the promoter and mutational effects, and still generating age-incidence curves which are proportional to the 4-6th power of age, Moolgavkar and his colleagues [M1, M2] have developed a two-stage model, with differential growth of normal or partially transformed cells (or both). This is an improved version of earlier work of Armitage and Doll [A2]. The Moolgavkar paradigm makes predictions similar to those of modified Armitage-Doll models [A1, W2] in regard to the effects of age at exposure and the incidence pattern as a function of time since exposure. It has been fitted to data on breast cancer [M5], where hormonal (and possibly dietary) effects are influential, and to data on smoking and lung cancer. The results are consistent with radiation being a mutagen for both of the mutational stages required in the model, if the known facts of breast tissue growth are taken into account. First, nulliparous women have fewer cells susceptible to transformation which will later undergo extensive mitosis [B1]. Second, the risk of post-pubertal radiation carcinogenesis decreases with increasing age at exposure, again agreeing with the circum-pubertal tissue growth. Finally, pre-pubertal irradiation should have less of an effect, since few breast cells are dividing at that time. Until recently, no pre-pubertal effect had been seen in atomic bomb survivors [T1]; however, this no longer is the case [T6, T7]. From the most recent data, it now appears that in fact the risk may be highest in ages under 10 years and greater than in ages 10-19 years. The longer the interval between irradiation and menopause, the longer will be the period during which partially transformed cells can proliferate and hence be vulnerable to a final transforming event; this age effect has been observed [B2].

130. A number of experimental observations support a model based primarily on the biological nature of tumour formation rather than on formal concepts. Within the framework of this model, two biologically different stages of carcinogenesis are singled out: initiation and promotion. To develop a specific model of radiation carcinogenesis based on a two-stage theory it is necessary to discover the mechanisms underlying these processes (for a comprehensive review see [F9, F10, P13, P14]).

131. The chain of events culminating in a clinically manifest tumour starts with the initiation process in a normal target cell. It is clear that in at least some tumours the event causing initiation is a mutation in the DNA. This can be a point mutation or a chromosomal rearrangement; many examples of both are known. Filyushkin and Petoyan [F9], Petoyan and Filyushkin [P13], and Sandberg [S42] have suggested a hypothesis relating carcinogenesis to symmetrical chromosome translocations (reciprocal translocations without loss of chromosome material). Initiation seems to occur frequently [G16, G17], but most initiated cells never result in a tumour. Several mechanisms ensure that most potentially carcinogenic cells do not cause a cancer.

132. One of the principal mechanisms preventing the development of a tumour, even though mutation has occurred, is the repair of the damaged DNA within a few hours or days of initiation. The time between a mutation and the next mitosis is critical for the final result: stimulation of proliferation after exposure results in a higher number of transformed cells [B32, K24]. This may be due to the diminished time available for repair before fixation of the lesion during mitosis [B34, M33]. Proliferation seems also to be essential with regard to the persistence of the potentially carcinogenic character of the initiated cell. Studies of three different cell lines in vitro revealed that between four and six mitoses must occur after irradiation to lead to a fixed transformation; the first mitosis has to take place within the first 24 hours [B33, K25, L14]. If it does not, the potentially carcinogenic character of the initiated cell is lost.

133. In radiation-induced mouse myeloid leukaemias a partial deletion of the long arm of chromosome 2 is necessary but not sufficient for the disease [H29, H30]. The cells with the deletion proliferate without manifesting malignant phenotypes in the mouse unless a second transforming step occurs [H30]. This stage may be explained as the loss of a suppressor gene or by a second somatic mutation at the gene located on the intact homologous chromosome, as occurs in retinoblastoma and other human cancers.

134. Another important, though seemingly trivial, fact should not be overlooked. An initiated cell may be the cause of a tumour only if the radiation-induced lesions are compatible with cell survival. In the high-dose range, there will be competition between cell transformation and cell death.

135. A fixed transformation still does not mean that a tumour will inevitably develop. The affected cells can apparently remain quiescent for a long time, during which they may be recognized and eliminated, perhaps by the immune system. This process surely takes place, even though it is poorly understood. If all of the mechanisms mentioned above fail, there is still the need for the transformed quiescent cells to start dividing. This activity is thought to be induced by a promoter. Hormones are of particular interest in this connection, as has been shown by different experimental approaches [N7, S43, Y5, Y6]. Generally, substances that stimulate cell proliferation enhance

carcinogenic processes [S44]. It is not clear to what extent radiation can act as a promoter [F1, U7]. Finally, the developing tumour must be vascularized when it has reached about 0.2 millimetres in diameter, in order to maintain an oxygen supply to the cells. Only after all of these processes have taken place and additional growth has occurred will a tumour be clinically manifest [S44].

2. Consideration of results of oncogene studies in statistical models

136. Recently, a rather elaborate picture of the nature of some of the genetic events involved in carcinogenesis has emerged. A limited series of genes, commonly called oncogenes, has been implicated in the transformation of cells to the neoplastic state. Some of these oncogenes seem to be incorporated into the cellular genome by viruses that transfect cells, but the genes themselves, or structurally very similar ones, are known to exist in normal cells. It has been shown in some cases that simple mutations in members of these gene families have transforming activity. Mutation in an oncogene can lead to a modified structure in the coded protein, or, by changing the mechanisms that regulate the coding and expression of such genes, it may cause the ectopic production of a normal gene product, or its production in improper amounts. The biochemical activity of several of these agents has been characterized; they appear to affect a variety of pathways in the control of cell division and proliferation. Other work has suggested that cell transformation may occur after a small number of events, possibly two or three, although in some instances (for example, retinoblastoma) recessivity at a single locus (i.e., two events) may suffice. In the case of recessivity at a single locus, genes of protective effect, now often called "anti-oncogenic", are turned off. This subject is reviewed in Annexes A and B of the UNSCEAR 1986 Report [U1].

137. In the case of these "anti-oncogenes" there is evidence that after a first mutation at one of these loci, a somatic recombination event occurs which replaces the normal gene on the unmutated chromosome with the mutated gene, leading to cell transformation. One recent report from an in vitro study of yeast cells has shown that radiation may induce somatic recombination, thus being able to affect both the initial and the second of these stages.

138. Evidence has accumulated that various carcinogens, including radiation, tend to break human chromosomes at specific locations. While these "fragile sites" are not yet well understood, some correspond closely to known cancer-related chromosomal break sites, for example, known rearrangement points or oncogene locations [Y1]. However, it is not clear whether radiation causes cancer in ways different from other carcinogens.

139. Several studies have shown that mouse cells may be transformed by the application of chemical carcinogens such as N-methylnitrosourea and benzo(a)pyrene [G7, M21, Z1]. This activates the

N-ras and H-ras oncogenes, and in one case [Z1] the transformed gene is due to a guanine-to-adenine (G-A) nucleotide substitution (a point mutation). In a different study, the c-K-ras oncogene was activated by gamma radiation, which also caused a G-A substitution [G6]. These findings suggest that, at the oncogene level, the carcinogenic effects of radiation are at least similar to, if not identical with, the effects of other carcinogens. The studies cited involved different tumour sites, so that more direct comparisons are difficult.

3. Does radiation induce unique cancer characteristics at the cellular level?

140. Several investigations have shown that the normal somatic cells of cancer patients differ from their tumour cells in respect to oncogene activation or other chromosomal changes. This finding documents the clonal nature of the tumour and, more importantly, the specific events involved in the tumour's origin. Similar studies should be undertaken in radiation-exposed individuals where it would be valuable to determine whether the tumour cells alone manifest the chromosomal or oncogene-related changes attributable to irradiation or whether the normal cells, too, manifest these changes. In particular, it may be important to examine affected and normal cells in individuals exposed in utero, in order to relate the effects of radiation to prenatal age at exposure, especially for those individuals exposed early in prenatal development.

141. For many reasons it is desirable to know whether the cancer cells produced by ionizing radiation differ cytologically or biochemically from the cancer cells produced by other carcinogens at the same organ site. A clinically detectable difference could have uses in screening and in testing. It could also be valuable in determining which cases of cancer are due to radiation exposure and which are not; this would be useful for epidemiology as well as for occupational safety, liability and the like. DNA sequences at certain loci affected by different mutagens in some experimental systems show characteristic patterns (e.g., base changes, deletions), suggesting that different mutagens have preferential effects at the DNA level. It has been possible, for some cancers, to determine whether or not radiation induces similar changes at the genetic level to those caused by other carcinogens. Experimental studies of chemical mutagens on cell lines and the finding of the "Philadelphia chromosome" in the Japanese atomic bomb survivors with chronic granulocytic leukaemia (as is observed in spontaneous cases) suggest no radiation-specific mutational pattern [F3].

142. The available information generally suggests that radiation induces the same cellular anomalies as other carcinogens. Data from Hiroshima and Nagasaki on breast cancer suggest no differences in histologic type nor tumour size by age at exposure or radiation dose [T9, T14], nor were atypical changes or residual proliferative lesions seen in women exposed to radiation but free of cancer. These observations led

Tokuoka and his colleagues to conclude that "radiogenic breast cancer does not differ histologically from spontaneously occurring (breast) cancer in Japanese women" [T9]. Similarly, Matsuura and his colleagues [M15], in an analysis of the histological types of stomach cancer seen among the survivors, found no compelling evidence of a radiation-specific histological type, although there was evidence that the degree of differentiation of adenocarcinomas is poorer in high-dose than low-dose groups. On the other hand, a comparison between exposed and unexposed stomach cancer patients from Japan showed a higher frequency of better-differentiated tumours in the exposed, who were also several years older than the unexposed [S35]. Twenty years ago, gastric carcinoma in the exposed occurred at the same age as in the unexposed.

143. While in all risk groups the lower third of the stomach was the site of most cancers, there seemed to be an increase in the degree of intestinal metaplasia of the gastric mucosa with increasing dose [M15, Y2]. The Japanese population in general has been prone to develop gastric carcinoma in the lower third of the stomach, in areas affected by intestinal metaplasia. This is also characteristic of stomach cancer in high-risk areas of Andean Latin America and may be related to dietary constituents. However, it is conceivable that the stomach as a whole was predisposed to carcinogenesis by irradiation and that in the lower third of the stomach the normal risk processes were accelerated. If this is true, it represents an interaction with environmental factors and will change, as the frequency of stomach cancer in Japan is changing.

144. An examination of the cytopathology of lung cancers in uranium miners in New Mexico, United States, suggests that the same array of cell types is observed in roughly the same proportion as would be expected [S20]; others have found some differences in proportion, but most of the usual cell types are seen [C4]. Some malignancies have not yet been shown to arise after exposure to radiation; chronic lymphocytic leukaemia and polycythemia vera, Hodgkin's disease and cervical cancer are examples.

145. In one autopsy series [K17], about 25% of the liver cancers caused by Thorotrast exposure were angiosarcomas, a tumour type also caused by chemical agents but which is otherwise quite rare. In this series of 29 autopsies of Thorotrast-induced angiosarcomas, the authors found that the cell types and histopathology were similar to those of angiosarcomas from other causes. Thus, while a radiogenic tumour may be of a relatively rare tissue type, it is not itself different from a non-radiogenic tumour of the same type. The presence of the Thorotrast as an internal, long-term resident in the liver may induce histological changes by means other than simply the radiation effect.

146. In a series of 180 autopsies of Japanese Thorotrast patients who had malignant hepatic tumours, Mori et al. [M31] reported a preponderance of cholangiocarcinomas and especially of haemangio-endotheliomas.

147. Biopsies of thyroid cancers from 31 patients who had been given external x-irradiation have been compared with biopsies of thyroid cancers from 389 non-irradiated patients. The irradiated patients were significantly more likely to have the papillary type of tumour, with a higher incidence of metastatic lymph nodes [T13]. While these results suggest that the tissue types are not unique to radiogenic thyroid cancers, they may depend on the external source of the irradiation and may not be comparable to the histopathology after exposure to internal nuclides.

148. A recent study [M34] has found that the distribution of cell types in radiogenic acute leukaemias in adult atomic bomb survivors and cervical cancer patients did not differ from that in spontaneous leukaemias. In spondylitis patients secondary acute leukaemias were of all cell types other than chronic lymphocytic leukaemia.

149. A general conclusion from the available data is that there is no diagnostic difference between the cells of radiogenic tumours and the cells of the spontaneous tumours of the same site. This conclusion is consistent with the fact that cancer is a mutational disease that can be caused by any mutagen.

4. Causal mechanisms: gene activation or inactivation?

150. As mentioned above, some tumours (especially retinoblastomas) are apparently caused by gene deletion, which presumably inactivates necessary genes or gene repressor regions of chromosome 13. The result, if both homologous chromosomes are affected, is cancer. In other tumours, cancer appears to be caused by the incorrect activation of a normal gene, or the activation of a mutant version of a normal gene; in these cases, the tumour occurs in heterozygous cells and the effect is "dominant" at the cell level. Oncogene amplification, one of the means by which oncogenes are activated, occurs in a variety of human tumours including neuroblastomas (where amplification of the N-myc occurs), retinoblastomas [L13], glioblastomas [L12], leukaemias and carcinomas. Radiation may work in different tissues by inducing chromosomal translocations, by deleting repressor sequences, by deleting or inactivating necessary genes or by causing point mutations in normal genes. Further studies will be required to identify the molecular nature of the lesions caused by radiation.

151. As noted earlier in the section describing dose-response models, there is a variety of evidence suggesting that high doses of radiation can damage cells to such an extent that DNA-repair mechanisms are ineffective; apparently, such cells are often so damaged that they are either non-viable or cannot replicate. At least, they do not seem capable of further transformation to malignant states. This form of cell inactivation has been found in several studies. Mole has argued that high doses of radiation to foetuses in utero seemingly show this effect [M7], though this has not been proven directly. Among adults, a relative deficit has been seen in osteosarcomas in radium dial workers subject to very high doses [R12]; in breast

tissue irradiated in the course of mastitis therapy [L6], in thyroid cancer after irradiation including ^{131}I ingestion for hyperthyroidism [D10, H12]; and in the pelvic organs of women who were heavily irradiated to treat benign gynaecologic disease [W6] and cervical cancer [B12]. Leukaemia in ankylosing spondylitis patients demonstrated a similar deficit [D11]. Finally, the deficiency in breast cancer among women treated for cervical cancer [B12] may be due to a different cell-sterilizing effect. Ovaries subject to substantial irradiation may become deactivated, thus indirectly protecting the breast from carcinogenic effects. Higher-order terms in dose-response curves may not be trivial ones, and dose-response estimates should take them into account; this is increasingly relevant as therapeutic radiation concentrates higher dosages on smaller and better-defined tissue areas. On the other hand, the relatively lower dose outside the primary target area may have the inadvertent effect of generating some secondary cancers in cells that would have been sterilized by less advanced equipment and techniques.

B.   TISSUE SUSCEPTIBILITY IN CHILDREN

152.   Tissues differ substantially in their susceptibility to radiation carcinogenesis, and the age and sex of the exposed individual may also affect their responses. These differences are seen in sites with very low or very high relative risks for given exposures, in patterns of latency or the cell types of post-irradiation tumours, in age and sex vulnerability, and in some aspects of the age of onset of such tumours. It is enlightening to examine the relationships between age at exposure and tumour onset and between proliferating and non-proliferating tissues, as well as the life-cycle events of specific tissues as they relate to susceptibility in that tissue.

153.   Data on these special tissue effects come from several sources, including (a) in utero exposure and (b) age at exposure for tissues with marked periods of proliferation or development. The special vulnerability or insensitivity of tissues is informative, for it may identify the process by which radiation induces cancer in specific tissues and the special risks attendant on certain types of exposure. Such knowledge could refine our understanding of which human subpopulations are more susceptible to radiation effects, relative to radiation protection guidelines or to medical therapeutic practice.

1.   Exposures in utero

154.   The risks to the irradiated embryo or foetus were discussed extensively in Annex G of the UNSCEAR 1977 Report [U2] and again in Annex C of the UNSCEAR 1986 Report [U1]. Those findings are briefly reviewed here, summarizing the best currently available dose-response estimates and considering how current data on prenatal exposure relate to the biology of radiogenic cancer.

155.   If cancer is caused by a series of mutational steps, along with the effects of growth proliferation

and promoters, the embryo or foetus should be highly susceptible to radiation-induced cancer. The available data are equivocal at best; indeed, animal experiments have failed to find a particular sensitivity [B5, U1]. There are basically only two ways to collect data on this topic. One is to examine the children of women irradiated, while pregnant, for diagnostic or thera-peutic purposes, and the other is to examine the children of women irradiated at the time of the atomic bombings. To date, the findings from the two sources seem contradictory. The findings are summarized in Table 14, which only provides published estimates of the approximate average relative risks, and does not directly reflect the controversial aspects of these studies, which will now be discussed briefly.

156.   Two large-scale investigations have undertaken to assess whether the fraction of children exposed to x-irradiation in utero was higher for children who died of cancer (generally, prior to age 10-15) than for control children who did not die of cancer. One of the studies was in the United States and the other in Great Britain; both have now been accumulating evidence for about three decades. The first to be reported was the Oxford survey [S5]. It suggested a radiation effect, a cumulative relative risk (which was only crudely correlated to dose) of around 8.25 in the first trimester and 1.45 in later trimesters, a linear dose-response pattern, a relative risk that decreased with historic time, and an age-onset distribution with a slightly higher mean age among cases judged to be radiation-induced than among all cases in the population [S6]; the reasons for the latter finding, if it is other than a statistical artefact, are not evident.

157.   This study [S5] has been criticized because the T65 data on the survivors of the atomic bombings at Hiroshima and Nagasaki exposed in utero, a direct and prospective set of observations, do not suggest such an effect [I1, J1] and because the British results apparently conflict with animal data (see [B5, U1]). In particular, it has been suggested that various biases exist in the data, factors that would lead a woman who was predisposed to bear children prone to juvenile onset cancers to be more likely to be irradiated during pregnancy (for example, to diagnose problems already manifest in the pregnancy) [D3]. That poor health might predispose one to be exposed to irradiation was suggested in a study in the United States showing an excess risk in white, but not in black children [D3]. The excess risk persisted after considering sources of bias, which were comparable between the two ethnic groups; this suggests that the effect is real in whites. However, the authors propose an ethnic-specific difference in radiation susceptibility, for which there is no other basis, making it more likely that aspects of black-white differences in socio-economic or environmental conditions are responsible.

158.   Stewart and Kneale [K1, K2] have addressed these issues in several ways, primarily by using Mantel-Haenszel [M6] multiple contingency table methods to assess associations between various risk factors, irra-diation and childhood cancer. The factors examined include socio-economic status, birth order of the affected child, age of the mother at pregnancy and

birth year. They were indeed found to influence the occurrence of childhood cancer, but a radiation effect persisted even after they had been taken into account statistically [K1]. Stewart and Kneale also contend that there is a detectable dose effect, that the first trimester is a period of high sensitivity, and that the extra x-rayed cases in their survey are indeed radiation-induced.

159. Mole [M7] has argued from data on twins that the selection factor was probably not a serious potential bias. Twins are known to be about five times more likely than singletons to be irradiated in utero, but Mole found their post-irradiation risk of cancer to be basically the same as that of singletons; hence, at least this particular factor predisposing to foetal irradiation did not seem to lead to an altered risk. Twin foetuses are not more susceptible to diseases than singletons so that their predisposition to be irradiated may be different from the data on non-twins reported by Stewart and Kneale. On the other hand, it is curious that twins do not, overall, experience more childhood cancer than singletons, as would be expected based on the greater likelihood of their having been irradiated [B15].

160. This was confirmed by an investigation of 32,000 twins in Connecticut, United States, born from 1930 to 1969; however, this same study found that the frequency of x-ray exposure was 2.4 times as high in twins who suffered childhood cancer as in a fourfold greater set of matched control twins [H11].

161. The Connecticut study was of twins who had received a dose estimated to range between 0.0016 and 0.04 Gy, with a median of 0.01 Gy. After follow-up to 15 years of age, the crude relative risk associated with pre-natal exposure was 1.8 (95% CI: 1.4-1.9), and even after adjustment for confounding factors which could be studied in the sample, the relative risk range was 1.4-1.9. The relative risk for leukaemia was 1.6 (95% CI: 0.4-6.8) and for all other cancers of childhood 3.2 (95% CI: 0.9-10.7). While the magnitude of the confidence intervals shows that not all of these results are significant, the data agree generally with those from the British and other United States studies, suggesting that the effect is real, even if a radiogenic cause cannot directly be proven.

162. T65 data from Japan [I1] reveal no dose-response pattern in those resident in Hiroshima and Nagasaki, although the zero-dose group had a higher rate of leukaemia than the not-in-city group. Further, the highest risk group, which had received 0.5 Gy or more as foetuses, showed no leukaemias. Hence, there is no evidence for an excess risk. Because subsequent analyses in Japan have continued to confirm this (and for leukaemias these analyses now include follow-up through 1979, i.e., adult ages as well as childhood [I1]), and for other reasons related to various aspects of the data available to Stewart and Kneale, the findings of the latter have come under frequent criticism. Most trenchant has been Totter and MacPherson [T2], who showed that the Oxford survey's x-rayed control individuals had not been similar to controls who had not been x-rayed in regard to confounding social and

biological variables (e.g., social class, birth order and age of mother), and that, therefore, the estimates of relative risk derived from these retrospective data, while valid in regard to the association they show between various factors, including foetal irradiation, do not demonstrate a causal relationship between prior irradiation and cancer. These criticisms have received response [K4, T3]. There are also problems with the effects-measure and the dose-response data. First, relative risks of radiation carcinogenesis, for similar estimated dose, have declined over historical time, for unknown reasons. Second, dose estimates are not directly available, and crude, uncertain measures (i.e., number of exposures) have been used as a surrogate.

163. In sum, these studies have shown an association of childhood cancer with prior irradiation but have left doubts about the nature of the sample, especially in light of the Japanese observations, so that one cannot be certain that radiation is involved. On the basis of all the evidence, a selective factor of susceptibility to general ill health in the exposed seems unlikely to explain the result, although limited medical care in Japan just after the war might account for some of the difference in the findings [I1]. Another study, in the United States, by Monson and MacMahon [M8] lends some support to the general conclusions of Stewart and Kneale by replicating some of their results. These authors compared exposure in a population sample of all births with that in a sample of retrospectively ascertained children who died of cancer, i.e., it did not rely on retrospective matching of controls.

164. In particular, the kinds of confounding noted by Totter and MacPherson were considered, but not found, in the Monson-MacMahon study, and there is no proof of better access to medical care for those destined to develop post-natal cancer, as Totter and MacPherson hypothesized. Thus, while there are problems with these studies, they suggest a 1.4 or 1.5 cumulative relative risk of prenatal exposure, with no reliable data on dose-response patterns. The relative risk of solid tumours is slightly, but not significantly, less than that of leukaemia. A study in Finland [S7] disclosed a comparable leukaemogenic effect, but it was not statistically significant. Other studies with similar findings include [D3], [M9] and [S8]; two small surveys [C3, O1] reported no increase but were not large enough to exclude a 40% excess.

165. Several other factors are of interest. The greatest effect in the Stewart and Kneale survey seemed to have been in the first trimester, and the discrepancy between their data and the atomic bomb data has been attributed to the greater cell-sterilizing effect of high, early prenatal doses [M7] or to radiation-induced immune deficiencies (e.g., [I1], [K3], [K5] and [U1]). However, there was an excess of overall mortality in Japan only in those who had been irradiated in the third trimester of their gestation [K6], but these children had no excess cancer [I1], and these are the foetuses most likely to survive irradiation. A bias does not seem likely, therefore, in the Japanese data. Monson and MacMahon [M8] showed that the only radiation excess was in those leukaemic individuals who had been irradiated in the third trimester of their

gestation. Hence dose-effects or gestational-age-effects are difficult to show or to assess, and no unmistakable pattern has been seen. It is also of relevance that dogs do not show the specific trimester effect. There remains the possibility that concomitant sources of variation, and not irradiation, produced the cancers. These problems are discussed in detail in the UNSCEAR 1986 Report [U1], which concluded that there was no firm evidence of a trimester effect.

166. Another relevant question is whether these data afford a basis for inferring a genetic susceptibility to radiation carcinogenesis. Such a susceptibility might be expected. or is at least plausible, given the known genetic susceptibility to perinatal cancers such as retinoblastoma and Wilms' tumour. Kneale and Stewart [K3, K5] found a correlation between childhood diseases and cancer in those who had been x-rayed, perhaps indicating susceptible genotypes. The fact that this was not observed in those who had not been x-rayed does not offer strong support for a genetic hypothesis; instead, it suggests that the irradiation may have had an immunosuppressive effect (but, see [L18]). Genetic susceptibility would be difficult to demonstrate, however, if such genes are rare and the probability of cancer, even in those individuals, is small.

167. The BEIR 1980 Report [C4] concluded that there was probably a cumulative relative risk of 5.0 for a first trimester exposure and 1.47 for later trimester exposures, with the increased risk appearing as tumours prior to 12 years of age for leukaemias and 10 years of age for solid tumours. The risk was estimated at 25 excess fatal leukaemias per 10,000 exposed children per PYGy, and 28 excess fatal cancers of other types. These estimates must be viewed circumspectly for a number of reasons, including (a) the lack of clear effect of gestational age on the occurrence of leukaemia and the small effect for other tumours in the study by Monson and MacMahon [M8]; (b) the fact that these authors found only a 1.06 relative risk in recent data for solid tumours; (c) the declining radiation risk over time observed in the Oxford survey; and (d) the finding of later cancer risk in survivors, now adults, exposed in utero in Japan [Y8]. Finally, although there had appeared to be a linear dose-response relationship at least down to doses between 20 and 25 mGy [S5], this, too, is now suspect, for it was not found by Monson and MacMahon [M8] and the Kneale and Stewart estimate was based on heterogeneous data in which exposures were not accurately known.

168. While it is not strictly classifiable as an in utero exposure, the exposure of a mother prior to conception may also provide information about radiation cancer risks. A considerable amount of work has been done in animals along this line (see [B5] and [U1]), but only a little in humans. The human data [G1, S8, S9, U1] have shown a significant excess of malignant tumours among the offspring of individuals irradiated prior to conception (even prior to marriage [S9]), though the effects are not large. The relative risks are about double the expected cancer rate. Again, these data are not consonant with data on the offspring of exposed parents in Japan. Here, within a cohort of 52,725 individuals followed prospectively, 50,689 of whom have individual T65 dose estimates, 36 deaths were attributed to leukaemia through 1979, of a total of 3,552 deaths [11, S22]. The frequency of death due to leukaemia is not functionally related to the sum of the parental exposures; indeed, Ishimaru found the standardized relative risk of the offspring of parents collectively receiving 0.01 Gy or more of gonadal exposure to be 0.8. Ten leukaemia deaths were observed where 11.9 had been expected [11]. There was, moreover, no indication of an increase in any of the solid tumours of childhood [S22]. These studies have, of course, relatively low discriminatory power; it was estimated, for example, that 23 cases of leukaemia would have had to have occurred among the 16,713 offspring born to exposed parents for a radiation effect to have been demonstrated.

169. It is appropriate to summarize the conclusions offered by the UNSCEAR 1986 Report [U1]. The lack of an effect on early childhood cancers even after higher doses in Japan is a ground for considerable caution in interpreting the positive effects from the medical irradiation studies, especially in light of the many possible confounding or biasing factors. In a similar way, the fact that early post-natal irradiation in Japan showed carcinogenic effects only many years later (agreeing with other data on post-natal radiation effects), whereas the medical series showed their effects soon after birth, raises serious radiobiological problems if both observations are strictly the result of radiation. The doubts are enhanced by the absence of serious effects in animal experimental data. Also, the constancy of relative risk values for many cancer sites in the medical series is at variance with other data that suggest site-specific effects. Finally, haematopoietic stem cell differentiation does not occur during the first trimester of foetal development, so that the excess leukaemogenic effect in first trimester irradiation is difficult to understand.

170. It is patent that the existing data cannot resolve the question of pre-natal irradiation with clarity or much confidence. However, it would be prudent to assume that pre-natal irradiation does have an effect, especially with regard to leukaemogenesis. If pre-natal irradiation is reduced or largely replaced by ultrasonography, the problem may become less critical, but it would be incorrect to assume that this reduction or replacement will be an immediate, world-wide phenomenon or that accidental or industrial pre-natal exposures will not occur. Thus, it is important to continue to collect data on this point.

2. Exposures in childhood

171. The age at exposure to radiation may have a profound effect on the susceptibility of the individual to the induction of cancer, especially in those ages that are known to be characterized by high rates of stem-cell proliferation. One of the most obvious of these cases is exposure in childhood. While in a sense childhood is a continuation of the in utero growth and

development (which would make childhood experience merely an extension of the in utero experience), in fact there may be different sensitivities in childhood and in utero.

172. There are several sources of data on childhood exposure, but four predominate: (a) children exposed to therapeutic radiation to treat other primary cancers; (b) children exposed for the treatment of non-cancerous diseases; (c) children exposed to radiation from the atomic bombs, to fallout from nuclear weapons tests or to accidental discharges from nuclear power reactors; and (d) female children whose breasts were exposed to radiation in childhood and peri-menarchial ages. These groups may not be comparable directly, because the first group is largely composed of individuals with a genetic predisposition to cancer. The groups will be considered separately, although risk summaries for the cancer-treated group and all other groups will be presented.

(a) Children exposed to radiation for treatment of primary cancers

173. Though the number of such cases is small, because childhood cancers are infrequent, second primary malignancies have occurred in children who received radiation for the treatment of an initial cancer. These populations are of interest because they contain a high fraction of children who are genetically susceptible to cancer. These individuals may be distinct from the general population of children. They are all, however, children in whom actively growing tissues had been subjected to high doses of radiation.

174. There have been two major studies of the risk of second primary cancers in children irradiated for cancer: one, by Li and colleagues, who used data from the United States National Cancer Institute [L1, L2]; and the other, a survey of data from the United States, Italy, Federal Republic of Germany, Canada, England, France, and the Netherlands, known as the Late Effects Study Group [M10, M28, T4, T17]. Both studies suggest a 15+ relative risk of a second cancer of any site (i.e., pooling data on all primary sites and counting all secondary sites), with a 3-12% or more cumulative probability of cancer by age 25. About 68% of all second tumours in the Late Effects Study Group survey developed in the field of the original irradiation. The median latency time was 10 years, but only 5 years for second tumours not associated with radiation. Retinoblastoma and nevoid basal cell carcinoma patients, however, had a reversed latency pattern. Good dose-response information is generally not available from these data.

175. Tables 15 and 16 provide basic data from the Late Effects Study Group [M10, M28, T4]. These Tables show two concentrations: (a) that of second tumours in patients originally treated for tumours of genetic origin, i.e., children probably genetically susceptible to cancer; and (b) that of primary tumours in sites known to be radiogenic (haematopoietic, bone). The presence of a primary tumour may imply that the child is especially radiosusceptible. Second tumours were frequently associated with radiation in children

known to be genetically susceptible to cancer: of 96 second tumours in such children, 42 (44%) were radiation-associated [M28]. The expected rates were based on the United States Connecticut Tumor Registry, although the cases were international. Hence, while the qualitative conclusions seem sound and agree with what is known genetically and biologically, the details of the results may not be precise.

176. In a study of the leukaemogenic risk posed by therapy in these children, it was found that the use of alkylating agents was associated with elevated risk while the use of radiation therapy was not [T18], consistent with the findings of other studies summarized in this Annex.

177. In a detailed study of bone sarcomas in the Late Effects Study Group, Tucker et al. [T17] found that among the 9,170 children in the analysis, the relative risk of bone sarcoma was 133 (95% CI: 98-176). There was a 20-year cumulative risk of 2.8%, or 9.4 cases per 10^4 PY. A comparison was made between 64 of these children for whom detailed treatment data were available and 209 children who had not developed bone cancer by the time of the study. The radio-therapy relative risk was 2.7 (1.0-7.7), after mean doses to the bone site in question estimated to be 27 Gy; there was a sharp dose-response gradient reaching a relative risk of 38.3 with doses above 60 Gy but decreasing above 80 Gy, and an overall excess relative risk of 0.0006/Gy. No excess risk was detected with doses under 10 Gy. Eighty-three per cent of the tumours were within the field of radiation. Osteo-sarcoma had the highest relative risk value, followed by chondrosarcoma.

178. An investigation of 64 cases of second cancers in children in the Federal Republic of Germany found mainly osteosarcoma, thyroid cancer, and acute non-lymphocytic leukaemia (ANL); 36 of 50 irradiated children manifested their second tumour in the irradiated field; a separate chemotherapy effect was not seen [G14].

179. Overall, these studies indicate that the general range of absolute risk per unit dose of a variety of second tumours is within about a single order of magnitude and much less than, for example, the variation in absolute risks for a comparable set of adult-onset tumours. Solid as well as haematopoietic tumours resulted from this irradiation, and they affected many organs. Although interpretations based on heterogeneous data collected retrospectively from a widely dispersed group of hospitals must be guarded, it is probably safe to assume that there is a general radiation-induced risk of second tumours in children.

180. To determine whether orthovoltage (140-500 kV peak range energy) or megavoltage (10 MV energy) therapy is safer, a study was made of 330 children in Minnesota, United States, who had been given mega-voltage therapy [P16]. Only second tumours arising five or more years after irradiation were considered, and all children known to be genetically susceptible were excluded. The 30-year cumulative risk of cancer was 9.6%; this is somewhat less than the orthovoltage

risks [L1]. Nine of 14 second tumours were within the radiation field; five children had received chemotherapy as well, and two tumours developed outside the radiation field in these children. Thus, the apparent radiosusceptibility in children treated for primary cancer cannot be ascribed solely to chemotherapeutic effects or to genetic susceptibility.

181. In the Late Effects Study Group osteosarcoma study [T17], mega- and orthovoltage therapy had similar risks. There were also comparable risks following chemotherapy in these patients, but the radiation was shown to have risks independent of chemotherapy.

182. Table 17 provides details of the cancer risk following irradiation for three cancers of which a substantial fraction are known to be familial (retinoblastoma, Wilms' tumour, Ewing's sarcoma). Most of the subsequent tumours are sarcomas, especially in irradiated bones; however, carcinomas can arise in heavily irradiated epithelial tissues, as the Wilms' tumour data disclose. The general range of risk is 1-3% at 10 years post-exposure, rising to 15-35% or more after 30 years, based on life-table methods of calculation. One can assume that virtually all of the in-field tumours were radiogenic; but the spontaneous rate in these patients is also quite high, sometimes nearly as high for all sites combined as for the irradiated field. Hence, radiation interacts with host susceptibility, perhaps causing it to be expressed in the specific target field.

(i) Treatment for retinoblastoma

183. Retinoblastoma is an embryonal tumour of the retina, usually occurring at, or shortly after, birth. It is easy to diagnose and is restricted in age, largely because it arises in a tissue where mitosis ceases at about the time of birth. Though it is a rare tumour, its epidemiological importance has motivated several studies of patients in major referral centres. One of the interesting facts about this tumour is that approximately 25% of cases are of a heritable kind; this is detectable either because the initial presentation is with bilateral and/or multifocal disease or because other family members are affected [V1]. Epidemiological and molecular data have shown convincingly that this heritable form of the disease is attributable to the inheritance of a single damaged gene region on chromosome 13; retinal cells which then suffer a somatic mutation at the same region on the homologous chromosome are malignantly transformed. The tumour cells are clonal descendants of the first transformed cell.

184. Osteosarcoma is a tumour to which genetic retinoblastoma patients are known to be at high risk as a second primary malignancy [F2, V1]. Studies consistently show that about one third of the second primary tumours in these patients are osteosarcomas; the remainder consist of soft-tissue sarcomas, brain tumours, leukaemias, and melanomas. Osteosarcomas may occur in the irradiated field, but will spontaneously occur in distal, non-ocular sites not subject to radiation therapy and in non-irradiated patients. While other malignancies are seen in retinoblastoma patients, about 80% of all second tumours occurring later in

childhood or early adulthood are osteogenic sarcomas. At present it seems that these cancers result from the production of a second mutation in an exposed osteoblast. The osteoblast becomes homozygous for the chromosome 13 gene deletion, just as the retinal cell does, leading to the neoplasm [D4, D19, H18]. This could even occur in individuals who do not carry the familial retinoblastoma gene [D19] and is being seen in some other radiogenic second tumours (osteosarcomas of the orbit [S41]). Because osteosarcoma occurs even in non-irradiated bones, bone growth and development must involve the same genes involved in the development of the retina. The concentration of osteosarcomas in these patients during childhood and early adulthood shows that the tumours occur during the normal cell proliferation periods for this tissue. It is now known that these tumours are generally caused by somatic recombination, leading to cellular homozyosity for the deleted or inactivated gene.

185. Family members of retinoblastoma patients who do not themselves manifest that disease seem to be somewhat more susceptible to other cancers than the general population, although the reasons for this are at present unclear [C5, S12]. There are no data on radiation effects in such individuals as yet.

186. A Japanese study of 2,609 cases of childhood cancer has found roughly similar results [T12]. Seventeen of 50 second cancers were in retinoblastoma patients, and most were related to radiation therapy. Of all second tumours, haematopoietic, bone, and thyroid made up the bulk. Thus the pattern is present in all ethnic groups that have been studied to date.

187. In several general studies, the risk of radiogenic second primaries has been estimated to be 1-15% in 20 years of follow-up [A8, F2, L1, T4, V1]; since the population risk of an osteogenic sarcoma of the orbital area (or even of the skull) is very low, the radiogenic risks are well over 100 times the baseline risk in most estimates. Current dose rates are 35-60 Gy, using megavoltage equipment; this has been reported to reduce the risk to 1-2% (see [F2] and [V1]), which is lower than the risk associated with orthovoltage equipment. It is not clear whether there is a cell-sterilization effect.

188. In retinoblastoma, not only genetic susceptibility but also concurrent chemotherapy must be considered. The literature is consistent in finding that almost all independent second tumours have been observed in familial cases [A3, D15, F2, V1]. The effect of combined therapy is discussed in section V.C, where it is shown that an excess risk is experienced, at least in genetic cases [D15].

189. Two studies warrant special discussion [A3, S26]. Abramson et al. [A3] followed 693 patients with bilateral, presumably heritable, retinoblastomas and 18 patients with unilateral retinoblastomas. These data are summarized in Table 18. Although previous estimates from this series on the risk of second tumours have been between 10% and 15%, they did not fully account for the variable length of follow-up. If the time-specific incidence rates are computed, using

the number of new cases divided by the number of individuals not yet affected up to the time of follow-up, time-specific cumulative risks can be calculated and a life-table cumulative incidence obtained. With this method, Abramson et al. found a mean latency of 10.4 years. For individuals undergoing neither radiation (or with second tumours outside the irradiated field) nor chemotherapy (and yet surviving, having been treated by enucleation alone), the incidence of tumours was 10% after 10 years, 30% after 20 years, and 68% after 32 years.

190. For all patients, the risks of second tumours were considerably higher. After 10 years, the risk was projected to be 20%; after 20 years, 50%; and after 30 years, 90%. This is much higher than reported in other instances, at least partially because of the method of computation which accounts for differential follow-up and at-risk periods. These results need to be confirmed. Tumours that developed outside of the radiation field (or in non-irradiated individuals) had significantly later ages of onset than those in the field.

191. By comparison, the Late Effects Study Group sample of retinoblastoma patients exhibited a 14% cumulative risk after 20 years [T17]; this group included a mixture of heritable and spontaneous cases, which may account for some of the difference with the Abramson study. It found that the relative risks of second bone cancers following primary therapy for retinoblastoma were similar to those following comparable therapy for other childhood cancers, presumably because the baseline bone cancer risk is higher in patients with retinoblastoma than in patients with other types of childhood cancer. That is, retinoblastoma patients have higher baseline osteosarcoma rates, so that a larger numerical excess number of cases produces only a modest relative risk.

192. Dose effects have been estimated in a general way for the Abramson study data. Thirty-seven patients received orthovoltage therapy only, with doses ranging from 3.5 to 260 Gy. Thirty-five received betatron radiation (3.5-120 Gy). Fifteen received combinations of these with some other miscellaneous treatments. Life-table analysis showed that the risks of second cancers following one course of betatron radiation (3.5-4.5 Gy) were not different from those following multiple courses (70-90 Gy). Similarly, patients treated with orthovoltage doses of less than 110 Gy had the same life-table risks as patients treated with more than 110 Gy.

193. In the second study [S26], Sagerman showed a 2.5% risk of second tumours for patients receiving 60 Gy. 5.5% of those receiving up to 110 Gy, and 32% for those receiving more than 110 Gy. The variability in follow-up times and the fact that those patients receiving higher doses had longer follow-up complicate the interpretation of these results. Lower doses have been used more recently, and hence have shorter follow-up times. The life-table methods of Abramson et al. did not demonstrate a difference related to dose. Hence, it is not clear how much dose reduction, fractionation or energy level of the therapy affects the risk in retinoblastoma patients.

194. A study of 882 retinoblastoma patients in Britain reported results that were qualitatively similar but that, quantitatively, showed less risk [D15]. In this series, 30 second malignant neoplasms were seen. The results are presented in Table 19. Twenty-six of the second tumours occurred in the 384 patients with genetic retinoblastoma; using life-table methods to account for differential follow-up times, the risk of a second tumour was estimated to be 8.4% after 18 years (6.0% for osteosarcoma alone). Of these 26 tumours, 12 had developed outside the radiation field (a risk of 3.0% after 18 years), all of them osteosarcomas (2.2% among those with neither radiation nor chemotherapy, i.e., the baseline risk level). The British population risk of osteosarcoma by age 18 years is about 10^{-4}, so that the relative risk in genetic retinoblastoma was 200 (95% CI: 50-500).

195. Within the radiation field, where second tumours are probably radiogenic, the risk in the genetic cases was 6.6% after 18 years. Average doses were 35-40 Gy, with little variation. While the radiation effects in these data are not dose-specific, they do indicate the nature of the risks. The follow-up period was shorter than that reported by Abramson et al. [A3]; otherwise, the difference in risk is probably due to different efficiencies in the ascertainment of secondary neoplasms. Whether the true actuarial risk is as high as Abramson et al. suggest, or somewhat lower, retinoblastoma patients are obviously at very high risk of secondary neoplasms.

196. A brief report by Koten et al. [K27] has given an estimate of 19% for second tumours after 35 years in patients in Holland. This is intermediate between the other studies.

197. All of these children were irradiated at or near birth, that is, at about the same age, so there are no data on the effect of age at exposure and no effort has yet been made to project the lifetime risk, although the two major studies do offer some indications. In Abramson et al. [A3], the cumulative incidence curve in those without radiation effect (but who are genetically susceptible) is slightly concave upward from birth to age 32, the maximum number of years of follow-up. The curves for tumours inside and outside the radiation field show similar shapes through age 25, after which the data are sparse. If this finding is correct, then radiogenic tumours are occurring at about the same ages as spontaneous tumours in these children, as is the case with radiogenic adult-onset carcinomas generally (as will be seen below). The cumulative increase rises non-linearly with age of follow-up, suggesting at least crudely that a multiplicative risk projection is more applicable than an additive projection, again in agreement with most adult cancer patterns. The non-linear cumulation of risk is also apparent in the study by Draper [D15], although less detail is given. As shown in Table 19, the absolute life-table probability of second cancers rises by a factor of two in the years 12-18, relative to the increase in the 12-year interval 0-11. This is true for radiogenic as well as non-radiogenic second tumours.

198. It should be stressed that retinoblastoma patients constitute the only significant group of human beings

in which the carcinogenic process can be observed, after radiation, in exposed cells in which (a) radiation is in a sharply delimited area and can be compared with the same area without irradiation and the rest of the body; (b) the cells at risk are effectively haploid in regard to cancer risk; and (c) all exposed individuals are of essentially the same age. The subsequent projection effect should differ in ways that are informative relative to multi-stage models, because only one second stage is needed for cancer to occur in these individuals. It would be useful to know how the effect of cell sterilization, which must occur in the periocular region after intense irradiation, manifests itself in regard to (a) the dose-response relationship and (b) the probably smaller number of carcinogenic events .1eeded to take place as a consequence of irradiation.

(ii)   Treatment for Wilms' tumour

199.   There has been considerable work, mainly by Li and colleagues (e.g., [L3]), on the risk of a second neoplasm after radiation treatment for Wilms' tumour of the kidney in childhood. After nephrectomy, patients receive radiotherapy to any areas that might be the site of further tumours or potential metastases, usually the renal fossa, elsewhere in the abdomen. or in the thorax. In 487 patients and 4,255 person-years of observation, Li et al. observed 11 second tumours, with latent periods ranging from 7 to 34 years. Most patients were given orthovoltage therapy with average doses of 25 to 30 Gy to the abdomen; other sites received varying doses. There was a second tumour in 2.8% of the patients. Nine of the second malignancies were solid tumours and occurred in areas that had been given 6-40 Gy. One was in a non-irradiated area. There was one case of acute myelogenous leukaemia. The cumulative risk of a second tumour was 18% (SE: 6%) in 34 years after diagnosis of Wilms' tumour.

200.   The relative risk of radiation itself was not estimable (i.e., was not finite), since no case occurred in the 75 non-irradiated patients. Another study has yielded similar results, with 2.3% of cases having a second tumour [S10]. A third study reported a variety of sites for second tumours, including the thyroid, gastrointestinal sites, and bone, all with relative risks over 80 [T4]; leukaemias were increased 13 times. Many of these sites, e.g., the thyroid, are unlikely to have been in the intended irradiated field, and the authors do not report radiogenic cases separately. Wilms' tumour, too, may be heritable in a large fraction of cases. Its controlling gene region, along with the gene for insulin and the H-ras-1 oncogene (rat sarcoma), is on chromosome 11 and, as is true for retinoblastoma, somatic homozygosity at the relevant loci may be sufficient to produce the disease.

(iii)   Treatment for Ewing's sarcoma

201.   Ewing's sarcoma is a form of bone cancer, typically treated by local irradiation and chemotherapy. Lately, long-term survival rates have improved, and several studies have demonstrated a substantial risk of secondary osteosarcomas in the irradiated field [G2, S11, T4]; there may also be a risk of leukaemia [T4]. These patients received 44-55 Gy, followed by a

10-15 Gy boost to a reduced field, over a six-week course of administration [S11]. Patients receiving orthovoltage radiation were ordinarily treated without chemotherapy, whereas those receiving megavoltage radiation had combined therapy. The increase in risk is consistent for all studies. A dose-response of 7.2 cases per 10^4 PYGy and a cumulative risk of 35% over 10 years have been estimated [S11]. There also seems to be an increased risk associated with combined therapy, i.e., newer modalities may have increased the risk of secondary malignancies. The evidence suggests that bone tissue is susceptible to carcinogenesis if it is irradiated before or during the adolescent growth spurt.

(iv)   Treatment for Hodgkin's disease

202.   Some information exists on the risk of second tumours after irradiation in childhood for the treatment of Hodgkin's disease. Although data from the treatment of this malignant disease in children are limited, the radiosusceptibility of certain tissues, specifically, bone. haematopoietic, and thyroid, has been reported [T4]. However, in children treated with radiation alone, solid second primary tumours have occurred, leukaemias occurred only when chemotherapy or combined radiation and chemotherapy had been given [M28]. This is consistent with findings in adult Hodgkin's patients. There was no indication of a familial susceptibility to Hodgkin's disease in these 40 children. Dose information is not available.

203.   To summarize, the evidence from children irradiated to treat a primary cancer shows very high susceptibility to second cancers and promises to be informative concerning the nature of the genetic changes caused by radiation and their relationship to carcinogenesis. However, since these children are probably not generally representative of the whole population, these results are not useful for estimating risk coefficients or for risk projection for the general population.

(b)   Children exposed to radiation for treatment of benign conditions

204.   There have been a multitude of uses of irradiation for the treatment of benign conditions in childhood. The exposures in question primarily involve (a) the head and neck, to treat tinea capitis (scalp ringworm) [M13, R1, R22, S16]; (b) the thymus, to treat what was thought to be a pathologically enlarged thymus [H1. S14]; (c) the neck, to treat tonsilar and nasopharyngeal conditions [S15]; and (d) various sites, but especially the head and upper body, to treat haemangiomas (benign superficial tumours usually present shortly after birth) [L10].

205.   The tumours induced by these exposures are primarily leukaemias and cancer (as well as benign lesions) of the thyroid. Risks of these tumours attendant on exposure of the head and neck in children are summarized in Table 20. At doses of less than 1 to about 8 Gy, the absolute risk of radiogenic cancer varied from <0.1% at 10 years to about 8% at 30 years after irradiation for malignant neoplasms of the thyroid and was much lower for leukaemias. One

study [S27] has reported an increased incidence of basal-cell skin cancer in tinea capitis children; risk rates are difficult to calculate because of the complex ascertainment of cases, mixed ethnicity, and other risk factors, but among white children, there is an increase. Some aspects of this study are discussed in the sections on host factors and on the interaction of irradiation with environmental factors. Other cancers have been reported as well: brain and parotid tumours have arisen in small but excess numbers in the tinea capitis series and bone sarcomas have developed in children treated with radium for bone tumours.

(i) Thyroid and thymus exposures

206. The thyroid gland is susceptible to radiation-induced cancer, especially when exposure occurs in the first two decades of life. The effect of internal irradiation in children exposed to ^{131}I in the Marshall Islands, where a special age effect was not seen, will be discussed later. The risk coefficient estimate from many studies is consistently in the range of 1.6-9.3 cases per 10^4 PYGy [C4] in mean doses which ranged from 0.09 to more than 10.0 Gy (see [S13], [S38]) in childhood exposures. These values are based on thymus irradiation [H1, S14, S38], on tonsilar x-irradiation [S15], head and neck exposure [M13]. and on the follow-up of the tinea capitis patients [R1, S16], as well as on the Japanese data. A summary estimate based on data from North American childhood exposure to under 15 Gy was 2.5 cases per 10^4 PYGy for exposure under age 18 when both sexes were pooled [N5]. Animal data and the Japanese atomic bomb experience suggest about a twofold higher susceptibility for childhood exposure (under age 18) [N5]. There is a marked excess of cases in females, in general 2-3 to 1 [N5, S13], uniformly across many studies; this ratio is similar to the sex ratio in spontaneous cases and does not indicate a particular radiosusceptibility in females [S13].

207. Several other studies of cancer after miscellaneous exposures of the thyroid have reported similar results [B6, C4, D5, M12]. Jewish children may be especially susceptible [C4, S13, S14, W11]; when matched to comparable non-Jewish children, the relative risk has been at least as high as 3.5 [S14, W11]. Whether this is an artefact of the exposure regimen or is due to other factors is not certain.

208. Because spontaneous thyroid cancer is quite rare, it is likely that most of the observed tumours are radiogenic. The bulk have been of the papillary type [C4], and there appears to be a latency period of at least 5 years [C4, S13], perhaps with a peak excess risk about 20 years later [C4], though excess risk has been seen to persist up to 40 years after exposure [S15, S38]. Consistent with studies of specific radiation exposures, a retrospective examination of female thyroid cancer patients (i.e., ascertained because of thyroid cancer not because of irradiation) showed an increased risk with radiation and with younger age at exposure, a relative risk of 16.5 overall, but 42.2 for exposure at less than 20 years of age [M14].

209. The best dose-response data come from Japan [W5] and from a study of the thymus-irradiated

children in the population around the city of Rochester, New York, United States [S38]. In the latter instance, a cohort of about 2,650 children irradiated from 1926 to 1957 and 4,800 sibling controls were followed for about 30 years. The doses ranged from 0.05 to 11 Gy, with 62% having received less than 0.5 Gy; the mean was 1.2 Gy. Those who had received higher doses were treated earlier in the time period and hence have a longer follow-up. The dose-response data are summarized in Table 21. Recently, the pathology of 75% of the reported benign thyroid nodules was studied, and many were reclassified as non-neoplastic, thus sharpening the dose-response estimates. Almost all of these children had been irradiated in their first year of life. In many ways, this makes the cohort similar to that of the retinoblastoma patients (who exhibit no excess of thyroid cancer following radiation of the orbit). The relative risk, after 29 years of follow-up, was 49.1, based on sibling controls, and the SMR was 44.6 (based on New York State cancer rate data); for benign thyroid adenomas the relative risk was 15.0. These values are significant at much less than the 0.001 level. They also show the sensitivity of the relative risks to the choice of controls.

210. Figure I indicates the dose-response pattern. An additive model yielded 3.46 ± 0.82 excess cases per 10^4 PYGy; the sex difference was marked with risks of 5.25 per 10^4 PYGy for females and 2.05 cases per 10^4 PYGy for males, which is similar to estimates from other studies. In Japan, exposed persons under age 19 showed a value of just over 2.1, with a sex ratio of about 2.9 (derived for all ages) [W5]. The dose-response pattern fitted a linear model ($P < 0.0001$), not improved by adding a quadratic term. The authors also fitted a relative risk model to their data, based on the Cox regression method. This fitted well ($P < 0.00001$) with a linear dose term (not improved
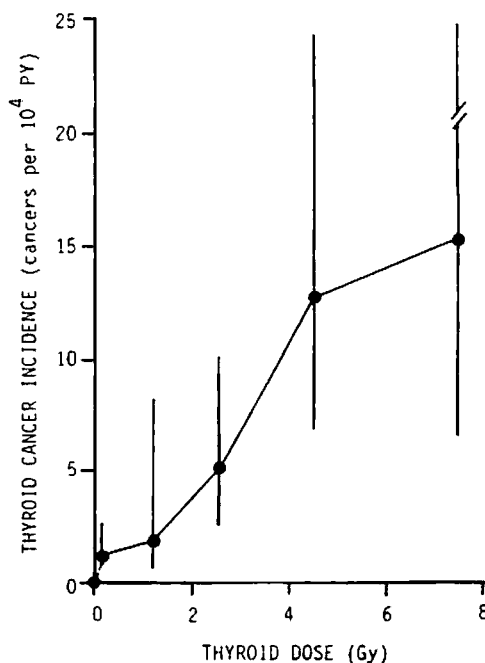
Figure I. Thyroid cancer Incidence In relation to thyroid dose.
[S38]

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by adding a dose-squared term), and the relative risk estimate after exposure was 1.58 times the prevailing risk. Data for benign adenomas were similar, both qualitatively and, to a great extent, quantitatively; the relative risk was 1.44. Figure I yields a risk coefficient similar to the figure from Japan, for lower doses, but in the Japanese data the risk falls after about 3.5 Gy.

211. This study [S38] also allowed a dose-fractionation assessment. Such data are rare in general, and the results are summarized in Table 22. In sum, the low-dose per fraction group had higher risks per Gy, which is not consonant with the decreased effect of dose fractionation that has commonly been theorized. The results were the same for adenomas (not shown in the Table). Thus, neither the number of fractions nor their dose was protective.

212. Finally, Shore et al. [S38] examined the projection effect in this cohort. The excess in thyroid cancer began 5-9 years after irradiation and seems to have continued even after 40 years of follow-up (i.e., in patients irradiated in the 1920s). However, there appears to have been a slight decrease in the excess after about 25 years (although adenomas continue to increase). The mean latency time was 29.3 years, with somewhat shorter latencies (27.4 years) for those having received the highest doses. The Japanese data also show a continuing effect after at least 35 years [W5]. These data follow the age-specific incidence distribution of spontaneous thyroid cancer in adults, which reaches a peak in early adulthood and changes relatively little thereafter.

213. This study agrees generally with the Japanese T65 data [P4] in suggesting a linear dose-response pattern for thyroid cancer in irradiated children (as well as adults). Data from tinea capitis patients are similar in this regard, although the slope appears to be steeper. Japanese data [P4, W5] suggest a higher risk in childhood than adulthood. In North American children having received doses in excess of 15 Gy, however, a reduction of effect appears to occur, presumably as a consequence of cell sterilization [N5].

214. Although these thyroid neoplasms are of the relatively benign papillary type (and radiation effects include purely benign nodules as well) they may eventually pose a serious risk. Thyroid neoplasms of whatever aetiology can become life-threatening, and the mortality after 25 years of follow-up is about 7% [N5]. Thus, the risk in children may be substantial, and further time may be necessary to assess its actual level.

215. As was discussed briefly earlier, there has been speculation on whether radiation-induced thyroid cancers differ from naturally occurring thyroid cancers. It has been found that radiogenic thyroid cancers, somewhat more often than their naturally occurring analogues, tend to be of the papillary type, and to have metastatic lymph nodes [T13].

216. Some concern has been expressed about whether the apparent excess in the exposed individuals is a function of the detailed follow-up to which many of them were subjected. However, a radiogenic excess of thyroid cancer may also have been reflected even at the population level. In a study in the state of Connecticut, United States, based on its tumour registry, an excess of thyroid cancer was correlated with the childhood time period during which these exposures occurred [P5]. In several instances, the risk has continued to be elevated as much as 35 years after exposure, so that the lifetime excess in thyroid cancers may be more substantial than the very small and uncertain excess in the first decade or so after exposure.

(ii) Leukaemia as a general outcome in exposed children

217. At present, the evidence for excess leukaemia in exposed children comes largely from two sources: children exposed in Hiroshima and Nagasaki and children exposed to treat various benign conditions of the head and neck, specifically of the thymus and scalp (tinea capitis). The Japanese data are reviewed in section III.B.2.c.

218. Studies of children with scalp irradiation to treat tinea capitis [R1, R22] have produced results in accord with the Japanese studies. The relative risk of tumours of the head and neck was 3 in a matched case-control study of 10,834 cases in Israel, and for leukaemia, specifically, 2.3. The marrow dose was about 0.3 Gy, leading to an increase of 0.9 excess leukaemias per 10^4 PYGy. There was also a clear increase in brain tumours. Mean follow-up time was 26 years. Children of less than 10 years of age who were irradiated had higher risk than those exposed at older ages. Latency for leukaemias was 9.3 years. No other causes of death were elevated. Other studies have found comparable results [A4, M13, S16].

219. In a study on thymus-irradiated children there was a relative risk of leukaemia of about 3.1 [H1], though a dose-response relationship could not be estimated.

220. There are no precise estimates of the dose-response risks of leukaemia in children. The general range of risk for single or short-duration exposures combining data from all ages, over the 25-year risk period following irradiation was estimated in the BEIR 1980 Report to be between 0.01 and 2.2 excess cases per 10^4 PYGy, or 0.25-55 cases over the 25-year risk period [C4].

221. Approximate risk coefficients from [R1] can be derived as follows. Ron and Modan report 10 leukaemia cases in 10,842 irradiated children and seven in 16,241 non-irradiated controls. They report that the sex-adjusted risk of leukaemia was 4.0 cases per 10^4 in males and 6.0 per 10^4 in females. These persons were followed for an average of about 22.8 years, so that the number of excess cases was 0.18 per 10^4 PY in males and 0.26 per 10^4 in females. At an average dose of 0.3 Gy, this corresponds to 0.60 male and 0.87 female cases per 10^4 PYGy. These are crude estimates which assume that age is not a material factor, so that all person-years of observation are equivalent. They agree

roughly with the BEIR estimates. Because the results are not statistically significant, only the mean estimate is given, with no confidence interval.

(iii) Exposure of the central nervous system

222. The Israeli tinea capitis study [R1, R22] has found an excess of brain cancers, with a relative risk of 2.5 (95% CI: 0.9-7.4), with males appearing to be more susceptible. The dose to the brain was 1.2-1.4 Gy to the upper layer and 0.95-1.2 to the layer 2.5 cm below. The risk coefficient estimates, in excess cases per 10^4 PY, were 2.3 for irradiation less than four years of age, 7.5 for five to nine years, and 3.2 for ages above 10. Another study of irradiated children has produced a risk coefficient estimate of 2.9 ± 2.4 brain cancers per 10^4 PYGy from five to 22 years after exposure [L11]. No significant increase in intracranial tumours has been seen in Japan among any of the age groups [S23].

(iv) Exposure of the skin to treat haemangioma and other skin disorders

223. Many children were irradiated to treat haemangiomas, in general in visible areas of the skin, from roughly 1910 to 1960. Treatment was by ^{226}Ra implants. Over 20,000 of these patients have been followed in Sweden [F12]. Among 10,000 of these patients [L10], 75 cancers occurred during the registry period 1958-1979. Only 55.6 had been expected, based on the same registry and a national birth record system, yielding a relative risk of 1.35. Although this was a prospective investigation in that a cohort was identified as being at risk and compared with the nation as a whole, cases were ascertained retrospectively from a registry, and some cases may have been overlooked. A preponderance of tumours of the central nervous system, breast, and thyroid was found [L10, H22], confirming both the radiosusceptibility of these sites and the reliability of the data. Furthermore, the frequency of birth defects among the mothers in this study was close to that expected, suggesting that this was a representative cohort. The occurrence of thyroid malignancy supports other studies and indicates that over-screening bias is not the only reason that excess thyroid tumours have occurred in other children given radiation to the head and neck area.

224. There has been widespread use of radiation (generally of "soft" x rays) to treat acne in adolescents. Some of the doses were administered with cone shielding, to protect the thyroid and other areas; others were administered without such shielding. Data from the United States thus far provide no evidence that this use of radiation has led to thyroid or other cancers [G8]. The doses were fractionated, and the patients were generally 16-18 years of age or older, when the thyroid appears to be less radiosusceptible than in early childhood.

(c) Children exposed to atomic bombings and fallout

225. Several groups of children have been studied who were exposed to radiation caused by the detonation of nuclear weapons. The best documented are the children exposed in Hiroshima and Nagasaki and the children exposed in the Marshall Islands (the latter

were primarily exposed internally, to ^{131}I). Three other groups have also received some attention; namely, children exposed to radioactive fallout from the distant atmospheric testing of weapons, children exposed to accidental discharges from nuclear power installations, and children exposed to relatively elevated levels of cosmic radiation by virtue of living on the Colorado plateau in the United States or at similar altitudes; the last-mentioned children have been studied only cursorily, e.g., all of them lived in industrialized countries and none lived at elevations as high as the Andean altiplano or the Tibetan plateau. The cancer risks resulting from these exposures are consistent with the risks from other exposures (reviewed above); there is a susceptibility to leukaemia, to thyroid cancer, and, in a special and only partially understood sense, to breast cancer (see below). In fact, the leukaemia risk has been satisfactorily studied only in Japan; other studies of it remain controversial.

226. *Thyroid.* The risk of thyroid cancer has already been reviewed in connection with other exposures, and some of the Japanese findings have been given. In Japan, about 3.6 additional incident cases per 10^4 PYGy were seen among females exposed before 20 years of age, as contrasted with one additional incident case among males in these same years. There is mounting support for a lessened susceptibility in those over 20-30 years of age at the time of the bombing [B5, P3, P4]. In the Marshall Island cohort, a group of 250 individuals that has now been followed for 30 years, the only substantial risk is that of thyroid cancer due to ingestion of ^{131}I, ^{133}I etc., with doses estimated to be 7-14 Gy in young children and perhaps 20 Gy in infants (< 1 year) [C5, C6]. No tumours were detected in the first 10 years of follow-up. Only one case of leukaemia has been seen. While there have been cases of benign thyroid nodules, it is uncertain how much excess of malignant thyroid cancer has occurred. Only papillary cases have arisen, and the relative risk of the non-metastatic carcinomas has been 0.82 for individuals exposed before 10 years of age and 3.94 for those exposed after this age (computed from [C5]). The risk shown in Table 20 is 1.8 per 10^4 PYGy for the children; curiously, this study is unique in finding a smaller risk in younger children, but this could be artefactual. The thorough search for thyroid anomalies has led to the surgical removal of most benign cases, perhaps sparing some individuals the risk of developing thyroid carcinoma. Furthermore, the long duration of the excess risk for this tumour means that increased risk may continue to reveal itself.

227. In an investigation of thyroid malignancy in children exposed to atomic testing near the Nevada test site, United States, there was an excess of cases relative to expectations based on data for the whole United States, but no excess relative to expectations for neighbouring states [Z3]. Sample sizes were small, and it was concluded that the numbers of exposed children might not be large enough, given current risk estimates for thyroid cancer, to demonstrate excess risk from nuclear-testing fallout.

228. The most recent report on the population of the Marshall Islands [H32] has found an inverse relation-

ship between the prevalence of thyroid nodules and the distance from the BRAVO explosion to the atoll of residence at time of exposure. The results suggest a linear dose-response relationship and an increase in the risk estimate by 33% to 11 cases per 10^4 PYGy.

229. Finally, a recent case-control study in Japan has found that irradiation of the head, neck, or chest in infancy to doses of 0.0002-0.4 Gy was the only identifiable risk factor for the occurrence of thyroid cancer in teenagers [Y7].

230. *Leukaemia.* The leukaemia data from children irradiated by the atomic bombings have recently been reviewed [e.g., C4, F3, P15]. Where it had once been thought that the distinction between Hiroshima and Nagasaki would be informative with respect to the different RBEs of high- and low-LET radiation, it now appears that there is little useful data in that respect, owing to the revision of the dose estimates. In Japan, the most informative data are the contrasts in risk after exposure between the 0-0.09 Gy and the > 1 Gy groups, under age 10. Figures II and III show the general risk pattern quite clearly for children and for adults (from [B24], based on T65 doses). The latent period is brief, beginning 3-5 years after exposure and reaching a peak 7-8 years later [F3], after which time the excess risk levels off; subsequent studies have shown that significant excess cases

disappeared by about 1959; that is, after 15 years or so [O3]. The latency time is shortest in exposed children, i.e., it is inversely related to age at exposure [I7]. Most cases were of acute leukaemias, and these showed the most age-dependent subsequent risk; chronic granulocytic leukaemias showed very little age-dependence [I7]. The subsequent risk can be fitted adequately to a log-normal distribution [I7].

231. At a dose of 1 Gy, the relative risks for children (< 19 years) and adults have been estimated to be 6.2 and 3.3, respectively [P15]. Overall relative risks (i.e., for all doses > 1 Gy and all ages > 15 years at the time of the bombing) are 31-33 [S17]. The risk coefficient for Japanese children has been estimated at 2.8 additional cases per 10^4 PYGy (T65 kerma), with a lower risk in those exposed between ages 10 and 19 [F3]. This finding is similar to that for adults, except that the cell types in children have been of the acute lymphocytic and the acute and chronic granulocytic, which are typical of spontaneous childhood leukaemias. The highest sensitivity seems to have been for chronic granulocytic leukaemia.

232. For leukaemias in children exposed at less than 10 years of age, sex ratios were 0.76 (M/F) for doses < 0.1 Gy; 1.90 for doses 0.1-0.99 Gy; and 3.71 for doses > 1 Gy. For children 10-19 at the time of the bombing, the respective values were 1.05, 10.32 and
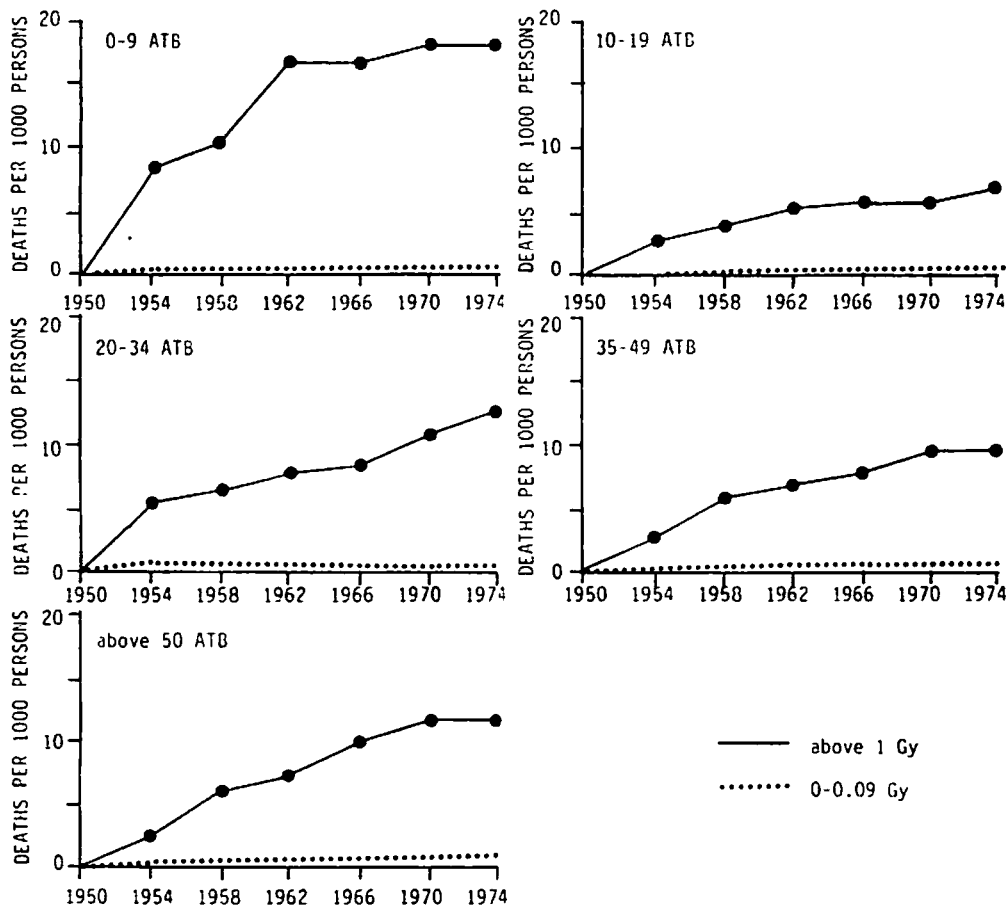
Figure II. Cumulative deaths from leukaemia, 1950-1974, per 1,000 persons alive in 1950, for various age groups at the time of the bombings (ATB).
[B24]
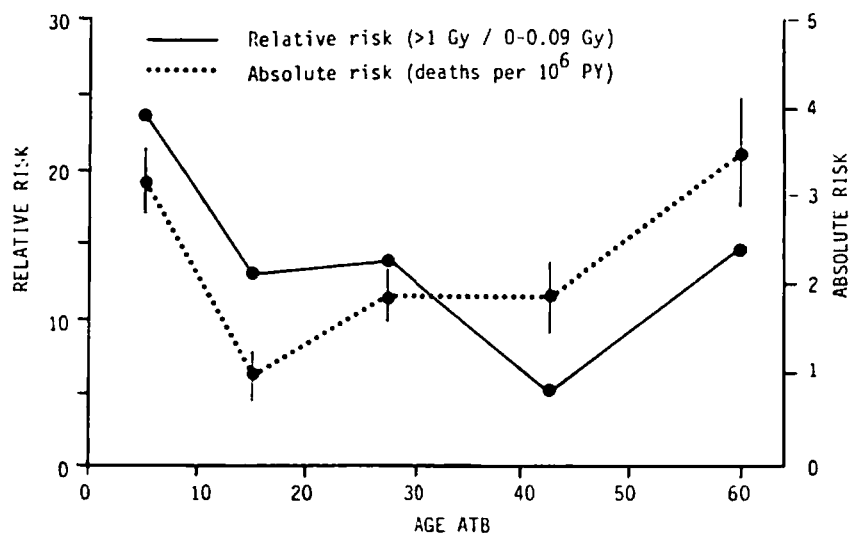
Figure III. Absolute and relative risks of leukaemia by age at the time of the bombings, 1950-1974, average for both Hiroshima and Nagasaki, T65DR doses.
[B24]

0.84 [C4]. However, the background rates are higher in males, and the relative risk is not statistically different between the two sexes [P15], an argument favouring a multiplicative projection model.

233. There is no excess of childhood cancers other than leukaemia and breast cancer in these children. Evidence is now available on their later adult experience, but to date there are no new adult-onset tumour risks clearly identified with childhood exposure, with the exception, perhaps, of stomach cancer (4.7 cases per 10^4 PYGy) [S17, W5].

234. Most of the controversy in the United States on distant nuclear fallout exposures has centred on its possible leukaemogenic effect. Comparisons have been made for all childhood cancers and separately for leukaemias, based on mortality data for counties with high and low exposure before, during, and after fallout periods. It has been argued that the data supported an excess in the high-exposure areas of southern Utah [L4], which excess was correlated in time with the period of exposure to fallout and which was not evident in low-exposure areas. This interpretation has been criticized, in particular because the data are not compatible with a simple radiogenic effect; rates in different areas over these time periods do not vary simply as a function of exposure, suggesting that other factors are involved (e.g., [B6], [L5] and [R4]). Reviewing a broader set of data, Land et al. [L5] argued that in southern Utah the leukaemia rate has been lower than in other parts of the United States in years prior to the exposure. Further, there was a deficit in juvenile cancers at the remaining sites in the exposed area.

235. On the basis of Utah-wide data on fallout, Beck and Krey [B7] have contended that the suggested low-dose area in northern Utah actually received higher mean doses, so that the gradient in risk described by Lyon et al. [L4], even if correct, does not correspond to exposure. Johnson [J2] used a large interview study of Utah Mormon families to argue for a very large

excess in cancer (at all ages) at known radiosusceptible sites. Because of problems with its methodology, the Johnson study has not generally been accepted as valid. In a study, which attempted to determine if Johnson's results could be correct, Machado et al. [M20] restricted their analysis to a small area of southern Utah. In the proper time period following exposure to fallout, 1955-1980, there was a small excess number of leukaemias with onset at ages 0-14 (RR = 2.84 for exposed children, much less than found by Johnson) [M20]. There was also an excess of cases at all ages (RR = 1.42). Machado et al. estimate that the doses were between 0.001 and 0.021 Gy, so that small effects, at most, would be expected.

236. There may, accordingly, be a small increase in the rate of leukaemias in these exposed children, although more accurate estimates of dose in other parts of Utah might reduce the size of this effect. However, since southern Utah rates were about 35% higher than expected from the rates in the United States as a whole, at least some of the increase is probably real. The individual doses are not known, so a dose-response analysis is not feasible.

237. Analysis of leukaemia mortality rates in the United States through the period of atmospheric nuclear testing has suggested patterns which are consistent with fallout effects [A18]. States were classified according to the level of exposure based on the assessment of strontium-90 in cow's milk samples in 1959-1960, in human bone in 1966-1967, and in total diet in 1964-1965. The leukaemia rates during 1950-1976 were correlated with exposure in states classified in high, intermediate and low exposure groups. The pattern of leukaemias showed a 5.5-year latency and a 15-year plateau, and were only of the acute and myeloid types, consistent with what is known from other studies of radiation-induced leukaemias in children. There was also a consistent nation-wide pattern of these types of childhood leukaemias, and no other exposures to radiation or other agents could be identified by the author to account for

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this. The estimated risk coefficient was 6.46 ± 0.16 excess leukaemia deaths per 10^4 PYGy. The author reviews other data on childhood leukaemia, arguing that his risk estimates are consistent with those, further supporting a fallout-related explanation.

238. Recently, two preliminary surveys of the frequency of cancer among young people living near nuclear power installations in the United Kingdom, specifically at Dounreay and Sellafield, reported an increase in leukaemia [G19, H26]. Since the estimated radiation doses in the vicinity of these plants seem too low to account for the increase, other studies were initiated. One of these addressed the situation at Dounreay [D23]. These authors conclude that their findings weigh heavily against the hypothesis that the increase had been due to radioactive discharges from the plants, unless the doses to the stem cells from which childhood leukaemia originates have been grossly underestimated. Cook-Mozaffari and her associates have undertaken a far more comprehensive study of mortality in the years 1959-1980 in the vicinity of all of the nuclear installations in England and Wales [C19]. Their findings are succinctly summarized in [F14]. Briefly, there was no evidence of a general increase in cancer mortality near nuclear installations in the 22-year period. Leukaemia in the age group 0-24 years may be an exception, however: standardized mortality rates for lymphoid leukaemia increased with increasing proximity to an installation. In Local Authority Areas where at least two thirds of the population resided within six miles of an installation, relative risks were invariably greater than 1, ranging from 1.12 (British Nuclear Fuels Limited, Capenhurst, not statistically significant) to 3.95 (Amersham, statistically significant at the 5% level on a one-sided test), as compared with Local Authority Areas not in the vicinity of nuclear installations and selected to have a similar urban-rural status and population size.

239. Over all installations, the relative risk for leukaemia within the six mile distance was 2.0. Since the individual exposures are unknown, no dose-response estimate was possible. The investigators noted that it was not clear whether the effect could be due to a general confounding of other environmental or socio-economic factors. One of these may be the venting of pesticides into the air when the cooling towers were cleaned. Although it is known that the subsequent risk of leukaemia among individuals exposed in the first two decades of life is substantially higher than among those exposed later in life, based on the Japanese experience and a linear dose-response model, a doubling of the risk would imply a dose of hundreds of mGy which seems unlikely given present estimates for exposures within a few miles of a nuclear installation. Thus, while the risk observed may be real, it cannot be accounted for on the basis of the doses received.

(d) Exposure of the female breast in childhood and at perimenarchial ages

240. In general, radiogenic breast cancer follows the natural age distribution for this tumour, suggesting that, as they do with spontaneous breast cancer, other

host factors, specifically the endocrine and cell proliferation status of the exposed breast tissue, modify the susceptibility and latency of radiogenic breast cancer [B6, H6, T6]. Data on age at exposure are available from women receiving chest fluoroscopies for pneumothorax monitoring in New York [L6, S1], Massachusetts [D8] and Canada [H6]; from women treated for mastitis in Massachusetts [B3, L6]; from women treated for benign breast disease in Sweden [B8], and from atomic bomb survivors [T1, T6].

241. These data consistently disclose a declining relative risk of cancer with increasing age at exposure, and a markedly high relative risk for exposure in adolescence and young adulthood. For individuals under age 25 at exposure, there is a latency period of at least 15 years, and excess risk persists for 40 years or more [H6]. A linear model gave the best fit in the Japanese [T6], New York, and Massachusetts series [H6], but a quadratic model fit better in a combined analysis of the Canadian fluoroscopy data [H6]. Except in the case of the Japanese study, the young women ordinarily received courses of treatment involving several (1-10) exposures and a total of about 1.5-2.5 Gy to the breast. With the possible exception of a large Canadian study (to be discussed later, in the section on adult breast exposures), the evidence does not document a fractionation effect [B6]. The absolute risk is in the range 3-8 additional cases per 10^4 PYGy [B6, T6] based on a linear model, with higher values having been found in women who were younger at the time of exposure. Women irradiated at the time of their first pregnancies were especially vulnerable [B6]. Because the Japanese women who were less than 15 years old at the time of the bombing are only now reaching the ages when breast cancer becomes most common, it is not yet possible to derive satisfactory lifetime dose-response estimates.

242. Several major findings have recently emerged from Japan [P15, T6]. In corroboration of the studies reviewed above, an elevated risk among women aged 10-19 at the time of exposure has been clearly shown. The relative risk for women who received 1 Gy when they were under the age of 19 has been estimated to be 2.51 ($\pm$ 0.75), compared with a relative risk of 1.45 ($\pm$ 0.24) for exposure over that age in the extended Life Span Study (LSS-E85) using the T65DR dose estimates [P15]. At present, the data are not completely consistent with respect to the level of risk for post-menopausal exposures, and further studies of the exposed cohorts are needed. The most important result may be the finding that women under age 10 at exposure exhibit an excess risk ([T6, T7, T14]; see Table 23). The excess is related to dose, but did not appear until this cohort reached the ages at which breast cancer normally arises, consonant with previous age-onset results. These are higher relative risks than observed in any other age group having received comparable doses. Absolute risks are high at ages 10-19 [T6], though they seem roughly comparable to ages < 10 [T14]; that is, childhood may be the peak years for susceptibility. The Japanese findings are summarized and discussed in more detail in section III.C.4 on adult exposures. Breast-tissue susceptibility

below age 10 has also been seen among infants irradiated for thymus enlargement [H19] and in children irradiated for other primary cancer [L12].

3. Tissues apparently not susceptible to radiation-induced carcinogenesis

243. There is accumulating evidence that certain tissues, generally those involving non-proliferating cells, are relatively non-susceptible to radiation-induced cancer. In children, cancer caused by radiation is restricted commonly to the white blood cell and bone-forming tissue and to the thyroid. Except for breast and perhaps stomach there are not much specific data in regard to solid adult cancers. However, the indications from the most recent Japanese (DS86) data suggest a high general susceptibility, expressed at the normal adult ages for carcinomas [S49]. Children surviving irradiation to treat childhood cancers may in coming decades reflect risk at a variety of irradiated sites.

244. The information presently available thus suggests that if there is an effect of radiation in childhood for other sites, the result will be similar to that found in the breast, in that excess cancers will arise at roughly the same ages at which they do naturally. If this occurs, then a variety of tissues may be shown to be susceptible to radiation in childhood, but perhaps without an unmistakable excess susceptibility due to the young age of the exposed tissues. This would provide an important contribution to our understanding of radiation carcinogenesis and of the tissue biology of epithelia.

4. Summary of exposure effects in children

245. In summary, the experience of children who have received substantial doses of ionizing radiation demonstrates the susceptibility of the thyroid, bone, bone marrow and the breast. The bulk of the children who have been successfully treated by radiation for cancer initially presented with tumours characterized by a large heritable component. From observations on some of those children who received neither radiation nor chemotherapy, it can be seen that they are obviously more prone to develop cancer than normal children. In general, certain sites are susceptible, and the evidence is now clear that this has to do with gene regions expressed in both the tissue involved in the original primary tumour and in the tissue of the second tumour, particularly in the case of secondary osteosarcomas occurring in treated retinoblastoma patients. Individuals with the hereditary form of this tumour are known to develop osteosarcomas away from the irradiated field or in the absence of irradiation. There is also evidence that other relatives of some retinoblastoma [C5, S12] and rhabdomyosarcoma [S50] patients are at excess risk of cancer of various types at a number of organ sites.

246. Current evidence, though not conclusive, suggests that children are susceptible to the induction of most cancer types by radiation, and that there are charac-

teristic patterns to the expression of that risk. Tumour types arise at ages that are typical of the spontaneous childhood tumours of the same sites, but exposure in childhood also appears to generate tumours that are typical of adults and that appear in the usual adult ages rather than in childhood. There are indications in the case of second tumours following retinoblastoma treatment that a multiplicative projection model may apply, as it does in the case of most adult tumours; data from other sources are at present still too sparse to reach any general conclusions.

247. With the exception of the Japanese data, the studies on childhood induction of cancer following ionizing radiation provide convincing evidence that there are effects, but they do not provide risk coefficients useful in lifetime risk projection for adult tumours.

C. TISSUE SUSCEPTIBILITY IN ADULTS

248. It is to be expected that age is a critical factor in determining the radiation risk, since childhood is a period of tissue generation and, for many tissues, differentiation. The question is, how different is susceptibility in the tissues of adults?

249. The bulk of our knowledge of dose-response, age and projection patterns after adult exposure comes from three studies: women treated for cervical cancer, patients (mainly men) treated for ankylosing spondylitis, and the Japanese exposed to the atomic bombings. These studies will be presented in detail in chapter VI. In this section, their results and those of the remaining literature will be summarized in the context of the biological issues involved.

250. As was seen with juvenile exposures, there may be biological differences between tissue types of adults relevant to their radiosusceptibility. The assessment of radiation effects must be made in the context of the exposed populations that are available for investigation. Most adult exposures occur as a result of treatment for disease; such individuals may not be biologically representative of the population at large, either because they are genetically different or because their disease itself changes their susceptibility to radiation. This is likely to be especially true of individuals irradiated for the treatment of cancer itself.

251. Two principal sources of possible non-representativeness are important in the interpretation of cancer induction in irradiated cancer patients relative to other adult cohorts. First, it is known that a fraction of any population is genetically susceptible to cancer, e.g., cancers of the colorectum and the breast. Second, most cancers are thought to result from specific environmental exposures [D13]; cancer patients may not be representative of their population in terms of their history of exposure to such risk factors. To the extent that this is true, their tissues may already have been partially affected by these risk factors. Comparing their post-irradiation experience with that of their age- and sex-matched peers may not be an appropriate way

to estimate the effects of radiation. Evidence on this point will be given later.

252. There are important informative cohorts of adults who were initially exposed for other diseases, including tuberculosis, mastitis, thyroid anomalies, benign gynaecological problems, conditions requiring diagnostic x-ray examinations, and ankylosing spondylitis. It is difficult to know, however, if these patients are random representatives of their populations; there are indications that some, at least, are not. Their risk should be compared with that of the most representative possible unexposed groups.

253. Several other cohorts of individuals, in effect randomly selected from their populations, have been exposed to large doses of radiation, and they are naturally the most reliable sources of data on the susceptibility of normal adults. They include occupationally exposed groups (radiologists, radium dial painters, miners, nuclear workers) and individuals exposed to nuclear testing or to the atomic bombings in Japan. To gain information on the biological aspects of radiogenic cancer, it must be determined if these groups have different experiences.

254. As essential as it is to consider separately the risk for individuals who may be susceptible to radiation carcinogenesis and the risk for those who are probably more representative of their population, it is equally essential to consider the risk in terms of the nature of the tissues exposed to radiation. There are different tumour groups in this regard. The first is haematopoietic tumours following irradiation of the bone marrow and osteogenic tumours. The risks here are unique. Due to the widespread distribution of active bone marrow, such tumours have been observed following many different exposures. The second group is nerve and connective tissue tumours, where tumours that occur in normally dividing cells should be differentiated from those in non-dividing cells. The third and largest group of adult tumours is carcinomas of epithelial tissues, which tissues have life-long patterns of cell division and specialization.

1. Adults exposed to radiation for treatment of primary cancers

255. Relatively little is known on a population basis about the risk of radiogenic second tumours in the many adults who have been exposed to treat a primary malignancy. To date, most of the evidence has been derived from investigations of the consequences of radiotherapy for cervical and ovarian cancers, for Hodgkin's disease and non-Hodgkin's lymphoma and for the tumours of childhood reviewed earlier. There has also been one large general study of secondary leukaemias in cancer patients.

256. Second tumours in adult cancer survivors may take the form of local solid tumours in the irradiated field, if cell sterilization has not been excessive. Radiogenic sarcoma has been observed to arise from the area of skin, or the underlying fascia, in an irradiated area or even from a radiation ulcer (e.g.,

[B20]). Second tumours may also be systemic ones such as leukaemias, presumably caused by a transformation of the cells in exposed bone marrow. Finally, second tumours sometimes occur at remote sites; whether such tumours could be radiogenic, e.g., due to scatter, is essentially impossible to determine.

257. Since many cancer survivors treated by radiotherapy were also treated by chemotherapy, it is necessary to ascertain what portion of the second-cancer risk is due to the chemotherapy or to an interaction between the two modes of therapy. This can be difficult. Alkylating agents have a high carcinogenic potency; they are delivered in large doses, and most of the body is exposed. Radiation is locally delivered, in general. Interactions will be considered in chapter V.

258. In the case of leukaemia following radiotherapy for lymphomas, it is presently difficult to differentiate between truly radiogenic second cancers (i.e., leukaemias) and leukaemias that have been caused by the conversion of an initial lymphoma cell to leukaemic form; this has been suggested to be a normal stage in the natural history of lymphomas, although some studies reveal that it is not [e.g., B10]. Molecular genetic methods may be able to resolve this issue if the original lymphoma cells have specific genetic markers for which one could screen the subsequent leukaemia cells.

259. Only a minority of irradiated patients develop radiogenic second tumours. The relative risks are often rather small, especially for cancer patients who are elderly and have fewer years of life during which to be at risk.

(a) Treatment for Hodgkin's disease

260. One of the most intensively studied groups of adult cancer survivors, in terms of risk of second cancers, is that of persons treated for Hodgkin's disease. While the treatment modalities varied, they often involved radiation to affected lymph nodes. In some patients, no other therapy (or only surgery) was carried out, but in the majority of long-term survivors of Hodgkin's disease, chemotherapeutic agents were also used. The results of several studies are reviewed here [B9, B10, B11, B37, C7, C8, G4, P12]; [B11] is a summary of results reported to 1984.

261. The most notable second cancer in these patients is leukaemia, specifically, acute non-lymphocytic leukaemia (ANL), although solid tumours and other leukaemias have also been observed. In the many studies reported, the results are similar. X-ray therapy alone does not seem to be a risk factor for the leukaemias, and it may or may not be a risk factor for solid tumours; evidence on the latter point is conflicting, and since the latency period is longer than for leukaemia, there may not yet be sufficient data on long-term survivors.

262. Boivin and O'Brien have analysed data pooled from seven reports of second-cancer risk after treatment for Hodgkin's disease [B37]. After radiotherapy, the

relative risk values for solid tumours were as follows: all sites, 2.2; bones and joints, 20.0; soft tissues, 18.3; non-Hodgkin's lymphomas, 8.1; melanomas of the skin, 6.7; buccal cavity and pharynx, 4.1; nervous system, 3.6; respiratory system, 2.5; and digestive system, 1.8. Unlike for leukaemias, no elevated risk of solid tumours was found in the chemotherapy-only group, possibly because the studies had shorter follow-up times.

263. Chemotherapy has been strongly associated with subsequent tumours and with the special risk of acute non-lymphocytic leukaemia; combined therapy appears to lead to an increased risk based on the interaction between the radiation and chemotherapy. However, support for an excess effect of x-ray therapy is weak [B11]; the relative risk of combined therapy versus chemotherapy without radiotherapy was slightly, but not significantly, lower (125 vs. 136) in one series of patients from the United States [B10, B11], and there was no interaction effect in another [C7]. Briefly, there is little evidence for a radiation hazard relative to secondary acute non-lymphocytic leukaemia in treated Hodgkin's disease patients. These data are summarized in Table 24.

264. It is appropriate to note that effective chemotherapy is relatively recent and that in the past, with only x-ray therapy available, survival was not sufficient to provide much information. Data are accumulating that may permit the statistical isolation of the independent effect of chemotherapy, but this will not be feasible until some years at-risk have accumulated. There are no systematic dose-response data as yet.

265. The cumulative relative risk of acute non-lymphocytic leukaemia due to chemotherapy of various types is high, sometimes in the hundreds; for other leukaemias it is about 10 and for solid tumours, about 3-4; individuals older than 40 at treatment are at higher relative risk than those who were younger, a somewhat unexpected finding [C7, G4]. The risk of solid tumours appears to be increased about 3-4 times by combined therapy. In a study of United States patients, Boivin and Hutchinson report that the risk of a solid tumour was 1.8, relative to the expected number, for those with no intensive therapy (raising a question about the appropriateness of the expected rates), 2.1 for radiation only, 1.8 for chemotherapy alone, and 3.3 for combined therapy [B10]. After a latency period of 10 or more years, the relative risks were statistically significant only in the case of the radiotherapy-only group, for whom the relative risk of solid tumours was 25 (95% CI: 8.1-58.4).

266. An increased risk of acute non-lymphocytic leukaemia has been seen in children treated for Hodgkin's disease [T4]; however, there was no case in children treated with radiotherapy alone [M28]. While it is conceivable that individuals with Hodgkin's disease have a natural proclivity to develop leukaemia, the evidence suggests that leukaemias occur after chemotherapy and in all stages of Hodgkin's disease, but very rarely in the absence of chemotherapy [B10, B11, G4].

267. A recent study of Hodgkin's disease patients treated with chemotherapy and radiotherapy at the United States National Cancer Institute has been reported [B35]. As had been found in other radiogenic leukaemia studies, the excess risk in this small series of 192 patients was expressed in only a small window of time, in this case from three to 11 years. Of course, such second tumours, all acute non-lymphocytic leukaemias, were only observed in survivors of the original disease; moreover, the authors did not isolate the effects of radiation therapy from those of chemotherapy. Two other studies appear to confirm this report [P12, T19], although there are reports of elevated risk in comparable groups for a period of up to 20 years [K26].

268. Recently, another indirect risk of treatment of Hodgkin's disease has emerged. In a study of female patients in Houston, Texas, United States, cervical conditions resulting from infection by human papillomavirus were found to be considerably more prevalent than expected in a general population of the same ages. A twofold to fivefold increase in the risk of carcinoma in situ and of invasive carcinoma of the cervix and anogenital region is seen in these women [K8]. Although this has not been reported in other Hodgkin's disease series, the connection is plausible but will require longer follow-up to be ascertained (this study entailed a detailed retrospective review of Papanicolaou tests of the patients over many years). In an immune-suppressed individual, vulnerability to human papilloma virus infection appears heightened (paragraph 302); this infection progresses over a period of years, in some individuals to carcinoma [K8]. It is not possible, from the available data, to identify radiation effects independently, because most patients received combined therapy.

(b) Treatment for cervical cancer

269. Cervical cancer is commonly treated by external beam therapy and/or by the implantation of intra-cavitary radium sources in the vagina and the uterus for extended periods of time. In the cohorts that have been studied, radiotherapy has usually involved two 36-hour applications of 2.6 10^9 Bq of radium, followed by 20-70 Gy from external beams delivered in 2-Gy fractions over several weeks [B12]. Both orthovoltage (200-400 kV cobalt-60) and megavoltage (2-33 MV photons from betatrons or other devices) external radiation have been used, with a typical dose being 20-70 Gy to the pelvis, delivered in fractions of several Gy over a 4-8 week period. Risk analysis was initially carried out by classifying the tissue sites into three groups based on general level of dose. The greatest dose is received by the entire pelvic area and the lateral lymph nodes; other heavily exposed organs include the bladder, rectum, endometrium, colon, ovaries and bone. The kidney, gallbladder, stomach, pancreas, and liver are exposed to an intermediate level of radiation. Finally, remote sites such as the buccal cavity, lung, breast, brain, salivary gland and thyroid receive little radiation. Nearby sites have doses in the tens of Gy; intermediate sites, 1-10 Gy, and remote sites, tenths of Gy [B12].

270. The largest study of second tumours in cervical cancer patients is the International Radiation Study of

Cervical Cancer Patients (IRSCCP) [B12, D9]. Over 182,000 women from eight countries (Canada, Denmark, Finland, Norway, Sweden, United Kingdom, United States and Yugoslavia) have been followed from the time of diagnosis of cervical cancer. Over 1.3 million person-years of observation have accumulated, including 623,798 person-years to women who were treated by irradiation and 178,243 person-years more than 10 years after irradiation. The average follow-up was 7.6 years. A high fraction of cancers was confirmed histologically, and it is believed that the participating registries were able to ascertain the vast majority of cancers that occurred; data from the separate registries and details of the investigation are reported most fully in [D9]. Since most other studies of cervical cancer have as their subject the same individuals included in [D9], only the latter results will be reported in detail.

271. In addition to classifying the sites according to distance (close, intermediate or remote) from the radiation source, the IRSCCP study divided the women into those with invasive cancer who were treated with irradiation, those with invasive cancer who were treated without irradiation, and those with in situ cancer of the cervix treated without irradiation. Relative risks for women followed more than 10 years are given in Table 25 (the table contains data from another study, to be discussed below). Interestingly, the pattern of relative risks was similar among the three groups. Of 5,146 second cancers, at most 5% (162) were attributable to the exposure to radiation. Pelvic irradiation with high doses seemed to be associated with some increased risk of cancer to the exposed organs, including the bladder, rectum, bone, connective tissue, ovary, small intestine and kidney. The risk of bladder cancer was also increased in women with similar diseases who had not been irradiated; however, the relative risk increased, over time post-exposure, only in the irradiated group, suggesting a radiation effect [B12]. The risk of cancer of the uterine corpus was consistently below expected levels. Figure IV provides the probabilities (relative risks) and confidence intervals for various second cancers in irradiated women at least one year after irradiation.

272. The risk of leukaemia was elevated in these data, but the elevation was similar for exposed and non-exposed. The dose to the bone marrow is estimated to have ranged between 3 and 15 Gy, and hundreds of radiogenic leukaemias would have been expected. However, fewer than 100 were observed, suggesting that cell sterilization was an important factor. The relative risk of non-lymphocytic and acute leukaemias was small, 1.4 (95% CI: 1.1-1.8), and may reflect lower levels of exposure at more remote marrow sites, where cell sterilization was not important. In one of the studies of which the IRSCCP series was composed

BLADDER
BONE
BREAST
COLON
CONNECTIVE TISSUE
KIDNEY
LUNG
OESOPHAGUS
OVARY
PANCREAS
RECTUM
SMALL INTESTINE
STOMACH
THYROID
UTERUS

CHRONIC LYMPHOCYTIC LEUKAEMIA
MULTIPLE MYELOMA

0.1 0.2 0.5 1 2 5 10
RELATIVE RISK

0.1 0.2 0.5 1 2 5 10
RELATIVE RISK

COHORT SERIES

CASE-CONTROL SERIES
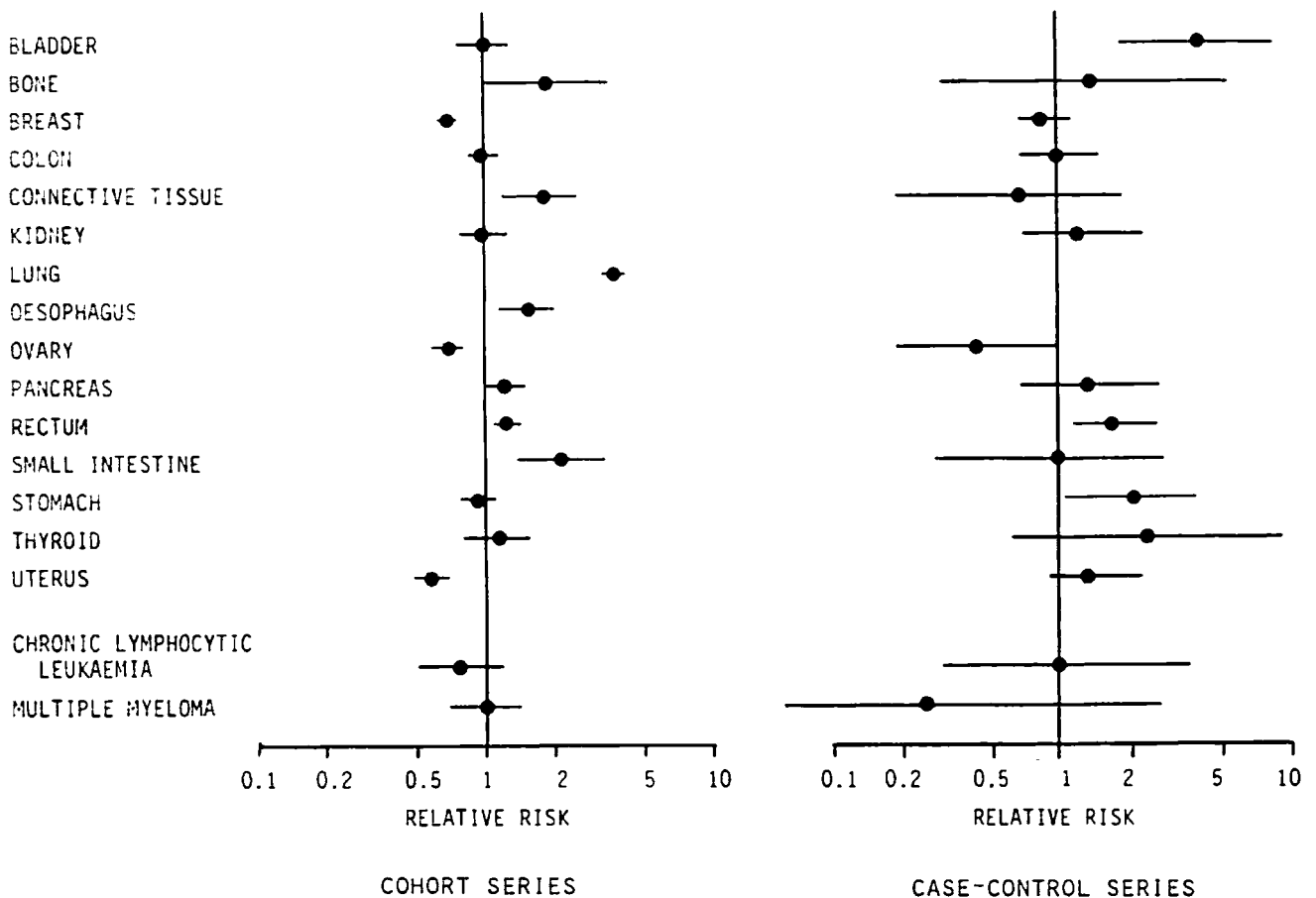
Figure IV. Relative risks of malignancy at specified sites after radiotherapy for cervical cancer based on a cohort series [B12] and a case-control series [B38].

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[S34], doses to the marrow of about 7.8 Gy did yield a relative risk of 2.5 for leukaemia; however, although the sample base was 25,718 women, this was not significant. Leukaemia was slightly elevated in the Surveillance, Epidemiology, and End Results (SEER) programme patients studied in the United States by Curtis et al. [C8], and the relative risk of leukaemias in another large case-control study in the United States [B26] was 2.3 (95% CI: 0.2-24.4).

273. To understand this apparent leukaemia deficit better. a case-control study of leukaemia in a sample of the IRSCCP patients has been done [B36], using individual patient records from 196 leukaemias and 750 matched controls (cervical cancer patients not developing leukaemia) to estimate the doses to each of 14 skeletal components of bone marrow. Using a marrow-component-weighted dose-response function, the best-fitting models included a negative exponential (cell-sterilization) term. Linear and quadratic terms, relative to the effects at low doses, could not be distinguished statistically in this study, although the latter yielded higher risk estimates at low doses and were preferred by the authors. This suggested to the authors that in therapeutic doses, cell killing is responsible for the deficit in leukaemias noted above. The risk of chronic lymphocytic leukaemia (CLL) (RR = 1.03) was not elevated. but the overall relative risk for radiogenic leukaemias was 2.1 (90% CI: 1.0-4.3); risk increased until 4 Gy, with a 0.88% excess relative risk per 0.01 Gy, and at 1 Gy the relative risk was 1.88, based on the linear term of the dose-response function. If the exponential term is included, the relative risk at 1 Gy reduces to 1.7 in this study. Women treated over age 55 experienced no excess risk. The difference between the relative risk in this sample and the relative risk of 2.3 for the entire cohort was attributed to increased sample sizes in the more recent study [B36]. The estimated excess number of cases per 10^4 PYGy was 0.48..

274. The authors [B36] concluded that this analysis, incorporating both cell sterilization and local marrow exposure considerations, not only explains the deficit in leukaemia in the IRSCCP group relative to other groups receiving smaller mean doses (e.g., women treated for benign gynaecologic problems and atomic bomb survivors) but also provides an estimate of the maximum leukaemogenic effect of radiation. This is a relative risk of about 5; doses sufficient to generate greater relative risk values will, by virtue of the cell sterilization effect, fail to do so. Radiotherapy was judged to be a much weaker leukaemogen than chemotherapy.

275. For unknown reasons, colon cancer occurred at similar rates in irradiated and non-irradiated women. This was unexpected, since other studies (e.g., [D11] and [S3]) have found evidence for radiogenic colon cancer, and the rapidly dividing cells of the mucosa of the colon should be susceptible to radiation. However, a study of Swedish patients, while revealing excess cancers of the bladder, endometrium, ovaries, and rectum, also did not find an excess of colon cancer relative to the general Swedish population [P17]. On the other hand, there is a report of teenagers sterilized

in German concentration camps during World War II who are now manifesting colon cancer in areas surrounded by radiogenic tissue damage [R15]. The lack of excess colon cancer in cervical cancer patients (at a statistically significant level) could be the result of cell sterilization [B12]; however, rectal cancer was increased in the same IARC series only among irradiated women, implicating the therapy [B12]. Since non-irradiated cervical cancer patients exhibited a risk pattern similar to that of those who were irradiated, other interacting factors must be suspected.

276. There was no excess of cancer of the stomach, pancreas or kidney, all of which organs had received intermediate doses in the IRSCCP patients. The results for pancreas and kidney are not surprising, because in other major series these sites were not highly susceptible. However, the stomach received substantial doses and would have been expected to show elevated risk.

277. For organs receiving low levels of exposure, no excess risk was seen other than to the lung and oral cavity. Younger as well as older irradiated women showed a reduced risk to the breast, for which the authors offer the explanation that radiation-ablation of the ovary has a protective hormonal effect; however, the effect was also seen in women irradiated post-menopausally [B12].

278. The deficit in uterine sarcomas is interesting, because an excess of such tumours occurs in women irradiated for benign gynaecologic disorders (see below); the deficit in the cervical cancer group may be due to a higher proportion of the women having undergone hysterectomy as part of their cervical cancer treatment, leaving fewer women at risk of uterine cancer [B12]. Excess risk to the uterus has appeared in a study in China, where 8,704 women treated for cervical cancer received 5.5-12 Gy to the uterus; in this group, 12 uterine cancers occurred five to 19 years after exposure [Y4].

279. Smoking-related sites (lung, oropharynx, bladder, oesophagus) have shown elevated risk in the IRSCCP series. Some excess was also seen in patients not irradiated. There may be an interaction between smoking and other factors to produce cervical cancer (see section V.A).

280. The IRSCCP study population has been used for a case-control study [B38] to provide more precise relative risk data than is possible with the more heterogeneous total cohort. The case-control study included 4,200 patients with second cancers for which histological confirmation was possible and 10,200 matched controls (patients without second cancers). These relative risk values and estimated excess cases per 10^4 PYGy are shown in Table 26 [B38]. Details of the dose-response patterns are provided in the original study [B38] but are too extensive to be given here; the results are broadly consistent with the full-cohort study [B12, D9].

281. In the case-control study of the same series [B38] it was found that the dose-response pattern

increased with dose, even for high doses, for most pelvic organs other than the colon. Indeed, rectal, bladder, uterine, vaginal and ovarian cancers all showed dose-response increases up through doses in excess of 100 Gy. These tissues should also have experienced a cell-killing effect, as indicated for the colon, and the fact that they did not casts some doubt on the explanation of the lack of colorectal cancer excess in this series.

282. Figure IV presents comparisons of the relative risks based on both the whole cohort and the case-control analyses of the cervical cancer series. There are some substantial, difficult to explain differences, highlighting the importance of using appropriate control or referent data.

283. A prospective study in Japan of 1,572 women treated with radiotherapy for cervical cancer (1,478 cases) and ovarian cancer (94 cases) revealed eight cases of leukaemia (five non-lymphocytic, one acute monocytic, and two chronic myeloid leukaemias) where 0.45 would have been expected, based on the rates for the general population [M26]. The period of follow-up ranged from six to 20 years. The relative risk was 11.2. The average mean marrow dose was 1.2 Gy, and the absolute risk coefficient was 0.45 excess cases per 10^4 PYGy to the bone marrow. Four of these individuals were in a high-dose-rate group treated with both a linear accelerator and remote afterloading using radium, and a fifth had been treated with the linear accelerator alone.

284. In a subsequently published series from Japan of 19,384 women with uterine carcinoma of whom 12,729 had been given either radiation alone (4,310) or radiation combined with surgery (8,419), statistically significant increases in leukaemia and cancer of the rectum were observed [A14]. The relative risks were 3.9 and 2.9, respectively.

(c)   Treatment for ovarian cancer

285. Two groups of patients from the United States initially affected with ovarian cancer have been studied by Reimer et al. [R11]. In all, 45,903 person-years of risk were observed, with a mean initial age of 56 years. Patients had been given varying treatments. There was an overall relative risk of cancer of 1.4; the relative risk was 1.5 in the irradiated patients and 1.1 in non-irradiated patients. Sites included the endometrium, colon, bladder, breast and haematopoietic system. In the first two years of follow-up, the risk was greatest for endometrial cancer. Since the rates of hysterectomy were not known for the computation of expected and observed rates, this finding may be spurious. However, the uterine corpus of post-menopausal women is known to be susceptible to rapid carcinogenesis after the administration of exogenous hormones (e.g. [S29]). Reimer et al. found a non-significant excess of breast cancer, raising the possibility that other hormonal or therapeutic factors interacting with treatment may be involved. Their data are summarized in Table 27. Values given in the table are relative risks. The study reported relative risks after less than two years, 2-4 years, 5-9 years and more than

nine years of follow-up, but there were no time patterns. The relative risk values were roughly constant from two to 9+ years, which is too soon after exposure to draw meaningful conclusions about projection effects. Dose information was not available.

286. In one of the groups, the non-irradiated patients had a relative risk of 0.3 of developing leukaemia, but irradiated patients had a corresponding risk of only 1.3 (not significant); however, in the other group, who had been given chemotherapy only, the relative risk was a significant 9.3 (95% CI: 5.2-15.3). In 1,399 ovarian cancer patients, Greene [G3] evaluated the risk of subsequent acute non-lymphocytic leukaemia as a function of treatment. In women treated by radiation alone, no acute non-lymphocytic leukaemia occurred; in those treated with both radiation and chemotherapy, the relative risk was not different from that in women treated with chemotherapy alone (combined therapy: RR = 120, 95% CI: 44-261; chemotherapy: RR = 100, 95% CI: 37-218) [G3].

287. Greene also reported an excess of colon, but not rectal, cancer after at least five years of follow-up, whereas, as noted above, in the cervical cancer group, rectal cancer was significantly elevated but colon cancer was not.

288. Lymphoma and bladder cancer were increased only in the irradiated group. No excess of leukaemia occurred in one of the series; however, in the other, there was a total excess of leukaemias (acute non-lymphocytic leukaemias), with RR = 171.4. Most of these cases had received radiotherapy, but all had also received chemotherapy. This study [G3] was the first report to raise the possibility of a causal role for radiation in bladder cancer and in lymphomas in ovarian cancer patients.

289. Another large study (9,726 cases) from the United States [C8] found the following relative risks of leukaemia: 10 for radiotherapy with no known chemotherapy and 9.5 for chemotherapy, both significant at the 1% level. When only acute non-lymphocytic leukaemia was considered, these relative risks were even higher (21.1 and 22.2, respectively). These results are not consistent with the minimal radiation effects in the absence of chemotherapy in other studies described earlier, and there is at present no clear explanation for the difference. However, chemotherapy is used increasingly to treat ovarian cancer and radiotherapy decreasingly; therefore, the estimation of the cancer risk from radiotherapy may be more relevant to radiobiology than to practical problems in human health. The Japanese investigation of cervical cancer, cited earlier, reported an excess of leukaemia in a population of 1,572, of whom 94 had ovarian cancer [M26]; whether this suggests a special risk only, or mainly, in the small subset cannot be determined adequately.

(d)   Treatment for breast cancer

290. In a series of second breast cancers in women irradiated for a primary cancer of the breast, Hankey et al. [H13] found no significant evidence of a

radiogenic risk to the second breast (from scatter) but did find a relative risk of 3.2 for all second primary breast cancers, when compared to the overall population. For breast cancer patients treated only with surgery, the relative risk was 1.2-1.4, perhaps reflecting a generally elevated susceptibility of patients with a primary breast cancer. This study involved a five-year follow-up of 27,175 patients in the state of Connecticut, United States. In a comprehensive study of the Connecticut Tumor Registry for the period 1935-1982, Harvey and Brinton [H20] found the relative risk of a second tumour to be 2.0 (95% CI: 1.9-2.1), compared to 1.5 (95% CI: 1.5-1.6) for women treated without radiation; 20 years after irradiation the two risks became equal (at RR = 1.7, based on the Connecticut population). The relative risk for a second breast cancer was 3.9 for irradiated and 2.8 for non-irradiated patients. Relative risk values for other second tumours are given in Table 28; the treatment data refer only to initial treatment, and there may be some false negatives. Note that an excess of chronic lymphocytic leukaemia was reported; this is not thought to be a radiogenic tumour and suggests that these results may confound other sources of variability.

291. Among 14,000 British women treated between 1946 and 1982, 194 developed a second tumour in the contralateral breast more than one year after the initial diagnosis [B28]. There was no evidence for radiation induction in the second breast, based on a comparison with a matched control group.

292. In another study of initial treatment for breast cancer [C8], the relative risk of leukaemia associated with surgical treatment alone was 1.0, for radiation-only 1.7, and for chemotherapy alone a significant 3.8 (Table 29). The risk for radiation alone, when all types of leukaemia were considered, was not significant, but the relative risk for acute non-lymphocytic leukaemia alone was 3.7 (95% CI: 1.6-7.2); compared with the significant RR of 6.7 (95% CI: 4.5-32.3) for acute non-lymphocytic leukaemia following surgery or chemo-therapy. The latency period suggested a causal effect of the treatment to the authors, because the excess risk did not occur until at least three years after irradiation (but, the same was true of the chemotherapy-only group). Patients with local disease had no excess leukaemias, but patients with regional stage disease exhibited relative risks of 2.7 for all leukaemias and 5.5 for acute non-lymphocytic leukaemia. The regional-local distinction was found for chemotherapy as well as radiotherapy. As this finding had not been reported in any previous systematic examination of breast cancer patients, the authors suggest that unreported chemo-therapy could have occurred, though there may be some radiogenic effect [C8]. No dose-response data were available for these patients.

293. A study of 1,359 Japanese breast cancer patients showed a 1.29-fold higher risk of second cancer in patients without a family history of cancer, but with a family history of breast cancer the relative risk was 3; a radiation-associated relative risk of 1.62 was observed, but no increase was associated with chemotherapy [Y3].

294. A small number of the survivors of the atomic bombing of Hiroshima and Nagasaki have developed more than one primary cancer [M16, R6]. Specifically, three women have been identified, all of whom initially had breast cancer and subsequently developed a second malignancy. All had undergone radiotherapy. Two developed acute granulocytic leukaemia, one four years after radiotherapy and the other eight years after; their estimated atomic bomb doses (T65DR) were 5.94 and 3.64 Gy, respectively. The third woman (atomic bomb dose 0.31 Gy) developed cancer of the lung beneath the treated breast some eleven years after radiotherapy. While it is probable that the carcinoma of the lung was radiotherapeutic in origin, it is moot whether the two cases of leukaemia were attributable to the therapy or to the atomic bomb exposure. However, the time that intervened between first and second malignancy was in both cases consistent with a radiotherapeutic origin, and the treatment doses had been high.

295. A study undertaken in the United States of 8,483 women has found a significant excess of acute myelogenous leukaemia after irradiation for breast cancer, but not in those not irradiated [F11]. Many of these cases had also received adjuvant chemotherapy. The post-irradiation risk was 1.29 ± 0.5% after 10 years.

2. Adults exposed to radiation for immune suppression

296. Total-body immune suppression has been induced in numerous patients to treat leukaemia or Hodgkin's disease, to prepare the patient for a bone-marrow transplant following the eradication of leukaemia or to prevent host-versus-graft disease in recipients of kidney transplants. The treatment effects have been discussed above. The use of a bone-marrow transplant to replace leukaemic immune system cells has been successful in up to 60% of cases with acute myeloid leukaemia, and, to date, only two second malignancies have been noted [B14, L8, T8]; doses range between about 7 and 12 Gy. It is too soon to summarize the risks associated with this treatment, for there are as yet few surviving patients. However, one report has shown a 2% risk of second malignancies, over 2-5 years, in individuals treated with total body irradiation [T8]. Complicating these results is the fact that some chemotherapy before or accompanying the irradiation has probably been given to these patients.

297. Some credence is lent to these estimates of risk by Greene et al., who have scrutinized individuals treated for non-Hodgkin's lymphoma (NHL) [G3, G9]. Among 517 patients, in whom marrow dose could be estimated, there were nine acute non-lymphocytic leukaemia cases observed where essentially none (0.08) had been expected, a relative risk of 105 (95% CI = 48-199). This was after 2,203 person-years of observation, a mean age at diagnosis of 43.4 years and an average of 4.3 years of follow-up. For total nodal irradiation, the relative risk for acute non-lymphocytic leukaemia was 28.0, and for total-body irradiation, 7.0, both significant. Greene et al. found suggestions of a correlation between cumulative radiation dose to the marrow and relative risk of subsequent

acute non-lymphocytic leukaemia, independent of chemotherapy effects, but the numbers were small and no dose-response pattern could be derived from the data.

298. In this study, the relative risk after combined chemotherapy and radiotherapy was 6.0, also significant (p < 0.05). Controlling for chemotherapy, there was still an increasing acute non-lymphocytic leukaemia risk with increasing cumulative bone marrow radiation dose, which was significant (p < 0.005). The relative risk was 8.1 for doses greater than 7 Gy, compared to doses less than 7 Gy. When acute non-lymphocytic leukaemia patients were compared to a fourfold larger set of non-Hodgkin's lymphoma patients without subsequent acute non-lymphocytic leukaemia, a risk coefficient of 0.03 additional cases of acute non-lymphocytic leukaemia per 10^4 PYGy was estimated.

299. It may be that the lower doses generally given to treat non-Hodgkin's lymphoma patients had produced acute non-lymphocytic leukaemia, whereas the higher doses given to treat Hodgkin's patients has had a cell-killing effect and produced no acute non-lymphocytic leukaemia.

300. These patients received total-nodal, hemi-body or total-body irradiation or some combination thereof, exposing large volumes of marrow to a relatively low and fractionated dose, with single doses of about 0.1 Gy given over a period of months and totalling a few Gy. Hodgkin's patients, by contrast, typically receive 2 Gy per day, administered over a period of weeks and leading to a cumulative dose of tens of Gy [G3] with substantial cell sterilization, which may explain the absence of radiogenic acute non-lymphocytic leukaemia in them.

301. Danish patients treated for Hodgkin's disease and non-Hodgkin's lymphoma had the following combined relative risks of developing acute non-lymphocytic leukaemia: 8.4 within 10 years of initial treatment and 8.9 thereafter [S39]. Other patients in this registry developed an excess of lung cancer (RR = 1.8), female breast cancer (RR = 2.1), and bladder cancer (RR = 2.6); the Connecticut Tumor Registry did not find an excess of bladder cancer, but did confirm breast and lung cancer, along with thyroid and buccal cavity cancer [C14].

302. Patients immune-suppressed for renal transplant seem, like Hodgkin's patients, to be susceptible to infection by human papilloma virus and hence to a risk of cervical and related tumours [K8, S21]. In these studies, the effects of irradiation and of chemotherapeutic immune suppression cannot be separated; in any case, the effects are not dose-dependent, because the result is not a directly radiogenic cancer but a susceptibility to cancer clearly produced by unrelated agents.

3. Leukaemogenesis in cancer radiotherapy generally

303. Curtis et al. have reported the results of a survey of 440,000 patients in the United States treated for all types of cancer [C8]. They assessed the risk of

leukaemia, specific to type of treatment administered for the primary cancers. A significant excess of leukaemias in general and of acute non-lymphocytic leukaemia specifically, for those patients given chemotherapy (Table 29), is described. Relative risks associated with exposure to ionizing radiation in the absence of chemotherapy were inconclusive: small, non-significant excesses were observed for cancers of the mouth, stomach, rectum, larynx, lung, connective tissues, breast, endometrium, ovary, prostate, testis, bladder, kidney and renal pelvis, and for multiple myeloma. The excess risk of bladder cancer associated with radiation for primary ovarian cancer agrees with the results found in the study of ovarian cancer patients discussed above [R11]. The overall relative risk of acute non-lymphocytic leukaemia among patients receiving neither radio- nor chemotherapy was 1.2 (not significantly different from 1.0); the corresponding risk was 2.5 with radiation and 4.5 with chemotherapy, both significant at the 1% level. All of the elevated risk was due to acute non-lymphocytic leukaemia. These patients may develop increasing relative risks with time, and solid tumours may also arise. Studies in the Connecticut Tumor Registry [C14] showed an increase in leukaemia after radiotherapy for cancers of the uterus or ovary, but chemotherapy as a joint cause was not examined in detail.

304. Although only three (3.9%) of the tests shown in Table 29 were significant at the 5% level, the overall result (not shown) was significant at p < 0.01 in both radio- and chemotherapy groups. Hence, the results do not appear simply to be statistical artefacts of multiple testing.

305. A case-control study of radiation-induced leukaemias in cancer patients has recently been reported, based on United States tumour registries from the states of California, Connecticut, Kansas, and Massachusetts [B26]. Cases consisted of individuals with two cancers, the second being leukaemia occurring more than one year after the diagnosis of the first tumour, and controls consisted of those with no second tumour. Controls were matched on sex, age at first diagnosis, site of first cancer, and survival after first tumour diagnosis; matching was 2 to 1. Chronic lymphocytic leukaemia was considered separately from all other leukaemias, which were pooled. This study involved 166 chronic lymphocytic leukaemia second tumours, 232 second leukaemias, and 781 controls.

306. As chronic lymphocytic leukaemia has not yet been shown to be a radiogenic tumour, it served as a data quality control. The relative risk of chronic lymphocytic leukaemia after radiotherapy was 0.7, that is, there was no significant difference from unity. For all other leukaemias collectively, the relative risk was 1.6 for all irradiated sites and 2.4 for only trunk sites. Both values are statistically significant. Among specific-site cancers, those of leukaemia after breast and uterine corpus were elevated, and in this and all other regards the results are similar to those of other studies of radiation of active bone marrow in adults. Results after cervical cancer were positive, with RR = 2.3, but not significant. No dose data were

available, and no information about the nature of the radiation treatments was given.

307. Study of the Danish tumour registry has found relative risks greater than 1 for acute non-lymphocytic leukaemia following initial irradiation to treat for head and neck cancers (RR = 1.1), genital cancers (RR = 1.9), female breast cancer (RR = 2.7) and lymphoma (RR = 8.4) [S39]; with the exception of lymphomas and breast cancers, for which the relative risk was 2.3, the risk for acute non-lymphocytic leukaemia 10 years after irradiation was not significantly different from 1.0.

308. The question of whether an interaction exists between radiation and chemotherapy in leukaemogenesis is of importance [see also G3, G9]. The incidence of excess acute non-lymphocytic leukaemia in Hodgkin's and non-Hodgkin's lymphomas is similar, implicating combined therapy or just chemotherapy with alkylating agents. Data from ovarian cancer patients, though inconsistent, suggest that chemotherapy is responsible, but those from non-Hodgkin's patients suggest an interaction. In the non-Hodgkin's patients, whole-body or broad tissue exposure is common, but the relative risks of acute non-lymphocytic leukaemia following total-body or nodal irradiation are both elevated (7.0 and 28.0, respectively). The results of the general study [C8] were inconclusive regarding radiation but agreed with other studies in showing a marked chemotherapeutic effect. Good dose-response data are not available from these general cancer-treatment surveys.

4. Adults exposed to radiation for treatment of benign conditions

(a) Haematopoietic tissue

309. The haematopoietic system, or some portion of it, is in the field of most radiation exposures. This system is actively mitotic throughout life and, with its own process of differentiation and cell division, is histologically distinct among tissues. It also behaves epidemiologically in a different manner from other tissues in regard to radiogenic cancer, in which respect it is similar only to bone cancer after brief exposures [C4]. Despite the sometimes negative findings of the above-mentioned studies on the effects of radiotherapy to treat cancer, where doses are often high, the haematopoietic system is highly vulnerable to radiation carcinogenesis. There are relevant haematopoietic data from most cohorts exposed to radiation; the results are remarkably homogeneous and permit a fairly unambiguous characterization of the risks.

310. *Leukaemia.* The bulk of our information comes from Japan and the British studies of ankylosing spondylitis patients, who received only short-term exposures. Before reviewing these data, the results of other exposures, in particular, those which occurred over long time periods, will be summarized. These results come from Thorotrast patients, from other patients given radium-224, from women exposed to radiation to treat gynaecological disorders, from radiation workers and from radium dial painters.

311. Thorotrast (thorium dioxide) is an alpha-emitter that was used from about 1930 through the early 1950s for a variety of diagnostic roentgenographic purposes. Two series of European patients have been followed in detail and have shown an excess of haematopoietic tumours [K16, M25]. In one, involving 3,772 Portuguese, Danish, and German patients [M25], the total cumulative whole-body dose was determined, 30 years after treatment, to have averaged 2.7 Gy following the use of 25 ml of Thorotrast, on average. The first appearance of leukaemias was eight years after treatment, with cases continuing at least to 1978. If, in fact, acute granulocytic leukaemia (AGL) can be induced at all by high-LET radiation, the small number of acute granulocytic leukaemia cases seen in this group of patients may be an indication of cell sterilization having occurred. Conjectures about the dose-response relationship in this and similar instances must be guarded, however, because of the wasted dose and the concentration of the isotopes in bone marrow. The long period of excess risk expression is not inconsistent with the results from single-exposure studies of radiogenic leukaemias, because the emissions in bone-resident nuclides persist indefinitely.

312. In another series of over 5,000 German patients [K16], exposures ranged from 0.5 to 4 Gy after similar Thorotrast dose levels. While the commonest resulting cancers were those in the liver (see paragraph 403), there were 27 leukaemias instead of the two that would be expected. The shortest time to appearance of leukaemia was five years. Most of these tumours were reticulosarcomas.

313. The effects of ^{131}I, a beta emitter, used to treat hyperthyroidism, do not appear to include leukaemia [H12, H14].

314. Radiologists who entered their profession between 1920 and 1939, had an increase in leukaemia, but those entering thereafter have shown no effects [C4, M18]. The doses received are difficult to estimate, but probably range from 6 Gy for those entering in the 1920s to 2.4 Gy for those entering in the 1930s. The extended time of exposure did not reduce the risk below that observed after single high-dose, high-dose-rate exposures [M18].

315. Some cases of leukaemia have been found in radium dial painters [C4, P19], but it is not obvious whether there has been a significant excess. Also not yet established is the possibility that these individuals have experienced an excess of myelomas. The data are reviewed in [R10]. One difference between the excess leukaemias associated with ^{232}Th and the apparent absence of leukaemia after exposure to ^{226}Ra and ^{224}Ra may be the length of time that the individual is exposed. The reasons for this difference require further study.

316. Table 25 shows that excess leukaemias were observed in several groups of women treated for benign gynaecologic disorders [W6]. In the benign disease patients, the risk of leukaemia declined as doses to the pelvic marrow increased. In a series from Massachusetts, United States, [B12], the latency period was similar to that in the Japanese survivors and the spondylitics; however, the numbers were quite small.

317. Detailed studies of the projection effects in Japan will be presented in chapter VI of this Annex; however, the T65 data on the Japanese atomic bomb survivors [Life Span Study (LSS)] and the British ankylosing spondylitis patients have been compared as well as analysed jointly [D11], based on the data described in [K7, S31]. The relative risks for leukaemia are given in Table 30. In both studies, the first manifestation of excess risk occurred within five years after exposure; the relative risk rose thereafter, and persists for at least 40 years [S49].

318. If one eliminates those survivors under 15 years of age at the time of the bombings and focuses on the risk within the first 20 years after exposure, the relative risk in the spondylitics (3.37) is much less than that in the Life Span Study group (13.50). Darby et al. [D11, D20] showed that in this restricted subset there was no trend in relative risk with age at exposure, in either group. There was no evidence in either study for an increase in chronic lymphatic leukaemia. There was no significant difference in relative risk between males and females in either study.

319. Age-specific relative risk models were fitted by Darby et al. [D11, D20]. For both groups of exposed individuals, the best model had the relative risk declining with time since exposure. In Japan, an age-at-exposure effect occurred, but it was due solely to the presence of individuals under 15 years old at the time of the bombing. The rate at which relative risks for acute leukaemias declined with time since exposure was a function of age at exposure, but the limited data on chronic leukaemias do not support such a difference. Figure III shows that there is a sensitive period for exposure under age 10, after which relative risk is roughly constant.

320. In Muirhead and Darby's analysis of model fitting to cancer data [M36, M37], in which the ankylosing spondylitis and Hiroshima data were studied separately, the constant relative (but not the constant additive) risk model was found consistent with the ankylosing spondylitis data; however, the constant additive (but not the constant relative) risk model provided a satisfactory fit for the Japanese data. Intermediate models provided somewhat better fits to both series, although not statistically significant, but the best-fitting parameter values for those models were markedly different for the two sets of data.

321. There are dose-response data of a general kind for women irradiated for benign or malignant gynaecologic conditions [W6]. Table 31 provides relative risks of leukaemia as a function of total pelvic marrow dose and mean marrow dose from several studies. In support of the cell-killing argument, raised earlier to explain the level of leukaemias in cervical cancer patients, it appears from these data that higher local doses are associated with lower relative risks of leukaemia.

322. Figures II and V provide a graphic summary of the relationship between single doses (or short-term exposures) and leukaemogenesis; Figure V has been used frequently to summarize the leukaemia findings in Japan. It is based only on the Japanese data [I7]

and on earlier dose estimates. The pattern has persisted in recent reports from Japan [O3, P6], but a thorough analysis of the revised dose estimates (DS86) is not yet available. For all acute leukaemias pooled, there is a distribution of excess cases which is a function of age at time of exposure. The younger the age at exposure, the shorter the latency. These patterns have been fitted empirically to a log-normal distribution.
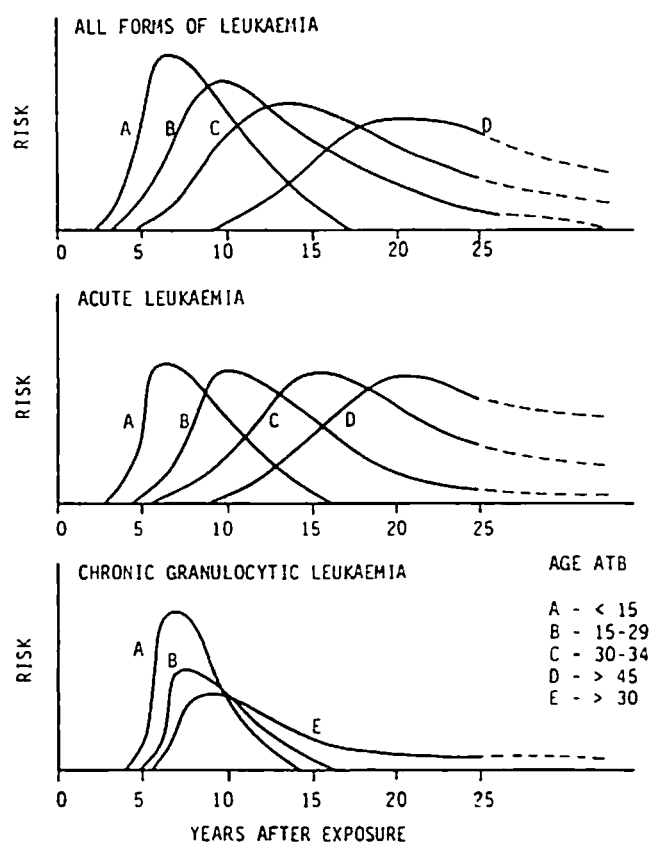
Figure V. Schematic representation of the relationship between age at the time of the bombings and time of occurrence of leukaemia in Japanese atomic bomb survivors receiving more than 1 Gy.
[I7]

323. Figure V shows that for chronic granulocytic leukaemia, there is less variation, with age at exposure, in the projection pattern following radiation exposure [I4, I5, I6]. Excess risk virtually disappears after about 20 years [O3, P6]. As with acute leukaemias, a log-normal distribution adequately fits the chronic granulocytic leukaemia data. Chronic and acute leukaemias may have a similar pathobiology, but they differ in the absolute effects produced by a given exposure level, so that the two types of tumour should not be considered jointly. The most recent data from Japan suggest that there may be some residual excess risk, even 40 years after exposure [S49].

324. Figure VI provides a different view of the T65 Japanese data, comparing them with the relative risk for leukaemia in the spondylitics from Darby et al. [D11]. Two variables were modelled, age at exposure and time since exposure. Interaction between these is modelled by standardizing each in terms of the other. The figure shows no apparent trends in susceptibility

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ANKYLOSING SPONDYLITIS SERIES

——— All types of leukaemia

LIFE SPAN STUDY SAMPLE

(above 1 Gy / 0-0.09 Gy)

——— All types of leukaemia
········ Acute leukaemia
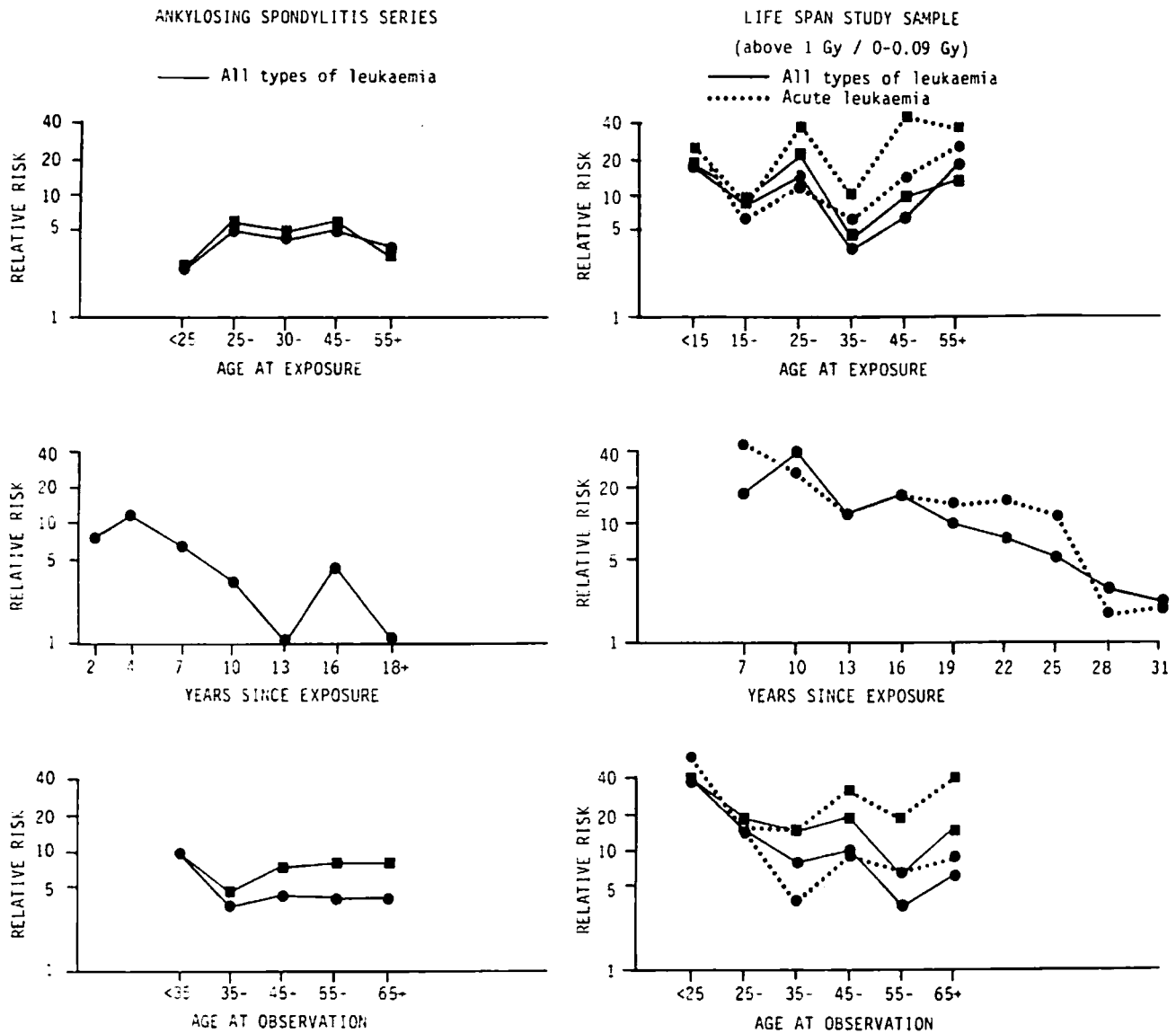
Figure VI.   Relative risk of leukaemia in relation to age at exposure, time since exposure, and age at observation for the ankylosing spondylitis series and for the Life Span Study sample (T65DR doses). Lines marked with circles are for unadjusted data. Lines marked with squares are adjusted by including a linear trend in log (relative risk) with time since exposure in the model. For the plotted points, time since exposure has been chosen so that the initial point coincides with the unadjusted value.

[D11]

(RR) with age at exposure, other than the excess susceptibility in those under age 15 (children) in Japan, discussed above. Darby et al. found evidence of a linear trend in log RR with time since exposure, so the data were analysed both including and not including this trend (see figure). In neither series was there evidence that the rate at which the excess risk declined with time since exposure was a function of age at exposure.

325.   Relative risk is higher in the Life Span Series, even after eliminating childhood exposures; this could be due to cell-killing in the spondylitics or to the effective amount of marrow exposed. The difference between acute and other leukaemias can be seen in Figure VI; when adjusted for a trend in time since exposure, the pattern of relative risk for acute leukaemias differs substantially from the unadjusted pattern. The most recent spondylitis data [D21] show that leukaemia excess RR does not disappear completely by 25 years after exposure.

326.   It should be kept in mind that the point of reference for the discussion in this section is the exposure of non-cancer patients in view of the possibility that cancer patients are more cancer-prone than the population at large. Indeed, the regular pattern of effects seen in non-cancer patients is less perceptible in patients treated for cancer. In particular, individuals irradiated for leukaemias and lymphomas have not consistently manifested leukaemia as a second radiogenic cancer [G3].

327.   *Multiple myeloma.* Multiple myeloma remains one of the most enigmatic candidates for the list of radiation-induced malignancies. The Japanese atomic bomb survivors have been studied in regard to multiple myeloma by Ichimaru and colleagues [H5, I2]. Data were based on 29 cases occurring in the period 1950-1976. The age-standardized relative risk increased with absorbed dose in the bone marrow, with no differences between cities or sexes. Based on the T65 doses, the excess risk estimate is 0.48 cases per

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10^4 PYGy. As in other series, latency is 15-25 years, with a long-lasting period of excess risk (at least 30 years). A longer latency after younger ages at exposure follows a carcinoma-like pattern. The spontaneous incidence of multiple myeloma increases with about the 5-6th power of age, which is similar to the behaviour seen for carcinomas.

328. Darby et al. [D11, D20] found evidence of elevated myeloma risk in their combined analysis. An increase in risk has also occurred among radiologists who entered their profession since 1940 [M18], and the Hanford radiation workers, as well as other exposed cohorts, appear to have experienced a small excess of multiple myelomas [C10, G12, H16].

329. Many chronically exposed occupational groups were reviewed by Cuzick [C10]: nuclear workers, radium dial painters, uranium millers and miners and radiologists. The overall relative risk is between 1.4 and 2.9. Multiple myeloma was also more common in radiation workers in the United Kingdom, based on a recent study of the Sellafield nuclear workers [S54], though not in another of the employees of the United Kingdom Atomic Energy Authority [B22].

330. Cuzick [C10] reviewed the effects of diagnostic and therapeutic exposures on the induction of multiple myeloma. The exposed groups included Thorotrast patients, spondylitics, and groups exposed during fluoroscopy or for treatment of gynaecologic disorders. Results were similar: although many studies yielded confidence limits that included a value of 1.0, there was, overall, a small increase in the relative risk, about 1.6 (range 1.1-3.3).

331. Cuzick also assessed the relative risk according to type of radiation to determine if the effects of internal alpha-emitters (radium dial painters, Thorotrast patients and nuclear workers) had been different from those of gamma-emitters or x rays (atomic bomb survivors, radiologists, nuclear workers, spondylitics, fluoroscopy patients and gynaecologic therapy patients). His summary is given in Table 32. Uterine cancer patients are an exception to the pattern of excess risk, and for them the risk is higher with high-LET internal emitters than with low-LET sources.

332. The IRSCCP cervical cancer study [B12] found only marginal support for an excess of multiple myeloma; however, the general deficit of leukaemias in this group, attributed to cell sterilization, may be important. Both leukaemias and myeloma are B-cell diseases, as are some cases of chronic lymphocytic leukaemia, which has never appeared to be radiation-related.

(b) Non-dividing tissue

333. Many tissues in adults are composed of cells that do not normally or frequently divide. These include muscle and the neuronal tissue of the brain and central nervous system (CNS). As reviewed earlier, tumours of the central nervous system are known to occur following exposures of the head and neck in children; rhabdomyosarcoma may also occur, rarely, as the second tumour in retinoblastoma or

other childhood cancer patients. However, some of these tissues are still growing in early childhood, and it would be worthwhile to determine whether normally non-dividing tissue is radiosusceptible.

334. In general, spontaneous adult-onset tumours in non-dividing tissue appear to be very infrequent. The most recent comprehensive reviews of radiation carcinogenesis, including the UNSCEAR 1977 Report, have either ignored radiogenic cancer at these sites or judged it to be rare or even absent [B6, C4]. Heavily irradiated parts of the central nervous system, excluding the brain, in ankylosing spondylitis patients have manifested excess cancer, although this finding is based on only four cases (0.5 expected) in 14,000 patients, two of which may already have been present at the time of irradiation [S28, S31]. The spinal cord is heavily irradiated in such patients. The paper by Smith et al. [S31] appears to be the first substantial report suggesting that these tissues are radiosusceptible. In the atomic bomb survivors, there is a similarly elevated relative risk of cancer associated with heavy irradiation of the spinal cord and nerves [S23], suggesting that the data in the spondylitics may be reliable. The cell type of these cancers was not given [S23, S28, S31].

335. Other individuals who may have received heavy doses to the central nervous system include the radium dial painters, who did not, however, experience an increase in brain tumours [R10]. Swedish patients treated with ^{131}I for hyperthyroidism exhibited only a slight, non-significant excess (cell type not specified) [H14]. Radiation workers, including radiologists, have shown similar results [e.g., M18].

336. A case-control study in Los Angeles, California, United States, of women irradiated for medical and dental diagnostic purposes found a relative risk of 4.0 for all forms of meningiomas after exposure under the age of 20 and of 2.1 for patients irradiated before 1945, both of which values are statistically significant. The majority of tumours arose after age 50. The authors think that there is an early age susceptibility, although these women, albeit aged less than 20, were not all irradiated as children [P18].

337. In sum, many individuals have received irradiation to considerable areas of muscle, nervous, and other connective tissue. The fact that tumours have only rarely arisen in these areas is in general agreement with the requirement that a tissue be mitotic to be radiosusceptible. If it can eventually be shown that radiation induces mitosis, or if these tumours are actually in mitotic cell types (e.g., glial cells), radiation may increase tumours in these tissues proportionately to their natural incidence. However, these tumours are so rare naturally in adults that it is difficult to detect a small increase from the available data.

(c) Dividing non-epithelial tissue

338. While much of the nervous and connective tissue of the body is not normally mitotic in adults, this is not true of all tissues. Notable exceptions are glial cells and the cells involved in the remodelling of

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bone. These divide, at least in response to stress or to demands for repair. As has already been noted, these tissues are radiosusceptible in childhood, and osteosarcomas and neuroblastomas of various kinds are among the most consequential childhood tumours.

339. The data on risk for actively dividing mesenchymal tissue are strongest, and clearest for cancers of the tissues in the periosteum, i.e., osteosarcoma and other bone cancers. Indeed, ionizing radiation is the only well-documented risk factor for such cancers.

340. There are, basically, three different kinds of exposure for which data on bone cancer exist: persons exposed to bone-seeking radionuclides, internally deposited, often of high-LET alpha-emitters; persons exposed to high doses of external irradiation; and adults irradiated to intermediate doses during a single exposure in Hiroshima and Nagasaki. Internal emitters have been of two types, long and short half-life isotopes, with differing epidemiological results.

341. Individuals receiving exposure to bone-seeking internal emitters include watch dial painters whose mastoid and other cranial sinus epithelial linings were exposed to radon decay products and whose bones were exposed to ^{226}Ra and ^{228}Ra and patients who were given radioactive x-ray contrast medium (i.e., Thorotrast). Underground miners, who are exposed to radon gas, have not exhibited an excess of osteosarcomas. There is much literature on this subject from animals (see Annex B of the UNSCEAR 1986 Report) [U1]. Osteoblasts are the most common cells of origin of osteosarcomas. The internal high-LET alpha-emitters, ^{224}Ra and ^{226}Ra, are among the best-documented radiogenic causes of bone cancer. Radium-224, a short-lived isotope, emits radiation on the surface of the bone where the active target cells are located, whereas ^{226}Ra, a long-lived radioisotope, is distributed more evenly throughout the bones, and its emissions are more effectively shielded from these cells.

342. Radiogenic osteosarcomas tend to occur in the same locations of the skeleton in which spontaneous osteosarcomas occur, especially near the epiphyses of rapidly growing long bones; risk is highest in the knee joint and lowest in the vertebrae. Even with high spinal doses, there has been only a single vertebral osteosarcoma in 14,000 ankylosing spondylitis patients [E3]. Bone sarcomas have been observed in individuals first exposed to ^{224}Ra at ages ranging from 2 to 56 years [M22].

343. The effects of exposure to long-lived alpha-emitting radioisotopes is largely known from the experience of the radium dial painters and other individuals totalling about 3,000 in number; this work is summarized in [R10]. An excess of osteosarcomas in various bone and head/sinus carcinomas has been observed; for example, Polednak and his colleagues [P19], in a study of 634 women who worked in the radium dial painting industry from 1915 to 1929, observed 22 deaths from bone cancer where only 0.27 had been expected on the basis of age/time/cause-specific death rates for United States females. Most, if not all, of these cases were probably due to radiation,

since the tumours are otherwise quite rare and the alpha-emitters provided continuous exposures. The excess occurred over an extended time, from seven to 59 years. The radioisotopes ^{226}Ra and ^{228}Ra have long half-lives (1,600 and 6.7 years, respectively) and are removed slowly from the bone. It is not possible to quantify the latency period of these tumours in terms of time after exposure, since the exposure was continuous. In such individuals exposure is not measured in terms of Gy but in terms of Bq, the inferred total systemic activity; however, the total exposure of the bone ranged from about 0.1 to 500 Gy. In 2,135 patients injected with Thorotrast, which contains ^{232}Th, a long-lived alpha-emitter, there were three bone cancers when one had been expected. Tumours of the sinuses of the head in these individuals may be due to the presence, for appreciable amounts of time, of radon gas (^{222}Rn) in the sinuses [e.g., R13].

344. The experience with persons exposed to short-lived alpha-emitters is different, because the exposure can be dated and the dose and dose-response relationship more easily quantified. The most important cohort is a group of 898 German patients given injections of ^{224}Ra to treat ankylosing spondylitis, bone tuberculosis and other diseases [M22]. These individuals experienced an increase in osteosarcomas, with onset from 3.5 to 25 years after the initial injection, which is very similar to the onset observed in radiogenic leukaemias (Figure VII). Such an early onset period contrasts with the continuing occurrence of bone cancer after ^{226}Ra exposure; presumably the shorter half-life makes the ^{224}Ra exposure more like a brief exposure. All ages were affected.

345. The mean dose to these patients was 11.0 Gy in children, administered over 11 months, and 2.05 Gy in adults, over six months. The distribution of induction times was the same in adults as in children. As noted earlier, this is not consistent with causation being a function of the number, or proportion, of actively dividing cells, which should be greater in children.

346. Unlike in groups exposed to radioisotopes having longer half-lives, there have been no sinus (paranasal, mastoid air cells) cancers in this group. This may be due to the fact that the decay products of ^{224}Ra do not include long half-life gases [M22].

347. The BEIR III Committee attempted to summarize the dose-response pattern, and their table of risks is reproduced as Table 33. Original dose-response patterns, developed by Rowland, were modified to remove exponential terms of the form $\exp(-cD)$ because these were numerically close to 1.0 [C4]. Both linear and quadratic forms have been given because it was judged impossible to differentiate confidently among the models based on the available data. For protracted exposure to alpha emissions from ^{224}Ra, Mays and Spiess have estimated 200 bone sarcomas per 10^4 PGy of average skeletal dose. They estimated a ratio of 7.5 for the effective endosteal dose to a given level of average skeletal dose; based on this, the risk coefficient is 27 per 10^4 PGy, as shown in the table [C4, M22]. As most of the risk experienced by the series of patients given ^{224}Ra in the Federal Republic

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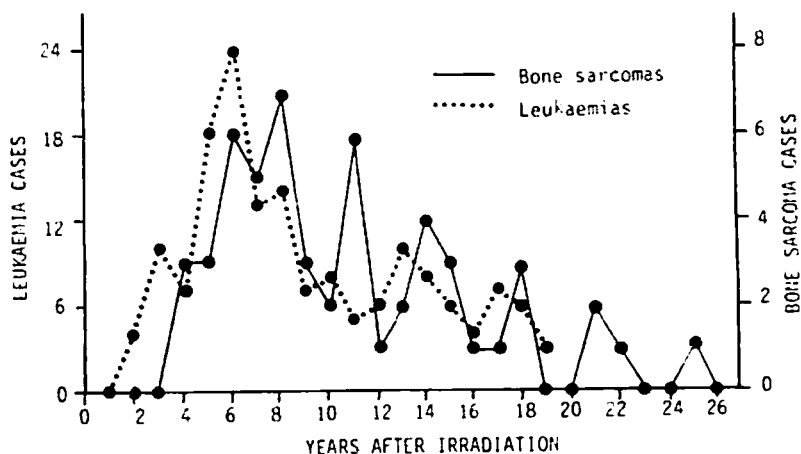
Figure VII. Bone sarcoma incidence in radium-224 patients and leukaemias in the atomic bomb survivors. The distribution of appearance times is remarkably similar for leukaemias, following prompt radiation, and for bone sarcomas, following relatively brief radium-224 irradiation.
[M22]

of Germany seems to have passed, this estimate should be close to the final risk for this series [M22]. Dose-response curves are difficult to compute because of the different types of radiation involved in exposed cohorts, but linearity cannot be excluded [C4].

348. Thomas and McNeill have fitted dose-response patterns for bone and head sinus cancers to a model with cell-killing:

$$RR = (1+bD^c)(0.5)^{D/d}$$

where b, c and d are constants to be evaluated in fitting the model [T11].

349. For bone cancer, these authors developed a relative risk estimate based on data from the watch dial painters and the radium-injected patients in the Federal Republic of Germany. They estimated the absolute excess risk to be 6.4 per 10^3 PY and MBq (2.36 per 10^4 PY and μCi) from exposure to long-lived ^{226}Ra and ^{228}Ra, where PY are counted after a five-year post-initial-exposure latency period and the dose is in terms of systemic intake. For short-lived ^{224}Ra, the estimates are 1.8 cases per 10^4 PYGy for juveniles and 1.0 for adults, measured in terms of skeletal dose. The authors found some evidence for non-linearity and cell-killing. These data are summarized in Figure VIII. The highly curvilinear nature of the dose-effect relationships should be noted when deriving risk coefficients in the low dose range.

350. For head carcinomas the authors used a 10-year minimum latency period and found that a linear model with cell-killing fit the data best. They estimated the risk of additional cancer deaths to be 5.4 per 10^4 PY and MBq (1.98 per 10^5 PY and μCi). The dose-response pattern fitted by them is given in Figure IX.

(d) Epithelial tissue

351. The epithelial tissues form the interactive surface of the respiratory, digestive, genito-urinary and secretory systems. As such, these tissues are the exposure interface between the inside of the body and

the environment. In radiation exposures, unlike many chemical exposures, the protective normal mechanisms, such as buffering layers of mucus, are ineffective. Epithelial tissues are all characterized by layers of stem cells, which normally divide throughout life to produce the differentiated functional cells that are the basis of the organ systems. The number of stem cells, their
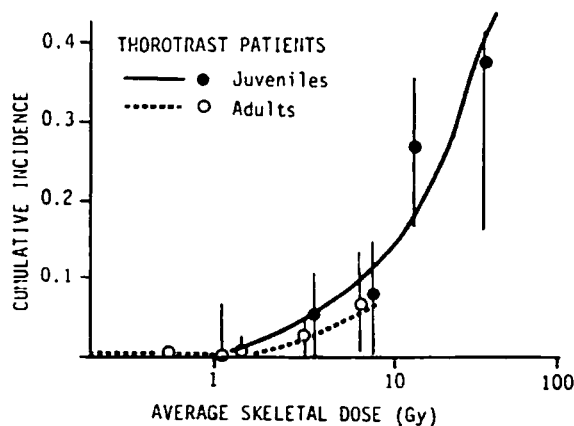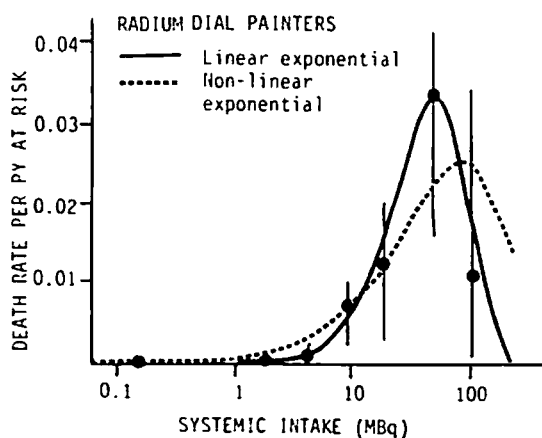
Figure VIII. Bone sarcomas In radium-exposed persons In relation to systemic intake or average skeletal dose.
[T11]

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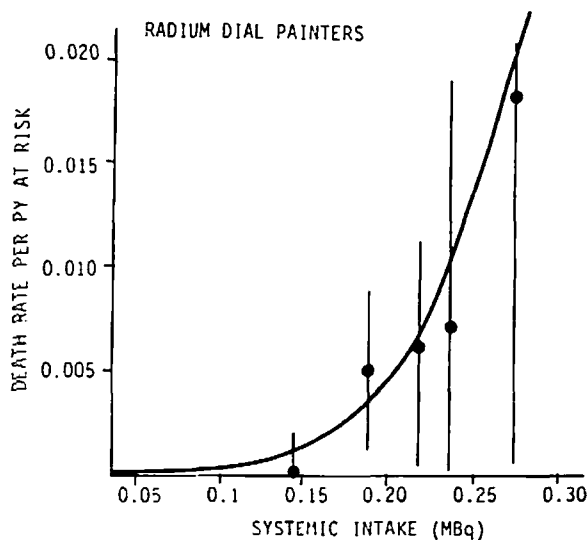
Figure IX. Death rates from head carcinomas in radium dial painters.
[T11]

architecture, turnover rates and metabolism differ for different organs, providing different size targets for radiation. In addition, epithelial tissues may be stimulated to divide or grow by a variety of agents, including hormones, irritation, cell damage and so on. Despite these differences, it would be valuable, from the standpoint of biological knowledge, to determine whether any generalizations can be made about the susceptibility of epithelial tissues.

(i) Skin

352. As a large and widespread epithelial organ, the skin is irradiated during most radiation exposures, yet the data on radiogenic skin cancer are fragmentary and inconclusive. That an effect exists has been known since shortly after the discovery of x rays. However, expected rates are difficult to determine since reporting is unreliable and skin cancers are not usually fatal. Most reports have centred on individual cases rather than on larger populations. The Japanese data reveal no radiation effect, and there are no estimates of risk available from diagnostic or therapeutic thoracic exposures. Occasional studies report excess cases, but the doses have usually been over 10 Gy.

353. The relative risk of skin cancer for radiologists in the United States has been between 2.4 and 3.3 over the past 65 years [M18]. Exposures have varied greatly over this period. In a series of about 2,200 children irradiated for tinea capitis, the relative risk was 7.1 [C4, S16, S27], and a relative risk of 5.4 was found in children who were thymus-irradiated [H1, C4]. Other studies of skin cancer following various types of radiotherapy have found similar results.

354. Table 34 provides data on the relative risk of skin cancer among whites exposed to treat tinea capitis, in terms of age at exposure and time since exposure [C4]. The expected numbers of cases were derived from national data from the United States; given the unreliability of such data for skin cancer, the excess could be attributable to closer follow-up or

other biases. However, trend analyses with respect to both age and time since exposure are significant at $p < 0.0001$ [C4]. Tumours arose in irradiated areas of the scalp in 41 of the 2,200 irradiated children, many of whom had multiple lesions, but in only three controls [S27].

355. A study of Czechoslovakian uranium miners has shown a relative risk of about 4.6 for skin cancers, primarily basal cell cancer of the face; alpha-radiation doses are estimated to have been about 1 Gy [S30]. However, since alpha penetration to the basal cell layer is doubtful, this finding is not universally accepted [R7]. A recent study of six groups of Czechoslovakian miners, updating the earlier data, has again confirmed an excess of basal cell carcinoma of the skin in uranium (but not in coal) miners [S51].

356. A total of 6,405 patients treated for benign diseases of the head and neck in the Netherlands were ascertained 19 to 48 years after treatment. Thirty skin tumours in 21 patients were diagnosed, and a dose-effect relationship of 40 carcinomas per 10^4 PYGy was estimated [V4].

357. Dose-response patterns have not been accurately estimable for radiogenic skin cancer. If any conclusion is warranted, it is that the skin is susceptible to radiation, but that excess cases are not common, especially at doses of less than 5-10 Gy. There is no apparent plateau after which risk subsides. Since skin cancer is rarely fatal, is often not reported and is associated with exposure to sunlight [S27] and other factors, it is difficult to generalize about the latency period. In the tinea capitis series, the latency appeared to be 20 years or more [S27], and the risk persisted for at least 45 years ([C4]; see also [V4]).

358. Doses in the tinea capitis series were 3-6 Gy [S27]. From the tinea capitis and the thymus-irradiated children, the BEIR III Committee estimated risk to be 1.02 and 0.44 excess cases per 10^4 PYGy, respectively [C4]. However, several chest-fluoroscopy studies have reported fewer cases than these estimates predict. This deficit may suggest a non-linear pattern, e.g., a threshold, but satisfactory or comprehensive risk estimates for radiogenic skin cancer do not currently exist.

359. In a study of the "soft" x-rays (Grenz, or Bucky, rays) used in Sweden to treat a variety of dermatological conditions in 14,237 patients from 1949 to 1975, Lindelof [L15, L17] found a RR of 1.45, significant at the 5% level, of non-melanotic skin cancer. Malignant melanoma was not elevated (RR = 1.07).

(ii) Breast

360. In this century, large numbers of women have received irradiation to the chest to treat a variety of medical conditions. Among these are chest fluoroscopy administered to follow the progress of artificial pneumothorax treatment, radiotherapy for various non-malignant breast disorders, including post-partum mastitis, and the radiation received by the atomic bomb survivors.

361. Although there are difficulties in estimating doses and in other aspects of these studies, risk appears consistently to increase with increasing dose and to decrease with increasing age. The bulk of the information suggests that the dose-response pattern is linear, although one Canadian fluoroscopy series has obtained a better fit with a quadratic model [H6]. Radiogenic breast cancers occur at the same ages at which breast cancers occur naturally; elevated risk appears to persist throughout life, after an initial latency period. Latency is rather long (> 10 years); it may also vary, being an inverse function of age at exposure. In general, cases of exposure at post-menopausal ages have not been studied in numbers sufficient to allow a reliable assessment of effects, and there may be a decreased susceptibility with increasing age [T14]. However, exposed Japanese of this age have a relative risk of 3.1 [L6, T6, T14]. The possibility of a cohort effect, associated with the increase in breast cancer in Japan since 1945, should be considered. As discussed earlier, it has now been shown that exposure at ages below 10 leads to a substantial risk of breast cancer.

362. The details of the relative risk of breast cancer from incidence data collected in Hiroshima and Nagasaki for the period 1950-1980 are summarized in Table 35 [T14]. A trend of increasing susceptibility with decreasing age, within a given dose level, can be seen. Figure X shows the decrease in relative risk with increasing age at exposure, for the 0-0.09 and the 0.5+ Gy (T65) groups [T14].

363. The Japanese results can be compared with those of two other studies from the United States, a Massachusetts tuberculosis fluoroscopy and a Rochester series of post-partum mastitis patients [B2, C4, L6, S47]. Howe has also reported fluoroscopy data from most provinces in Canada [H6]. Total relative risks, for doses from 1 to 4 Gy, are consistently between 2 and 3, with values of 4-6 for those exposed at younger ages. At doses higher than 4 Gy, most studies have only small samples; however, the largest of these has found a relative risk of 14.6 at high doses [H6]. Incidence data from Japan suggest a corresponding relative risk of about 4 [W5], indicating perhaps that survival from breast cancer depresses the true relative

risk estimated from mortality data. Relative risk data from these four study populations are summarized in Table 36. Table 37 provides details on relative, as well as absolute, risk differences for three of the major investigations, subdivided according to age at observation and age at exposure; the similarities in the different data sets can be seen.

364. A recent case-control study of breast cancer following irradiation to treat tuberculosis in Denmark has found no significant increase [S53]. While the study was too small to rule out an effect, it was large enough to confirm that other studies in the literature are not underestimating the risk. A similar negative result, and interpretation, has also been reported by Davis et al. [D27] based on a study in Massachusetts. Doses were smaller than in other series (0.66 Gy) and the average age at exposure higher (28) than in other studies.

365. Acute post-partum mastitis patients have now been followed for up to 45 years, with an average follow-up time of 29 years [S47]. Relative to controls and female siblings of patients, the RR value for breast cancer in the irradiated breast, age- and interval-adjusted, is 3.2 (90% CI: 2.3-4.3). The risk increased by 40% per Gy with an essentially linear dose-response except for a diminution at doses above 7 Gy, with no fractionation effect. A multiplicative projection model was a better fit than an additive one, and the RR did not change with time since exposure.

366. The absolute risk in Japan has been estimated to be between 3.0 and 4.0 ± 0.7 cases per 10^4 PYGy, with a pattern that is roughly linear and no inter-city difference [T9, T14]. Risk coefficients in the various fluoroscopy and mastitis series range from 6 to 8.5 cases per 10^4 PYGy [C4]. As previously noted, with the exception of the Nova Scotia series, these data are consistent with a linear dose-response pattern (see Figure XI and Table 38). The New York mastitis data for uni-lateral breast exposure suggest that doses of 4-14 Gy have a cell-killing effect [B2, C4, L6]. However, for bilateral breast exposure, even at higher doses (in some instances tens of Gy) no downturn in the dose-response curve was observed. The fluoroscopy series, especially in Nova Scotia, were highly frac-
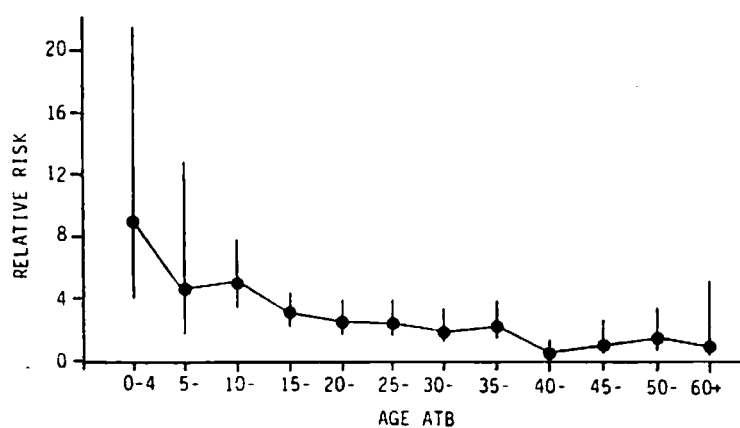
Figure X. Relative risk of breast cancer in atomic bomb survivors for the 0.5 or more Gy relative to the 0-0.09 Gy dose group (T65DR kerma doses).
[T14]
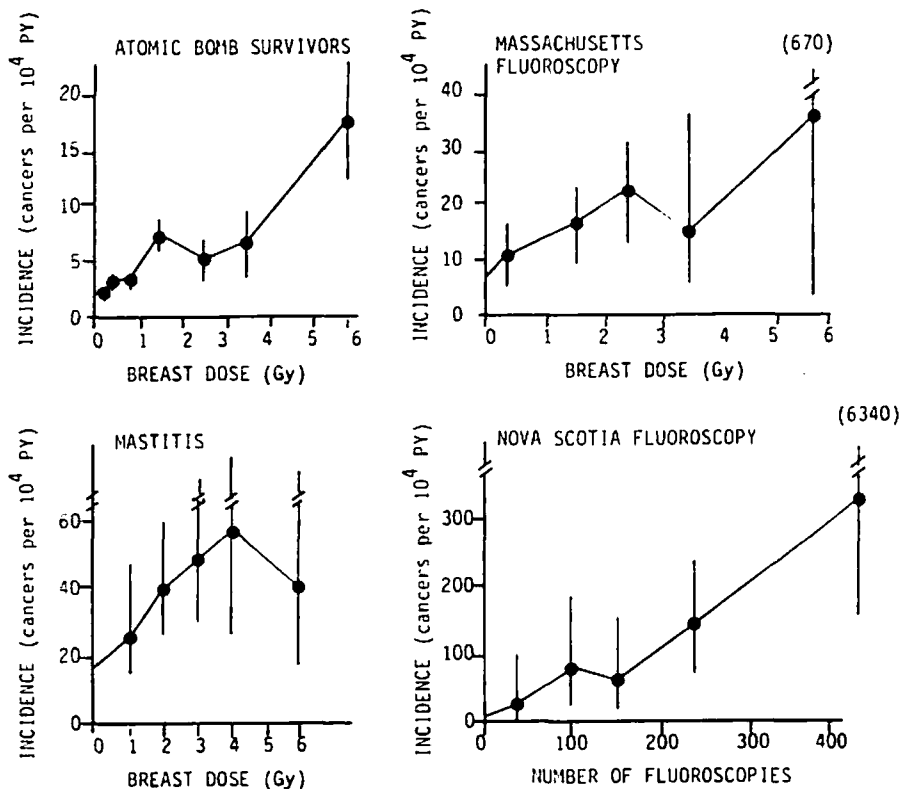
Figure XI. Breast cancer incidence in relation to radiation dose in atomic bomb survivors (T65DR doses), mastitis patients, and fluoroscopic studies in Massachusetts and Nova Scotia.
[B2]

tionated, and this may make a difference at high doses. Mastitis may also have its own biological relationship to breast cancer after irradiation [L6].

367. Besides the slight indication of non-linearity at high doses in [S47], the other exception to a simple linear model is from a record-linkage study of data from nearly all of Canada. A pure quadratic model appears to fit these data best, though a linear-quadratic model fits almost equally well [H6]. The departure from linearity is evident in the lower response per unit dose of women in the Canadian provinces other than Nova Scotia, where the doses ranged up to much higher values [H6]. In Nova Scotia, the patients were examined in the anterior-posterior position (facing the x-ray tube) whereas in the other provinces the patients were mainly examined in the reverse position, resulting in doses per fraction about 20 times smaller. The absolute risk on a linear basis in the range 0-2 Gy, which contains the major fraction of the cancer cases, appears to be about three times smaller for those provinces than for Nova Scotia alone. Based on the evident lack of excess cancer for the lower dose range (0 to 0.99 Gy) in the Canadian study as a whole [H6], this factor would be considerably greater at low doses. This one series contributes the bulk of the data above 4 Gy. Howe argues that because in other instances high-dose information is relatively sparse, and because it is in the high dose range that non-linearity is expected to be most apparent, a linear-quadratic model is the prudent model to adopt in the establishment of breast-cancer dose-response patterns [H6].

368. Two studies have examined the possibilities of synergism between several other risk factors in women irradiated for post-partum mastitis [B30, S37]. These factors include family history of breast cancer, late age of parity, oral contraceptive use, menopausal hormone use and various ovarian-related factors. Women with benign cystic breast disease and those irradiated at the time of their first childbirth were at increased risk, but other women were not.

(iii) Lung

369. Most of the exposures to the breast or chest also involve the lung, and there are several cohorts of individuals who received internal exposures specifically to the lung, principally underground miners who inhaled radioactive radon gas. Exposures to the lung from therapeutic radiation have been experienced by patients with ankylosing spondylitis. These and the other groups have experienced most of the kinds of exposures needed to understand the radiosusceptibility of the lung. In particular, the miners were exposed to moderate doses of high-LET radiation over long time periods, the atomic bomb survivors were exposed to a single dose, and the radiotherapy patients received fractionated, moderate-to-large doses over a short time period.

370. There appear to be no risk differences between males and females, after accounting for the effects of smoking. Most of the available information, however, comes from males; data on both sexes come primarily from Japan and clearly suggest no difference except that which is due to smoking [S49].

371. Relative risks from exposures to brief external x- and gamma-irradiation are 1.2-2.0 [K7, S28, S31, W5]. In the miners, who had variable levels and durations of exposure to inhaled alpha radiation, because relative risks are dose- and duration-dependent and because there may be interaction between the exposures and smoking, this aspect of the data will be discussed in section V.A. The mining data come from uranium miners in Czechoslovakia [S19, S51], the United States [C20, 111, S20] and Canada [C4, G10, H15, M19]; from Swedish metal and Canadian gold miners [A9, D12, E1, M19, R5, R7]; and from a few other reports [C4, R7, T11, T20]. Thorotrast patients were exposed to thoron (^{220}Rn) gas, also an alpha-emitter, as an exhalant; these patients manifest an excess of lung cancer (40 cases vs. 34 expected) after doses ranging from 0.3 to 14 Gy [K16]. The smoking habits of these patients do not differ from those of the general population of the Federal Republic of Germany.

372. Radiogenic lung tumours appear preferentially in the epithelium of the upper bronchial tree, unlike in experimental animals given radioactive inhalants or intratracheal instillation. One mechanism for the upper bronchial effect of natural exposures to radon daughters is the adsorption of the free-ion fraction, that is, ions not bound to dust particles (see Annex G of the UNSCEAR 1977 Report [U2]). Most data suggest that the cell types do not significantly differ from those in non-radiogenic lung cancer [C4, C12, S20].

373. The ages of onset of radiogenic lung cancers are similar in general to those of spontaneous lung cancer; there is little evidence for excess risk before age 35 [C4]. This suggests that the latency period is a function of age at exposure; however, not all of the data are consistent. The minimal latency period has usually been at least 10 years, roughly independent of age at exposure in spondylitis patients and in Swedish [R5] and Canadian miners [C4]. In other mine studies and in the Japanese atomic bomb survivors, latency has been dependent on, and negatively correlated with, age at exposure: early exposure has led to longer latency and, perhaps as a result of increased years at risk or increased years at observation, higher absolute or lifetime excess risks. The data from the United States are not entirely clear. In one study of Colorado miners (where dose rates may have been higher than elsewhere), there was a shorter latency period in exposed smokers than in non-smokers, but doses may have been overestimated due to the way in which exposures were sampled [C4, R5]. Moreover, the follow-up times for individuals initially exposed at younger ages may be insufficient. Excess risk is known to persist for at least 50 years after exposure began.

374. The overall data suggest that the relative biological effectiveness (RBE) of alpha-radiation to the lung relative to gamma-radiation, is 20, although there is much uncertainty in this estimate, largely ascribable to the difficulty of converting data on WLM to absorbed doses in Gy [C4]. A reference conversion is 6 mGy per WLM for mean bronchial dose and usual conditions in mines [111]. This results

in unit risk of 1.0 per 10^6 PY-WLM corresponding to 1.67 per 10^4 PYGy.

375. Thomas and McNeill have fitted the dose-response data to additive and multiplicative models for exposure to alpha-emitting radionuclides [T11, T20]. Results are provided in Table 10. The models fitted were linear cell-killing models of the form (using their notation)

$$R = (a + bD^c)(0.5)^{D/d}$$

where a, b, c and d are the parameters estimated from the dose-response relationship, fitted by weighted least-squares, and R refers to both additive and relative risk (in the case of additive risk, a was set at 0.0, and in the case of relative risk, to 1.0). The second exponential term models cell-killing effects. A linear dose-response is modelled by setting c = 1.0. For details on the justification of this dose-response model, see [T11, T20]. Thomas and McNeill found some evidence of a departure from linearity in the dose-response patterns of the mining data (Figure XII).

376. An extensive analysis of lung cancer in miners exposed to radon daughters has been published, reporting on results from four studies of six miner groups in Czechoslovakia [S51]. The lung cancer rate increased as a function of exposure. Excess risk appeared about 5 years after the onset of exposure, peaked at 20 years, and, though excess persisted, it was no longer significant after 30 years (the approximate limit of follow-up to date in these subjects). Unlike some other studies of miners who began exposure under age 30, there was a detectable excess risk before age 40. However, relative risks were higher with greater age at onset of exposure. The data from the Czechoslovakian uranium miners appear to be essentially complete for group S (miners first exposed between 1948 and 1957) [S51, K28]; the total lifetime risk can thus be calculated directly without the use of a projection model, suggesting an average lifetime risk of approximately 4.5 10^{-4} per WLM. Other findings of importance were: (a) a documented excess of lung cancer at total exposures less than 50 WLM; (b) an approximately additive effect of smoking; and (c) possible evidence for a cell-sterilizing effect at high doses for small cell lung carcinoma, but not for epidermoid cancers.

377. Further data on the Ontario miners have also become available [M40, M42]. These too indicate that the minimum latency period for appearance of excess lung cancers after first exposure to high concentrations of radon daughters is 5 years, not 10 years as previously assumed. This conclusion is substantiated by studies of the Eldorado uranium miners in Canada [H25, H31]. It also appears that excess lung cancers in these uranium miners reached a maximum about 10-15 years after first exposure and decreased towards zero about 20 years after last exposure [K28, M40, S51]. The risk coefficient derived from the Ontario miners study suggests an average lifetime risk of about 1.7 10^{-4} per WLM for miners exposed to 1 WLM per year from age 20 to 55.

378. The range of risk coefficients derived from various studies of uranium miners is very broad but is

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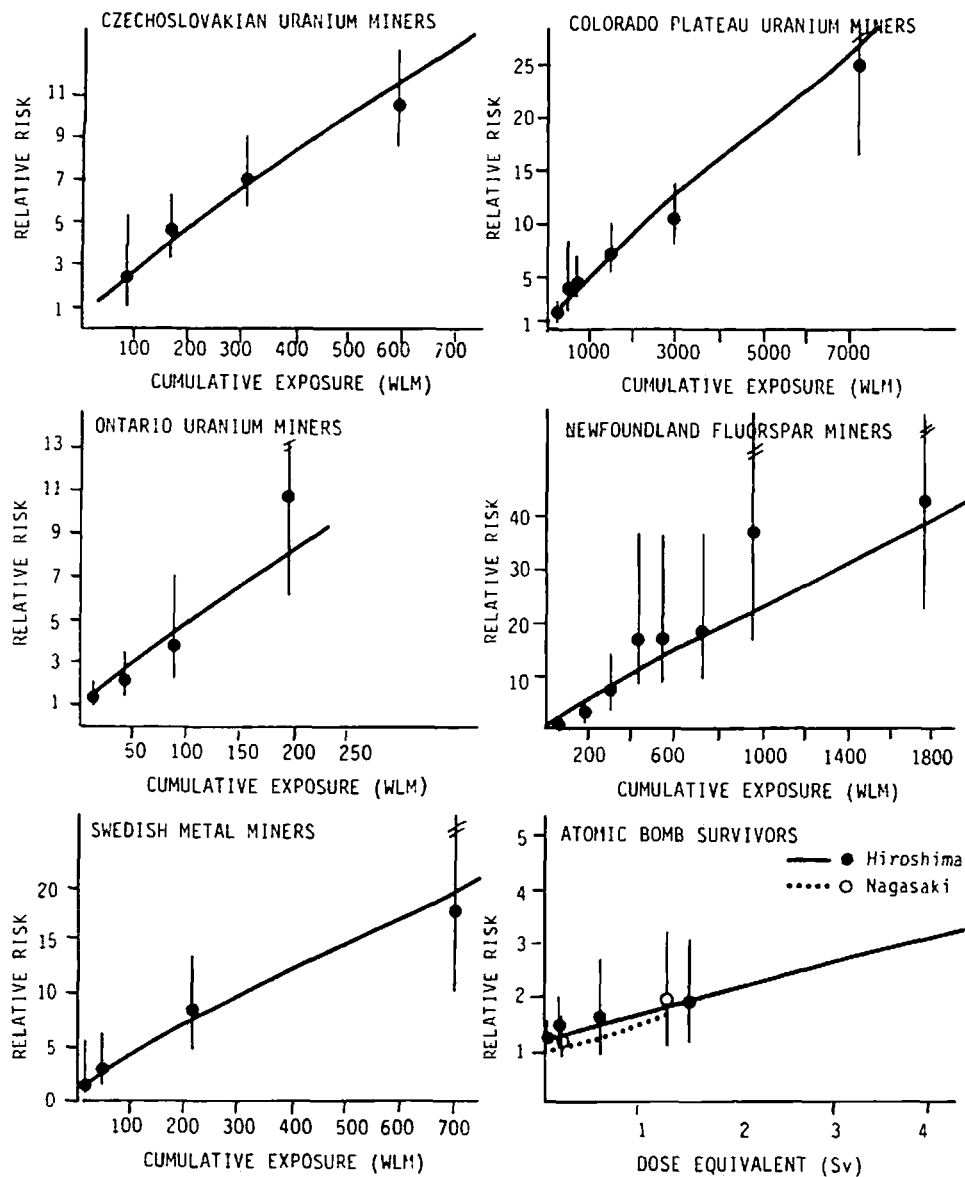
Figure XII. Lung cancer risk in five groups of miners and in atomic bomb survivors (T65DR doses).
[T11]

in general compatible with the central value of about 10 excess cancers per 10^6 PY and WLM (additive risk model) or about a 1% increase in normal incidence (as suggested in ICRP 50) of lung cancer per WLM (multiplicative risk model). When applied to the adult male population of North America, these risk coefficients suggest an average lifetime risk of about 3 10^{-4} per WLM for uranium miners age 20 to 55 at the time of exposure [M40]. Recent data from those studies in which most attention was given to reassess exposure data are compatible with the range of 1.5-4.5 10^{-4} per WLM for adult male miners, as was estimated in ICRP 32.

379. As mentioned briefly in chapter I, in many areas of the world houses have been built with or on materials which contain ^{226}Ra from which radon gas is released into the air of the living space. Exposure to the alpha emissions from the radon daughters is a potential risk factor for lung cancer, as demonstrated in miners, but the risks from exposures in homes have

only recently begun to be estimated. Extensive indoor survey results are becoming available, but there are, as yet, few studies of the lung cancer risks associated with living in such environments for long periods.

380. In an initial study from Sweden, Svensson et al. reported on a case-control study of the association between lung cancer and radon in houses in the area around Stockholm [S52]. Study subjects had lived in the area for 30 years or more. There was a statistically significant relative risk of 2.2 (95% CI: 1.2-4.0), and 4.1% of cases in this group appeared to be attributable to the exposure. There was an indication of a dose-response pattern, with increasing cumulative exposure, as seemed similar to results from miners in the United States and in Czechoslovakia.

381. Other data have not shown an effect of domestic radon daughter exposure on lung cancer. A recent study by Gjorup and Hansen [G20] compared Denmark to Sweden, which has 2.1 times the radon exposure levels

in homes. There was no evidence for an excess of lung cancer in Sweden. Potential differences in other risk factors, such as smoking, were not studied in this report.

382. The ICRP issued in 1987 a summary of the risks associated with exposures to radon [I11]. This study covered the existing literature in detail up to about 1986, and considers many aspects of exposure of the lung to high-LET radiation. Its conclusions and lifetime risk projections are given in chapter VII.

383. The BEIR IV Committee [C20] has recently issued an appraisal of the effects of radon exposure. This report was received too late for review by UNSCEAR, and only a brief Secretariat review is considered here. The BEIR IV Report reviews all of the high-LET data available to it through 1987, for all types of exposure, and provides extensive dose-response modelling and statistical fitting, as well as lifetime risk projections.

384. After reviewing the literature on radon, the BEIR IV Committee considered the best way to obtain a single numerical estimate of the risk from radon exposure is with the following equation:

$$r(a) = r_0(a) [1 + 0.025g(a)(W_1 + 0.5W_2)]$$

where $r(a)$ is the lung cancer mortality rate at age a; $r_0(a)$ is the baseline lung cancer mortality in the United States 1980-1984 population; $g(a)$ is a coefficient equal to 1.2 for ages less than 55 years, 1.0 for ages 55-64 years, and 0.4 for ages 65 years and over; W_1 is the cumulative radiation exposure in WLM from five to 15 years before age a; and W_2 is the cumulative exposure 15 years or more before age a. This is a relative risk model which accounts for age at risk.

385. The BEIR IV Committee [C20] considered only occupational data. On the assumption that the occupational results can be applied to radon exposures in houses, BEIR IV estimated that 1 WLM per year would increase the number of lung cancer deaths in both sexes by a factor of 1.5 with current patterns of cigarette smoking. Occupational exposures to 4 WLM per year from ages 20-40 were estimated to increase the male lung cancer deaths by a factor of 1.6, most of the cases being in smokers. Note, however, that the exposure estimates for two of the studies used for the calculations done by the BEIR IV Committee, notably the Beaverlodge data [H25] and Swedish iron miners [R5], have been questioned by Frost, and Swent and Chambers (see [C20]). It has also been argued that a large part of the difference in risk estimates for the general population is due to differences in the assumed lung cancer rates in the reference populations rather than to differences in the risk coefficients in BEIR IV [C20] and ICRP 50 [I11]. The BEIR IV Committee modelled the smoking data as interacting multiplicatively with radiation, but acknowledged that a sub-multiplicative (but not additive or sub-additive) model was consistent with the existing data.

(iv) Thyroid

386. The best data on thyroid cancer are from children irradiated for a variety of conditions; these

have already been reviewed (paragraphs 206-216). Adults have been treated with radioactive iodine for hyperthyroidism, without showing any documented excess of true thyroid cancer [C4, H12, H14]. In adults as in children, the anaplastic, and highly dangerous, form of thyroid cancer apparently has not occurred following irradiation.

387. A recent report has examined thyroid cancer in adults as well as children exposed to fallout from the Nevada, United States, atomic test site [Z3]. No excess was observed, and it is apparent that very large samples would be required to detect such an excess. The doses received by the Nevada population are in the range 0-1.5 Gy, usually below 0.4 Gy in adults. Based on these and other data, including the risk to the thyroid from external x rays, the authors estimated the absolute excess risk to be between one and four cases per 10^4 PYGy. The BEIR estimate was four carcinomas per 10^4 PYGy, including some occult carcinomas [C4]. There is insufficient information on which to base estimates of the effect of age at exposure.

388. Two reports from Sweden have examined thyroid cancer in adults and to a smaller extent in children following the administration of diagnostic amounts of ^{131}I which delivered doses to the thyroid gland of 0.5-1.5 Gy at dose rates of 2-6 mGy per hour [H27, H28]. In the first and preliminary study [H27] the incidence of thyroid malignancies in about 10,000 patients receiving typical administrations of 2 MBq was compared with the expected number of malignancies computed from the age- and sex-specific incidence in the Swedish Cancer Registry. Eight cases were found in the patients after a follow-up of 17 years compared with 8.3 expected. The authors estimated that an excess of at least 16 would be expected based on risk estimates for adults in the Japanese atomic bomb survivor population (external acute low-LET irradiation). This study was analysed further in a report of the United States National Council on Radiation Protection and Measurements [N5] which concluded that a risk reduction factor of at least 3 was applicable to iodine-131 irradiation compared with high dose rate external irradiation. Another review of this study is contained in the UNSCEAR 1986 Report [U1] which points out several factors which might account for the failure to observe the predicted excess.

389. The above study has recently been expanded [H28] to 35,000 patients receiving diagnostic ^{131}I administrations with a mean absorbed dose of 0.5 Gy, followed for an average of 20 years. Again the incidence of thyroid malignancies was compared with the expectation based on Swedish Cancer Registry data. Record linkage identified 50 thyroid cancers occurring 5 or more years after the initial ^{131}I administration compared to 39.4 expected based on general population rates. Patients who were examined for a suspected thyroid tumour received the highest doses and were at the highest risk. Patients given ^{131}I for other reasons were not at increased risk and neither were those who were observed for 10 years or more. An expected excess of 41 thyroid cancer cases was computed from the age- and sex-specific risk

coefficients estimated by the United States National Institutes of Health, Committee on Radioepidemiologic Tables for external high dose rate irradiation by x or gamma rays [U4]. The authors concluded that the thyroid cancer risk from irradiation of the thyroid gland by ^{131}I might be up to four times lower than with acute external low-LET radiation.

390. An excess of thyroid cancer has occurred in Japan [C4]. The approximate estimate for both cities, based on T65 doses, is 0.92 male and 2.40 female cases per 10^4 PYGy [C4]. Relative risks have been about 4, with the excess appearing 15 years after the bombing and persisting thereafter; whether risk has begun to decline is not certain. Generally, the adult pattern is similar to the pattern in children, with latency and subsequent risk behaving as they do for other adult epithelial tumours. Despite the difference in the absolute risk of spontaneous thyroid cancer between males and females, the 3:1 female to male case ratio is about the same as that in the unexposed population.

391. A recent summary of thyroid cancer risks issued by the National Council of Radiation Protection and Measurements [N5] expressed risk as follows:

$$Risk = R \times F \times S \times A \times Y \times L$$

where R is the absolute risk per 10^4 PYGy for both sexes in ethnically similar populations of children exposed to external x-irradiation after a minimum induction period of five years. For the United States population, based on estimates derived from externally irradiated children, the report [N5] takes this value to be 2.5. F is a dose-effectiveness factor equal to 1.0 for external x- or gamma-irradiation and for [132]I, [133]I and [135]I and equal to 1/3 for ^{131}I and [125]I. S is a sex-correction factor equal to 4/3 for females and 2/3 for males, assuming that females are twice as susceptible as males and that the value R is based on populations comprising equal numbers of males and females. A is an age-susceptibility correction factor equal to 1 for exposure at ages under 18 and 1/2 for exposure at older ages. (If sex-specific R values are used, then S = 1.0). Y is the average number of years of post-exposure risk in the group being evaluated. L is lethality, equal to 0.10, assuming that only 1 case in 10 is lethal (this factor is to be used only when estimating the lifetime deaths due to radiogenic thyroid cancer).

392. The risk can be calculated for any study group using this formula. As an example, Table 39 provides risk estimates for an exposed United States population [N5]. The report of the National Council on Radiation Protection and Measurements compared absolute and relative risk models and found little difference in lifetime estimates. This model was also tested against the Marshallese data, from which direct estimates of risk are not reliable, and it gave an adequate fit [N5].

(v) Other epithelial tissues

393. The literature on lung, breast, and thyroid cancers has been reviewed separately because, of all epithelial cancers, these are the ones for which the best data are available. There are, however, many other epithelial tissues in the body. Data on cancer in these tissues come mainly from three groups of individuals;

namely, the atomic bomb survivors, the ankylosing spondylitis patients and women irradiated for malignant and benign gynaecologic disorders.

394. For many years it had been thought that some organs were relatively insusceptible to radiation carcinogenesis. This notion stemmed from the lack of evidence for a statistically significant excess risk or to the low background risk of the malignancy itself. It now appears that most (indeed, probably all) organs are vulnerable to radiation-induced cancer, given the right conditions of exposure. In Japan, data still do not support an excess risk or dose-response for cancers of the buccal cavity, rectum, pancreas, small intestine, uterus or malignant lymphoma [P15]. These sites may achieve significance as the exposed cohort passes through the years of greatest background risk, since in the last decade several sites not previously thought to be affected have shown a dose-response relationship. In patients irradiated for benign gynaecologic disorders, tumours of the buccal cavity, as well as of the kidney and urinary bladder, have relative risks of about 2, which are comparable to the relative risk in high-exposure Japanese (> 1 Gy) [W5] and in spondylitics (average exposure 2 Gy).

395. In their comparison of the data from Japan and the spondylitis patients, Darby, Nakashima and Kato have suggested that there may no longer be any truly radio-insusceptible epithelial tissues. This opinion is set forth in [D11] and [D20]; the latter contains the data on which the computations were based. Their conclusion was arrived at only when the data from the two groups were combined and analysed jointly, increasing the sample sizes sufficiently to show statistically significant excesses. A summary of the risks based on this joint analysis is given in Table 40. For example, gallbladder cancer was significantly more frequent than expected in the combined series than in either series alone. Darby et al. also described an excess of central nervous system tumours in their combined analysis, but see [P15]. This joint analysis will be referred to in the following paragraphs. However, it should be noted that these estimates, while they are the only joint estimates currently available and the only estimates based on a sample size large enough to detect significance for some sites, are based on obsolete doses and a shorter follow-up than is now available. The estimates have been revised recently, and while no new joint analysis is available, the revisions will not reduce the qualitative evidence for excess risk at the sites reported by Darby et al.

396. In addition to the cervical cancer patients, several other cohorts totalling about 14,000 women exposed to pelvic irradiation for a variety of benign gynaecologic conditions have been followed [B6, C4, S3, W6]. While these women add information on epithelial sites, they also pose further questions and uncertainties. Relative risk data for them were presented in Table 25. Both radium and x-ray treatments were involved [B12, D9], and the exposures were external, low-LET (x ray) and internal, high-LET [W6]. Doses ordinarily ranged from 20 to 70 Gy, given in fractions of a few Gy over periods of 4-8 weeks [B12].

397. In women treated for benign disorders, uterine sarcomas were increased about eightfold and female genital and urinary organ tumours about twofold. Exposure to radiation may lead to relatively advanced, aggressive uterine tumours when the original reason for pelvic irradiation is to treat a malignant, rather than a benign, condition [M35]. An elevated risk of uterine sarcomas was seen in one ovarian cancer series [R11] but not in another [C8] nor in the cervical cancer series [B12].

398. The joint analysis of the Japanese data and the spondylitis data [D11, D20] (see Table 40), serves to summarize the available literature on a variety of exposed sites. A multiplicative projection model describes the combined data reasonably well. Age-specific relative risk is roughly constant as a function of age once the latency time is over. For heavily irradiated sites, both sets of data show a positive correlation between the excess risk and the baseline prevalence of the tumour (Figure XIII). This correlation suggests that radiation magnifies processes already at work multiplicatively.

399. In their analysis of the Life Span Study data for the years 1950-1978, Kato and Schull [K7] concluded that the mortality experience of this cohort supported a relative risk model more strongly than the additive one. This assessment has been further supported by the more formal adoption of the relative risk model in the Life Span Study Reports 10 and 11 [P15, S49]. Muirhead and Darby reached similar conclusions [M36, M37]. The excess deaths from all cancers other than leukaemia and bone cancer increase with age at death for the same age cohort in proportion to the age-specific death rate from cancers in the population of all Japan and do not show a constant excess value by age at death for the same age cohort, as predicted by the absolute risk model.

400. Darby et al. also examined the post-exposure risk for a pooled series of selected epithelial sites for which data are available from both the spondylitis series and the > 1 Gy group in Japan [D11, D20]. These sites, which the authors referred to as "selected sites", include the pharynx, oesophagus, stomach, pancreas, larynx, lung, ovaries, skin, and bones. They

EXCESS RISK

LIFE SPAN STUDY SAMPLE (above 1 Gy / 0-0.09 Gy)

RELATIVE RISK

LIFE SPAN STUDY SAMPLE (above 1 Gy / 0-0.09 Gy)

ANKYLOSING SPONDYLITIS SERIES
(Leukaemia and cancers of
heavily irradiated sites only)

ANKYLOSING SPONDYLITIS SERIES
(Leukaemia and cancers of
heavily irradiated sites only)
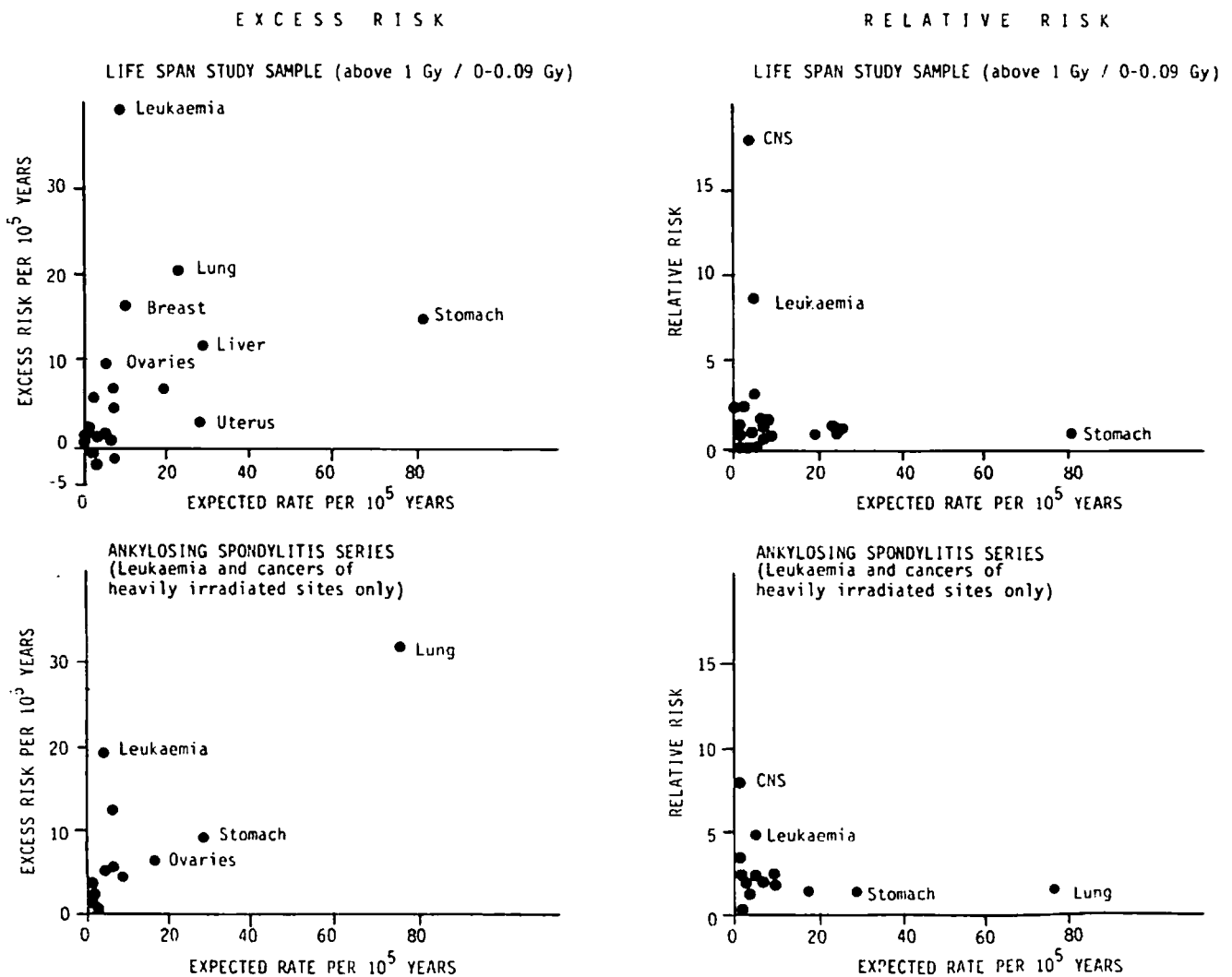
Figure XIII. Excess and relative risks of cancers in the Life Span Study sample (T65DR doses) and in the ankylosing spondylitis series for various cancer sites compared to expected population incidence rates.
[D11]

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also found that the relative risk model describes the data on the pooled sites.

401. However, the latest report from the ankylosing spondylitis series [D21] differs somewhat from the other data in regard to epithelial cancers other than colon cancer. The authors have found that 25 years after irradiation, the RR values return approximately to normal, contrary to the essentially permanent effect seen in other studies. Age at irradiation did not significantly affect the subsequent relative risk for these tumour sites (no patients where such an effect has been seen were under age 15).

402. The relative risk is higher in females than males in Japan for many epithelial sites (it is lower for leukaemia). This is shown in Table 41, taken from Life Span Study 10 (T65). For oesophageal and lung cancer, the difference is probably due to different smoking habits.

403. Because differences have appeared between the Japanese and spondylitis study, and the doses have been revised, one must interpret the parallel analysis of Darby et al. with caution. However, the new data seem unlikely to change the support for the relative as opposed to the absolute risk model for excess solid cancer risk, even if the relative risk is found to be a function of sex, age at exposure, and time since exposure, as suggested by Muirhead and Darby [M36, M37]. Similarly, Darby et al. used pooled data to demonstrate excess cancer risk at many sites for which an excess could not be documented in either study alone. This is probably a reliable indicator that those sites are susceptible to cancer from exposures to ionizing radiation.

404. In analysing the available data on these epithelial tumour sites, especially those of the digestive system, a variety of observations are worth summarizing.

405. *Digestive system.* Little data exist on salivary gland tumours from Japan and the spondylitis series, partly because of the low exposure levels. However, from the essentially consistent results of eight studies of medical therapeutic exposures, Land [L11] estimates that the absolute risk of salivary gland tumours is 0.26 ± 0.06 cases per 10^4 PYGy after the first five years post-exposure, with little evidence of an association between response and age at exposure. The data are summarized in Table 42. Most of these exposures are in children, including two tinea capitis series [M13, S16], and head and neck exposures in five studies [H1, J4, M11, S15, S40], or in middle-aged women treated with radioactive iodine [H21]. In the Japanese data, dose estimation is complex, but the risk is estimated as 0.056 ± 0.036 per 10^4 PYGy for malignant salivary gland tumours and 0.063 ± 0.035 per 10^4 PYGy for benign ones [O4, T15]. Recent data have established the existence of a dose response for oesophageal cancer and for stomach cancer, but it is still difficult to obtain accurate estimates of the lower bounds of the effects [O3].

406. No single data set supports an excess for gallbladder cancer; the main risk factor for this very rare tumour is gallstones, which are relatively rare (but becoming more common) in Japan and more common in women. Most of the spondylitics were men; the gallbladder was given little dose in the cervical cancer patients. There is little statistical power in the available data, although the recent report [P15] from Japan estimated a small effect (relative risk at 1 Gy about 1.15).

407. The pancreas seems to be of uncertain susceptibility [L11]. Risk cannot be assessed from the available data, and expected rates are complicated by problems in late and sometimes difficult histologic diagnosis. In many countries pancreatic cancer is a common cancer, and one might therefore expect the evidence to be more clear-cut; this is not the case at present.

408. Cancer of the small intestine is generally rare, and it is still difficult to know if there is a radiogenic effect. The data come mainly from some cervical cancer patients, but, as noted earlier, both irradiated and non-irradiated subjects had similar excesses. Colon cancer has already been discussed in the context of the cervical cancer patients, where inconsistent results were obtained. In Japan, mortality data show an increase in the Life Span Study sample using the T65 doses [K7, P15] and the new DS86 doses [S48]. Only a non-significant increase was reported in the spondylitics; however, a possible association between spondylitis and ulcerative colitis casts doubt on that result [D11]. Rectal cancer seems to be a consequence of exposure to ionizing radiation, but a dose-response pattern is not estimable and the dose may need to be more than 1 Gy to produce a detectable effect.

409. *Genito-urinary system.* The mortality data from Japan still do not support a dose effect for uterine or uterine cervix cancer, and the evidence comes almost exclusively from those women irradiated for gynaecologic disorders. The only evidence of the inducibility of prostate cancer comes from the Nagasaki Tumour Registry; considering all cases, including those discovered only at autopsy, the absolute risk is 2.1 cases per 10^4 PYGy based on a linear model [L11, W5]. This has not been confirmed, at least as yet, in the mortality data [S48]. Prostate cancer is a disease of advancing age, and most cases are not discovered clinically and would not be reflected in mortality data. Land speculates that a small radiogenic risk would be even less detectable in the much higher background prostate cancer rate in Europeans and North Americans [L11].

410. A recent study in Japan [T21] has shown a statistically significant dose-response pattern for both malignant and benign neoplasms of the ovary, with a latency period of at least 15-20 years.

(vi) Liver

411. Somewhat more detail is available for liver cancer after radiation exposure. The liver had been regarded as being relatively radio-insusceptible. However, the Japanese data have now revealed a slight increase in liver cancer, when "not otherwise specified" cases are included [P15, S49]. It bears mentioning that the liver is a common site of metastasis for other radiation-induced cancers, e.g., those of the lung, stomach and breast, and that death certificates will

commonly fail to distinguish between a primary and a secondary malignancy, particularly in the absence of supportive pathological information. The increasing use of radioisotopes for diagnostic liver scans or other radiotherapeutic purposes makes more data available and also underscores the importance of a better knowledge of the liver's susceptibility. The best data come from the Thorotrast patients (indeed, Thorotrast use was stopped in about 1955, when its liver carcinogenicity was discovered [M26]). Most cancers caused by this agent are bile duct carcinomas, hepatocellular carcinomas or angiosarcomas [C4].

412. Thorotrast data are reviewed in [C4], and details specifically from the Federal Republic of Germany series are in [K16]. The average dose to the liver from the 25 ml of alpha-emitting substance injected was about 0.25 Gy per year; about 65% of the amount injected was deposited in the liver. From these exposures, the risk estimate was about 300 liver cancers per 10^4 PGy [C4], projecting cumulative risk to the lifetime of the exposed cohort of individuals. For an average of 23 years at risk beyond the first 10 years in this group, the estimated risk rate coefficient was 13 liver cancers per 10^4 PYGy. Complicating this assessment were the conceivable effects of Thorotrast toxicity, on the one hand, and radiation-produced cell sterilization, on the other. Tumours began to appear about 10 years after initial exposure, and the period of elevated risk may have extended beyond 40 years [K16].

413. The cumulative incidence of liver tumours in the Federal Republic of Germany series is presented in Figure XIV, for different liver dose rates measured by x-ray film and whole-body counter assessment. Because deposited radioisotopes can be visualized and quantified on x-ray film, the dose-response pattern has been estimated for liver cancer. Risk as a function of time since exposure rises more steeply in the more heavily exposed [K16].

414. Data are also available from Japanese military patients treated with Thorotrast to diagnose war injuries [M29, M31]. In these patients the risk for hepatic cancer was 40.0 relative to a military control group and 22.2 relative to population-based controls; the relative risk in both cases was 1.3 (not significant) for other tumours, which included a variety of sites. After 35-43 years, there have been 50 hepatic tumours in 254 subjects, a cumulative incidence of 19.2%. Based on autopsies from these individuals, the mean dose rate for the individuals with hepatic cancer was estimated to have been 0.29 Gy per year, low-LET equivalent, with a mean total dose of about 9.20 Gy [K18] of this high-LET exposure, after a mean 36.1-year latency period.

415. Other individuals have been exposed to alpha-emitters deposited in the liver, particularly ^{239}Pu, in the case of nuclear workers. The available data do not show an effect but are compatible with an effect no greater than 10 times that of Thorotrast [C4].

5. Occupationally exposed adults

416. As was noted earlier, studies of the effects of ionizing radiation on adults exposed in the course of their employment or military service have focused largely on radium dial painters and radiologists in the United States and the United Kingdom or on individuals engaged in nuclear weapons research and fabrication, in the activities of nuclear power stations, in the maintenance and outfitting of nuclear-powered naval vessels, primarily submarines, or in nuclear weapons tests. The findings on the radium dial painters and radiologists have been described elsewhere in this document; this section summarizes the findings of one large case-control study of radiological technicians [J5] and of the other studies of occupational, including military-service-related, exposure.
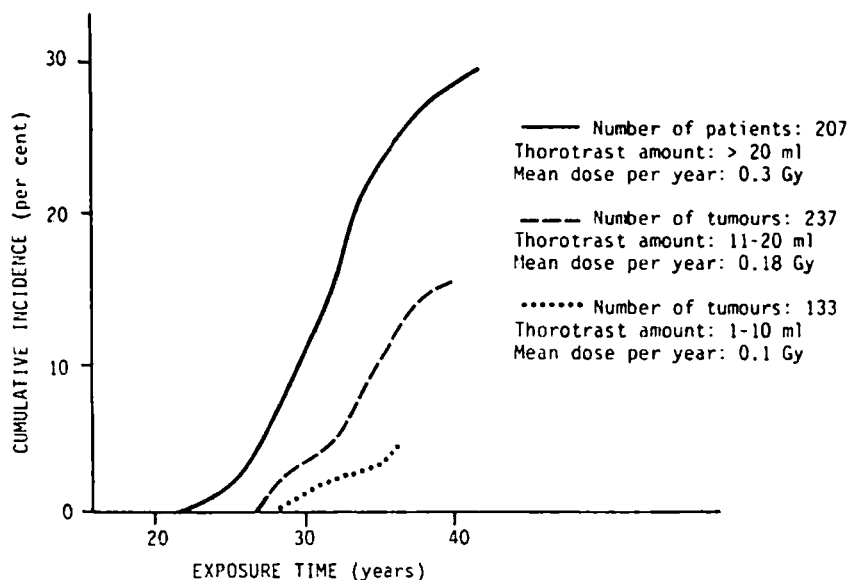
Figure XIV. Cumulative incidence of liver tumours in Thorotrast patients.
[K16]

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417. Jablon and Miller [J5], in a study of 6,560 radiology technicians in the United States Army in the Second World War, found no statistically significant differences between them and a control group (6,826 medical, laboratory and pharmacy technologists) with respect to the frequency of individual sites of cancer or deaths from other causes. More specifically, for 174,500 PY of risk, they observed 12 leukaemia deaths (including one case of chronic lymphocytic leukaemia) among the radiological technicians and 7 among the controls (P = 0.12, one-tailed test). While the doses are uncertain, their exposures may have been 0.05-0.15 Gy per year, based on the experience of similar technicians at the Cleveland Clinic (United States) in 1953. Most of these radiology technicians did not pursue the same kind of work after they had left the Army, where their average stay had been less than 3 years.

418. Efforts have been made to determine whether individuals employed in the nuclear industry do or do not have increased risks of cancer. In 1978, for example, Najarian and Colton [N6], in a study of 1,722 death certificates for a variety of workers at the Portsmouth Naval Shipyard (New Hampshire, United States), found six deaths from leukaemia among the 146 former workers presumed to have been involved in activities where exposure could have occurred, whereas 1.1 deaths were expected. A subsequent retrospective cohort mortality study [R17] of all the workers at this shipyard failed to confirm the finding. Among three cohorts, (a) 7,615 nuclear workers (doses 0.01-0.91 Sv; mean 0.03); (b) 15,585 non-radiation employees; and (c) 1,345 with no measurable exposure, on whom vital status could be ascertained in 96% of cases, Rinsky et al. found no increased mortality for the exposed groups as contrasted with the other two groups, nor did they find evidence of a dose-response relationship within the exposed cohort. The standardized mortality rate (SMR) for leukaemia was 84 (95% CI: 34-174). As is true in many occupational settings, some uncertainty surrounds the actual doses involved: for years prior to 1974, the estimates are based on film badges, but for subsequent years, they are based on calcium fluoride dosimeters. A study of the employees of all of the nuclear shipyards in the United States, government and private, is presently under way. While it has not yet reported its findings, the study may eventually clarify the issue. Similarly, in 1981, Austin and his colleagues [A16] reported a threefold increase in the frequency of malignant melanoma among the employees of Lawrence Livermore National Laboratory (United States). Again, a substantially larger, later cohort study of the workers at Los Alamos National Laboratory (United States) [A15] failed to support this. Among 11,308 employees, only six cases of melanoma were ascertained where 5.69 would have been expected based on age and sex-specific mortality rates (SMR = 105). In neither of these studies was evidence presented that the cases had received higher exposures than other employees.

419. The situation with respect to the employees at the Hanford Facility in the state of Washington, United States, is equally perplexing. Kneale, Mancuso and Stewart [K20] purported to show that a variety of

malignancies, including multiple myeloma, are elevated among the workers at this laboratory, but a more thorough and statistically sounder study [G12] does not bear out their contentions, although it does find a greater frequency of multiple myeloma than expected. It should be noted that even this result rests on three cases. Whether this increase is, indeed, a consequence of exposure is therefore moot, but multiple myeloma has been found to be elevated among the atomic bomb survivors, presumably as a result of their exposure, and the effect could be real. More recently, Beral and her colleagues [B22], using standardized mortality rates, examined the causes of death among 39,456 individuals employed by the United Kingdom Atomic Energy Authority (UKAEA) between 1 January 1946 and 31 December 1979. They found mortality to be increased for only four causes of death, namely, testicular cancer (SMR 153: 10 deaths), leukaemia (SMR 123: 35 deaths), thyroid cancer (SMR 122: three deaths), and non-Hodgkin's lymphoma (SMR 107: 20 deaths), but in no instance was this increase statistically significant at the 5% level. The SMR for myeloma was 83 (95% CI: 36-163). Cumulative dose estimates are available for approximately half of these employees; few (84) had received a cumulative dose in excess of 0.5 Sv. Among the workers for whom there were dose estimates, prostatic cancer was the only cause of death clearly related to exposure (SMR 594 for employees with exposures exceeding 10 mSv; four deaths). Although the numbers are small and the evidence is perforce weak, the data suggest a greater risk among workers exposed to tritium than among workers exposed to other sources of ionizing radiation (SMR 889; 6 deaths). Beral et al. [B22] estimate excess mortality for leukaemia and all cancers were 2.2 and 10.5 deaths per 10^4 PYSv, respectively. Neither of these estimates is significantly different from zero, but at face value they both agree reasonably well with the Japanese and other studies. It is interesting to note that when the UKAEA findings and the Hanford findings are combined, neither the increase in prostatic cancer seen among the former nor the increase in multiple myeloma seen among the latter is any longer significant [D24]. This suggests that both individual findings could be due to chance.

420. Possibly the most thoroughly studied of these special cohorts has been the plutonium workers, particularly those individuals who were involved in working with this element at the time of the Manhattan Project, when the potential hazard associated with the inhalation of plutonium particles was poorly recognized. Some 37 years of follow-up have failed to disclose an increased frequency of any malignancy; the number of workers involved is small, but their exposures were undoubtedly large [V2]. Studies of plutonium workers at the Los Alamos facility [V3] as well as of workers at other installations in the United States [W18] have also failed to find a significantly elevated risk of malignancy, generally or site-specifically. Although the number of years at risk are already large, these studies continue, and it is conceivable that an effect could still emerge.

421. In 1979, a preliminary report [C16] indicated that eight cases of leukaemia had been identified

among 3,224 former servicemen who had participated in the nuclear weapons test code-named SMOKY, one of a series known as PLUMBBOB, conducted at the Nevada Test Site, United States, in 1957. Only 3.5 cases would have been expected on the basis of age- and sex-specific population rates (RR = 2.3). Subsequent studies of this same cohort [C17] extended the observations to the incidence of all types of cancer and other specified causes of death. No increase in other cancers was seen, but 10 cases of leukaemia (including one of chronic lymphocytic leukaemia) were found where 4.0 were expected (RR = 2.5). Similar claims, based largely on scanty epidemiological evidence, have since been made for Australian and British participants in weapons tests carried out by the United Kingdom [K21].

422. Stimulated by these reports, the Medical Follow-up Agency of the United States National Research Council launched an investigation of the participants in five series of tests occurring in the years 1951 through 1957 [R16]. This investigation embraced a cohort of 46,186 individuals. A total of 46 deaths from leukaemia were ascertained (52.4 expected on population rates). No significant excess was found among the participants at any test series other than PLUMBBOB or among PLUMBBOB participants not represented at SMOKY. The earlier findings of Caldwell and his colleagues with respect to the SMOKY test were confirmed. No other form of cancer was consistently elevated; overall, only 1,046 deaths from malignant neoplasms were identified where 1,243 were expected based on population rates (SMR = 0.84). While the doses of the individuals involved in all of these tests are poorly known, film badges suggest that the highest dose received by any one of the participants in SMOKY who subsequently succumbed to leukaemia was 0.036 Sv (most received doses of less than 0.005 Sv). At the present, then, there is no consistent or statistically significant evidence for an increase in either leukaemia or other malignant neoplasms in nuclear test participants.

423. Darby et al. [D26], updating the study of Knox et al. [K21], have summarized the cancer mortality and incidence among 22,347 men who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programme, and have compared these findings with those on 22,326 individuals matched with the participants for age, type of armed service, rank (officers and other ranks; socioeconomic class for civilians), and the date of entry to the study. The latter individuals were drawn either from among servicemen who did not participate in the weapon test programme, or, for the civilians, from the roster of employees of the Atomic Weapons Research Establishment who had not visited a test location or attended tests in the United States. Thirty-eight causes of death were examined separately.

424. Mortality from leukaemia and multiple myeloma in the participants was slightly greater than would have been expected from national values, but it was substantially lower in the controls. However, the rates of leukaemia and multiple myeloma showed very little difference between groups characterized by recorded

doses from external radiation. These authors cautiously concluded "Participation in the test programme did not seem, in itself, to have caused any detectable effect on the participants' expectation of life, apart from possibly causing small risks of developing leukaemia and multiple myeloma".

425. Rinsky et al. [R21] have described the results of a case-control study of lung cancer in civilian employees at the Portsmouth Naval Shipyard (United States). Their study involved 405 cases and 1,215 controls drawn from the roster of civilian employees matched on age, year first (last) employed, age at date first (last) employed, and length of employment. The distribution of cumulative radiation doses among the cases differed little from that among the controls save in the percent exposed to 0.01-0.05 Sv where the radiation-related excess was statistically significant. However, when exposures to asbestos and welding fumes were taken into account, the radiation-related risks at all levels of exposure were reduced, suggesting a greater exposure to these factors. This confounds the observed association between radiation and lung cancer. Analysis of mortality by time since exposure revealed no pattern of increase as latency increased. Data on cigarette smoking and socioeconomic status were not available. These authors conclude that their study does not preclude an association between lung cancer and exposure to ionizing radiation (at the levels obtaining among nuclear shipyard workers) nor does it provide evidence in support of such an association.

426. Checkoway et al. [C21] have described a historical cohort mortality study of 6,781 white male employees of the nuclear materials fabrication plant known as Y-12 at Oak Ridge, Tennessee, United States, in the years 1947-1979. Among monitored workers, the mean cumulative alpha-radiation dose to the lung was 0.082 Sv, and the mean cumulative external whole-body penetrating dose from gamma-radiation was 0.0096 Sv. Mortality excesses were seen for cancers of the lung, brain and central nervous system, but not for other sites of cancer nor other causes of death when the rates among workers were compared either to national or state rates. No dose-response trend was observed for mortality from cancer of the brain and of the central nervous system, but the rate ratio for lung cancer, based on contrasting workers receiving 0.05 Sv or more with workers receiving less than 0.01 Sv, was 4.60 assuming zero-year latency and 3.05 on a 10-year latency. These rate ratios are, however, based on only three deaths and one death, respectively. Thus, the evidence of an increase in lung cancer mortality at these dose levels is far from compelling.

427. Workers for British Nuclear Fuels at the Sellafield plant have been studied [S54]. Among 14,327 known to have been employed at the plant from 1947-1975, 572 of 2,277 deaths were due to cancer, 5% less than expected based on death rates for England and Wales (overall mortality was also slightly less than expected). Radiation workers had deficits of liver and gallbladder cancers, lung cancer, and Hodgkin's disease, and excess deaths from myeloma and prostate cancer. Neither excess was significant, and there was no excess in leukaemias. Dosimetry showed positive

associations between accumulated dose and death rates from bladder cancer, multiple myeloma, and haematopoietic neoplasms. These were significant in regard to doses accumulated up to 15 years prior to the time of death, but not if doses up to two years before death were included.

6. Exposures to elevated cosmic and terrestrial radiation

428. Although levels of exposure to cosmic radiation vary as a function of altitude, and although some correspondence exists between cancer rates and altitude, there have been few convincing studies to show whether cancer rates at high elevations are substantially different from those elsewhere [C4]. Many correlated factors could explain the data that are available (see [A5] for a review). Studies designed to assess firmly whether cosmic radiation itself causes cancer would require prohibitively large samples.

429. A large-scale investigation of background radiation has been undertaken in China [H24, Z4], where cancer mortality levels in a high-background area in Yangjiang country were compared to those in a control area with one third the exposure levels. After age adjustment, there were no significant differences, even though chromosomal and other indications of radiation exposure did differ.

430. A separate study has compared the effects of radon alpha-exposure in high-background areas of Guangdong Province of China [H24] with a control area. High-background area exposures were about 0.38 WLM per year, and control-area exposures were 0.17 WLM per year. No difference in age-adjusted lung cancer rates was found.

431. A study of total background radiation in Japan [U5] found an effect only for male liver cancer. This effect fitted a linear dose-response model, but it is difficult to determine if there were other factors correlated with background exposure or if the result is a statistical artefact of some kind, as one due to multiple testing. Liver cancer is not usually reported as a radiogenic site, unless doses are also high enough to induce excess cancer at most other sites as well. In Connecticut, United States, where there is a tumour registry and an airborne gamma survey of the entire state was taken, there was no association between terrestrial radiation and cancer in the period 1935-1974 [W16]. The authors concluded that even a population currently in excess of 3 million persons is too small to detect the level of excess risk which might be associated with the observed level of background radiation.

7. Summary of exposure effects in adults

432. In respect to the radiation exposure of adult human subjects (see also [B21]), several generalizations seem permissible. Regardless of the reason for the initial exposure, it is evident that (a) a single exposure can be carcinogenic if the dose is large enough; (b) there is no uniquely radiogenic cancer cell type; (c) though most, perhaps all, of the common cancers

probably can be caused by ionizing radiation, until now the data have not shown a risk for chronic lymphocytic leukaemia, squamous-cell cervical cancer, or Hodgkin's disease; (d) the breast, thyroid, and bone marrow are particularly susceptible; (e) leukaemia, especially acute non-lymphocytic leukaemia (ANL), can be produced by radiation; it has a latency period of less than 5 years, peaks rapidly thereafter and then declines, but some excess risk persists for at least 30-40 years; (f) solid tumours have an age-onset pattern similar to that of non-radiogenic tumours at the same sites after a latency of about 10 years. For many sites, the latency period is a function of age at exposure. In the existing studies, relative risks have been between 1 and 3 for many epithelial sites after many different kinds of exposures of about 1 Gy; risk persists for 30 years (for life, in some studies); (g) age at exposure is the most general host susceptibility factor, with higher risk associated with younger ages at exposure; (h) atomic bomb survivors and most other study cohorts have yielded comparable results, with a few notable exceptions, and the latter appear explicable in terms of the exposure regimens used and other factors; (i) some individuals may be genetically more susceptible to radiation-induced cancer than others, but good data to demonstrate this unambiguously are very limited.

IV. HOST FACTORS THAT MODIFY RISK

433. There are many biological differences among human beings that may affect their susceptibility to radiation-induced cancer. These biological variables are commonly known as host factors, referring to the risk that the exposed individual will become a host to a tumour. There are many possible host factors for which some data exist. Among these are (a) sex; (b) age at exposure; (c) genetic constitution; (d) health status; (e) life-style; and (f) ethnicity. Since the publication of the UNSCEAR 1977 Report, some information has become available on the potential role of each of the factors listed.

A. SEX

434. Current data generally suggest that sex has little or no effect on radiation carcinogenesis. Tumours in an irradiated population exhibit a sex ratio very similar to the same tumours in a non-irradiated population. There is a strong preference for females in thyroid cancers produced by radiation, but the sex ratio is similar to that observed for spontaneous thyroid cancer. So far, breast cancer following radiation has essentially been found only in females and this corresponds with the extreme rarity of male breast cancer. Cancers in the organs usually manifesting adult onset occur in the typical sex ratios, which for many sites (for example, the lung) show a male preference and there is no evidence that the radiation-related relative risk is higher. The male excess of lung cancer is probably a temporary one related to the history of smoking habits. Squamous cell carcinomas and adenocarcinomas of the lung in Hiroshima and

Nagasaki, for example, seem to develop more rapidly in males than in females, but no difference appeared after smoking habits were taken into account [H10, K22]. Adenocarcinomas are more frequently slow-growing than are lung cancers of other histology. The evidence of a slightly higher relative risk for females than for males in Japan at many epithelial sites was reviewed earlier (see Table 41); most of the difference is probably due to interaction with other sex-associated risk factors rather than to a radiation effect.

435. Radiogenic leukaemia in Japan has a similar relative risk in both sexes, although the excess risk per 10^4 PYGy is significantly less in females (1.95 in males and 1.20 in females). Background incidence of leukaemia is two times more frequent in males. For other fatal cancers, shown in Table 41, only multiple myeloma has a higher background incidence in females; however, the excess risks are, from a statistical standpoint, not significantly different in the two sexes. Since the background rates are higher in males, the relative risks are somewhat greater in females [P15]. Sex may influence tumour growth and, indirectly, survivorship.

B. AGE OF ONSET OF TUMOURS IN EXPOSED ADULTS: SINGLE AND CHRONIC EXPOSURES

1. Exposure to the atomic bombings in Japan

436. The carcinogenic effects of single exposures of external radiation are known almost exclusively from data in Japan. There, the relationships between dose, age at exposure and age at expression of excess risk have been studied in detail [K7, P15, S18, S48, S49, W5]. Because the results have been reviewed extensively elsewhere in this document, only those facts that relate to tumour sensitivity as a function of age at exposure and age of onset will be examined here. For most tumours, there is a decreasing sensitivity with increasing age at exposure, in terms of subsequent risk of excess cancer. The solid tumours of adult onset increase in frequency only at the ages at which they naturally appear in non-irradiated individuals. For leukaemia, the additive risk rises with age at exposure, while the relative risk declines rapidly with age over 10 [K7]. Leukaemia, a classic radiogenic tumour with other special characteristics, is usually treated separately. The characteristic pattern for breast cancer has already been discussed in relation to childhood exposures (see paragraphs 240-242). Basically, all tumour risks seem to decline as age at exposure increases. The same reports also show the positive correlation between risk and dose at all ages. There is an unexplained difference between the data in Japan and uranium miners, the latter showing increased risk with increased age at exposure [S51].

437. In addition to the fact that susceptibility to radiogenic tumours decreases with increasing age at exposure, the characteristic latency periods are related not so much to age at exposure as to the tissue involved. The leukaemias have the most definite pattern, with a latency of 2-5 years and a decline in additive risk after about 25-30 years; a similar pattern

exists for bone cancer. However, the solid tumours of adult onset have latency periods of a decade or more, and the excess risk persists indefinitely, probably throughout life, although this will be determinable only after the entire cohort experience in Japan is known.

438. The subsequent risk of cancer fits a multiplicative risk projection model. The delayed latency period, the persistence of risk throughout adult years, and the age pattern of excess cases are all consonant with multi-stage carcinogenesis, as for example, the model proposed by Moolgavkar [M1, M2], which posits two stages with selective proliferation of partially transformed cells.

439. Under such a model, increased risk should be seen soon after exposure to a single dose, if (as seems likely) radiation acts as an initiating agent (see section III.A.1). However, if this effect is small in the contrasted groups, the excess risk will not be detectable for some time after it has actually arisen, given the available sample sizes. It can be shown that, under such a multi-stage risk model with multiplicative projection effects, because of the nature of the change in the risk function and the effects of competing causes of death (which effectively terminate the observational experience at age 85 or so), the mean age and the age distribution of cases in exposed adults will be similar to those in the population at large [M4]. For these reasons, the age patterns of risk for those exposed to single doses are in agreement with a multi-stage model, and no special life-history or tissue sensitivity characteristics are required, other than in those cases, e.g., breast, bone and leukaemia, where tissue life-history plays an obvious role in sensitivity.

2. Exposures to nuclear tests and fallout

440. The estimated dose-response pattern and its possible significance for those who have been exposed to fallout from a single nuclear detonation (adults in the United States and British military service, Japanese fishermen and Marshall Islanders) are discussed elsewhere in this document. In sum, the numbers of exposed persons were too small and too heavily weighted towards young adults to provide good data on age effects. Adult Japanese fishermen, although few in number, and Marshall Islanders [C6] seem not to have exhibited an excess risk. Non-haematopoietic tumours do not appear to have arisen in these groups in detectably higher frequencies.

441. For adults exposed to chronic doses of radiation either occupationally or through the ingestion of radioisotopes for therapeutic purposes or as a result of nuclear testing, the duration of exposure is too long and, typically, the dose too low to provide useful information about special effects of age at exposure.

C. GENETIC CONSTITUTION

442. Given the genetic variability that exists between individuals within a group and between groups, it is

reasonable to presume that the risk of cancer may vary among individuals of the same sex, age and apparent life-styles when exposed to the same amount of ionizing radiation. A number of relatively rare, largely recessive disorders are known in which fibroblasts from trait-bearers are deficient in the repair of some radiation damage in vitro; it is also known that these individuals are at increased risk of a variety of malignancies, especially malignant lymphoma and leukaemia [K11]. Cell lines from patients with one such disorder, xeroderma pigmentosum, in which UV light is a mutagen, did not disclose a cross-sensitivity in regard to cell-killing with gamma radiation, but enhanced sensitivity to cell-killing has been reported in vivo in irradiated children. Some cell lines from patients with heritable diseases, including cancer-prone ones, have shown cell-killing sensitivity after such radiation [A7, G5, P10, P11], but this is not always found [W10]. One study [F7] has reported that cell cultures manifesting a variety of chromosomal aberrations have shown similar low-dose response estimates.

443. The carriers of one major disease, ataxia telangiectasia (AT), may have been subjected to irradiation in numbers sufficient, eventually, to show an excess of cancers, if it exists. The gene for AT is relatively common in Israel, where it is expected that at least some children irradiated for tinea capitis would be carriers of the gene. The latest report [R22] suggests that Moroccan children, who have a high frequency of AT carrier status, are especially susceptible, among the total Israeli tinea capitis study series. This study did not report thyroid cases. However, in another report from the Israeli series, the thyroid cancer pattern may also reflect this fact, although genotyping has not been done on the cohort and only some of the children were given ionizing radiation as opposed to UV therapy.

444. The cells of these individuals carry two copies of the "susceptibility" allele, one on each parental chromosome, i.e., they are homozygous for an abnormal allele (form of the gene). However, in their families there will be many heterozygous individuals whose cells have only one copy of the abnormal gene, the other being normal. Indeed, not only in these families but also, by virtue of the frequency of the susceptibility allele, in the larger population, there will be a substantial number of individuals, perhaps several per cent, who are heterozygous "carriers" of the abnormal allele. For them, affected relatives will be unlikely and would arise only when a heterozygote and another carrier marry, a relatively rare occurrence. Substantial speculation has centred on the likely cancer risks of individuals heterozygous for these genes. Little direct information exists as yet since there is no simple, easy test for heterozygotes. However, on the presumption that the parents of affected individuals must be carriers (except for very rare instances in which a mutation occurred in the child), some testing of the radiosensitivity of fibroblast cultures from these parents has been carried out. This work, though still tentative in nature, suggests that there is an intermediate level of radiosensitivity, measured by cell survival, between affected and normal homozygotes

[P10]. While it is unlikely that excluding very small subsets of abnormally radiosensitive individuals would alter population risks importantly, their existence will require separate estimation.

445. The Li-Fraumeni syndrome is a dominantly inherited genetic susceptibility to cancers of many organ sites [L13]. Normal fibroblasts from Li-Fraumeni family members are resistant to killing by radiation; Chang et al. [C18] found that in non-irradiated cultures of such cells, the c-myc oncogene has a threefold to 18-fold increased expression and that c-raf-1 expression was also elevated. Kasid et al. [K23] have found that elevated expression of the c-raf-1 oncogene is associated with a cell line of laryngeal carcinoma which is radioresistant (in vivo and in culture). Why this oncogene should apparently be associated with carcinoma risk and radioresistance is not clear.

446. In retinoblastoma when the individual is an obligate heterozygote for a cancer-related region on chromosome 13, the subsequent risk of radiogenic tumour is a reflection of the susceptible genotype.

447. Less has been written, indeed less is known, about the role of genetic predisposition to specific malignancies and the relationship, if any, of this predisposition to radiation-induced risk. Are, for example, women who come from "breast-cancer families" more prone to develop breast cancer after irradiation of the breasts than women who do not come from such families? One study in Japan may begin to provide an answer [Y3]; there was an increased risk of second tumours in women with a family history of breast cancer relative to those without such a history, and there was evidence suggestive of an interaction with radiation in producing this risk. A substantial fraction of colon cancer cases is familial, although to date no study has looked for an excess susceptibility in irradiated persons from high-risk families. A variety of shared environmental factors could lead to a familial appearance of cancer, so that a definitive answer to the question of carrier susceptibility must await the development of practical tests for genetic susceptibility.

448. As reviewed in detail above, many second tumours following radiotherapy occur in individuals whose primary tumour was of a heritable kind. In some of these families there is an excess of cancers of other types in the relatives of the probands. Such relatives do not suffer the index disease, but they may be carriers of some modifier allele at a different genetic locus or, for some other reason, predisposed to develop cancer. Retinoblastoma and childhood sarcomas have both been involved in such studies. If these probands are from cancer-susceptible families, or if their cancer reflects a cancer-proneness, dose-response estimates for them may be of little value to the population as a whole, but the identification and characterization of susceptible genotypes may be extremely important in their own right.

449. Data relevant to these issues are sparse, but those that are available suggest there may be a small

but non-trivial fraction of the human population that is prone to develop cancer and, as a consequence, may be much more liable to develop radiation-related cancers. This may mean that the average dose-response pattern is a relatively poor indicator of individual risk. It may be too low for those individuals especially predisposed, and too high for those individuals who are not at special risk. However, to improve the estimation of risk, one must be able to, identify the susceptible individuals, which is not practicable at present.

450. In ankylosing spondylitis patients there is strong association with specific genes at the histocompatibility loci, in particular an allele known as B27. Individuals with at least one copy of this allele are much more susceptible to spondylitis than are those with other alleles. It is thought that this may involve the development of auto-antibodies in such individuals after exposure to some agent, possibly an unidentified virus. At present there is no evidence that the HLA type is related to cancer or to cancer induction, so that from this point of view the ankylosing spondylitis patients may be thought of as representative of the general population.

D. ETHNIC CHARACTERISTICS

451. Shore et al. [S16, S27] have suggested that radiation-induced skin cancer is functionally related to the degree of pigmentation of the exposed individual. No increase in skin cancer with exposure has been seen among the 2,226 blacks who made up 25% of their tinea capitis population, but 41 cases occurred in the white children who made up the remaining 75%. Nor has an increase been seen among the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki [C4, O2]. These results correspond to the prevailing skin cancer rates in blacks and in Japanese. This suggests that partially transformed cells, exposed to the DNA damage of UV radiation in light-skinned individuals, may become fully transformed. However, no UV-radiation cross reaction has been found in cell lines carrying UV-sensitive genotypes (reviewed above).

E. HORMONAL EFFECTS

452. A deficit in breast cancer has been observed in the cohorts of women who had been treated for gynaecologic disorders (malignant and non-malignant) [B12, L11, W6]. At the same time, ovarian cancer was seen to be reduced in women who had been treated for gynaecologic cancer [B12]. These observations agree with a cell-killing effect at the ovary, depriving the breast of oestrogenic compounds that may contribute to carcinogenesis in partially transformed breast cells. However, breast cancer was also reduced in women treated for benign conditions, who did experience elevated ovarian cancer [W6], the explanation is therefore not obvious at present, and non-representative subjects (i.e., subjects who present an inappropriate expected risk) may be responsible.

453. A study specifically designed to detect interaction between various hormone-related variables and breast cancer risk in women irradiated for postpartum mastitis was conducted in 571 patients and 993 controls in Rochester, New York, United States [S37]. This study found that women with benign cystic breast disease were at excess risk following radiation, but because the benign disease occurred after irradiation, a causal relationship could not be established. Oral contraceptive use, family history of breast cancer, late age of parity, menopausal hormone use and ovarian-related factors (cysts, missed menstrual cycles) were tested, but no interactive relationship with radiation was detected. Another United States study reported similar results [B1].

454. In the Japanese data [T14], breast cancer risk seems to be less if the radiation exposure occurred after menopause. However, this may be a cohort effect, attributable to different levels of hormonal stimulation in the United States and Europe on the one hand, and Japan on the other. Japanese-American women are developing age-specific breast cancer frequencies much like those of other Americans, and breast cancer is becoming more frequent at older ages in Japan. If this is a cohort effect, and if radiogenic breast cancer is related to the hormonal stimulation that appears to be responsible for these international differences, post-menopausal radiogenic breast cancer may increase in Japan [T14].

455. Tokunaga et al. found a slight but nonsignificant excess risk among women who had borne their first child after age 30 [T14]. Nulliparous women may also have elevated radiogenic risk [B1]. Similarly, irradiation after the first childbirth seemed to lead to elevated risk; age at first childbirth is certainly related to the occurrence of breast cancer, but how this interacts with radiation is not known. This and other studies seem to suggest an age effect on breast tissue susceptibility.

F. OTHER DISEASES

456. It has already been discussed whether individuals irradiated for the treatment of cancer suitably represent the general population in terms of their susceptibility to radiation-induced cancers. In general, most studies find similar patterns of radiation risk. An exception to this is excess sensitivity among children who have genetic predispositions, which suggests that children exposed for cancer treatment should not be considered for general risk estimates. Presumably some adults also have greater genetic susceptibilities for cancers, but these individuals cannot be identified in general populations.

457. Although the non-random HLA genotypes in ankylosing spondylitis patients (reviewed above) may not affect their radiation susceptibility, they clearly suffer from proportionally different causes of death than the general British population [S28]. Their pattern of relative risk for a variety of causes is given in Table 1 of [S28]. In addition to the colorectal cancer which may be confounded by the higher risks

of colitis and its associated cancer risks in these patients, many other causes of mortality are different from a general population. Even if this does not apply to their general cancer susceptibility, it clearly affects the interpretation of relative risks derived from the United Kingdom baseline cancer and general mortality rates.

V. ENVIRONMENTAL FACTORS THAT MODIFY RISK

458. It has been asserted, based on world-wide cancer data, that 85-90% or even more of all cancers are avoidable; that is, that they are due to exposures to environmental carcinogens, e.g., smoking, diet, personal habits and the like [D13]. This assertion is based on the observation that age-standardized incidence rates for virtually every type of cancer vary greatly among the populations of the world. Doll and Peto, in their review of cancer patterns in the United States, have estimated that 1-1.5% of all cases in that country are radiation-induced (non-occupational sources of radiation) [D13]; some of these cases will be due to natural background radiation, but the remainder will be due to man-made sources of exposure.

459. The most systematic data on variation in site-specific cancer incidence, by age and sex, is the series of volumes published by the International Agency for Research on Cancer (IARC) [W17]. They provide the best available baseline cancer risks and, while they include the effects of radiation on a population basis and cannot be used specifically to identify environmental causes, they can be used in computations of risk assessment, as discussed in chapter II. Radiogenic effects will be functions of the baseline risk. In addition, as seen in chapter III in regard to second cancers in patients irradiated to treat cancer, radiation risk is highly dependent on the effects of other risk factors.

460. The observed pattern of world-wide cancer variation is not highly correlated with ethnicity in any simple way that would suggest that this variation has a genetic basis, so it is generally assumed that environmental factors must be responsible. It is usually also assumed that in any population a large fraction of the baseline cancer rate, for any tumour site, is determined by local exposures to various agents (including radiation). Smoking and diet, pollutants in the environment, endogenous as well as exogenous hormones, and many other agents are known to be associated with variations in cancer risk.

461. Among the more elusive of the host factors and environmental factors that can influence the occurrence of a radiogenic cancer are the health status and life-style of the exposed individual. Their roles have been difficult to assess, for the variables themselves are difficult to define and to measure adequately. Smoking habits are more than just the sum of the cigarettes one smokes daily, weekly, annually or in a lifetime of smoking; moreover, these habits change with age and perception of risk. Data are beginning to be available

that are relevant to three questions, namely: (a) what roles do smoking, diet, and the like play in cancer risk? (b) are life-style attributes related in any way to the absolute or relative risk differences in the irradiated? (c) can an understanding of the interaction of risks lead to an understanding of the action of radiation?

462. Regardless of the answers to these questions, relative and absolute excesses of cancer attributable to radiation must at present be evaluated in the context of local baseline patterns. For the cohorts of individuals who have been exposed to large doses of radiation, the levels of environmental risk exposure have been changing in the populations in which they live. Without adequate cognizance of these changes, it will be difficult to identify the effects of radiation, per se, or to say whether the effects of radiation are the same in populations with vastly different socio-cultural environments.

463. In addition to changes in mean levels of exposure within a population over time, there will be inter-individual differences in exposure that are relevant both to the analysis of specific cohorts and to the estimation of future risk. Although the data are limited, in many study cohorts it has been possible to make observations, or plausible inferences, about the role of certain environmental co-variates. These will now be reviewed.

A. SMOKING

464. Clearly, cigarette smoking is one of the most definite, and easily assessed, risk variables; it applies to cancer of the lung in smokers whose lungs are exposed to radiation, as well as to certain other tumours. However, Kato and Schull [K7] found no evidence that smoking increased the radiation-induced lung cancer incidence in Hiroshima and Nagasaki disproportionately. Prentice et al. [P7] and Kopecky et al. [K22], in a more elegant and broader analysis of the same data, reached a similar conclusion. Persons heavily exposed to both cigarette smoke and radiation had significantly lower cancer mortality for all cancers except leukaemia, stomach cancer and digestive cancer other than stomach cancer than predicted with a multiplicative risk model. The lung cancer relative risk function could not be distinguished as either a multiplicative or an additive form, though there might have been a slight preference for the latter.

465. Women treated for gynaecological disorders have experienced an increase in the incidence of cancer at smoking-related sites, including lung, bladder, oropharynx, and oesophagus [B2, B12, W6]. This has been observed in irradiated and non-irradiated patients. Since smoking is a well-established risk factor for cancer of the cervix, which typically selects for women of lower socio-economic status, some of the excess risk of smoking-related cancers in these women may be due to their smoking habits; alternatively, it may be that they were susceptible to cervical carcinogenesis for a variety of reasons; among them, smoking. They may have been more susceptible to smoke than the

population from which their expected rates were computed [B12, W6]. In a case-control analysis of a subset of the cervical cancer series, Boice et al. [B38] were able to show an association between smoking and smoking-related cancers, as well as for other known risk factors and their associated cancers (i.e., nulliparity effects on breast cancer risk, and obesity and menopausal oestrogen therapy for endometrial cancer).

466. The relative risk of lung cancer in the international cervical cancer study of women under age 40 was more than 12, a much greater risk than can be accounted for by the effects of smoking in the patients [B12]. For women who had not received irradiation, the relative risk was the highest of any group in the study, about 3, and a similar excess of bladder cancer was found in the women treated for benign conditions [B12, W6]. A different series, of 2,500 French women treated for cervical cancer, observed 10 cases of bronchial carcinoma, with only 28 months, on average, intervening between the diagnoses [S36]. This latency time is too short for radiation to have induced cancer in the lung. The possibility that the excess lung cancer, at least, reflects the misclassification of metastatic cervical cancer has also been considered [B12, D9, S36], although these authors argue that the persistence of excess risk in the large international study after 20 years suggests some of the excess may be real. Given the low dose of radiation received by the lung, a truly radiogenic effect would be difficult to detect [B12].

467. One extensively studied potential interaction is that between smoking and radiation in occupationally exposed underground miners. The alpha radiation of the radon daughters present in the air of underground mines provides long-term, generally low-level exposure to the lungs, as does smoking. Some aspects of these studies have been mentioned earlier.

468. Most of the miner populations studied had a high percentage of smokers, so that the independence of the two effects has been difficult to evaluate accurately. However, Navajo Amerindian men working in mines in New Mexico, United States, also developed excess lung cancer and relatively few of them were smokers [S20]. None the less, the data on smoking and radiation with respect to miners are complex and inconsistent [C4]. One study of iron miners in northern Sweden indicated that smoking had, roughly, an additive effect in the exposed miners [R7], while another [D12] purports to find an interactive effect. In their recent study of six Czechoslovakian mining groups, Sevc et al. [S51] found smoking to have an additive effect. Thomas et al. [T20] have found an effect intermediate between additive and multiplicative. However, in an analysis of data from uranium miners in the Colorado plateau (an area including parts of the states of Colorado, Utah, New Mexico and Arizona, United States), Whittemore and McMillan [W12] found strong support for an interactive relationship between smoking and radiation exposure. It should be noted that the dose estimates were uncertain and may have been higher than in other series. This could explain some of the difference in results [C4]. Also,

while earlier analyses of these data had not revealed an interactive effect [C4], the more recent study used proportional hazards analysis, a better method than categorical analysis because it compares risk within the exposed cohort and is not dependent on assumptions about control group risks. Whittemore and McMillan also demonstrated that the models fit the data better when cumulative exposure (to both smoking and radiation) was used, instead of average annual exposure. The best data on this topic show that the interaction between smoking and radon daughter exposure is intermediate between additive and multiplicative [S51]. This was also the conclusion of the BEIR IV Committee [C20].

469. There is clearly a radiogenic risk of lung cancer in the absence of smoking as a co-factor. In general, the difference between the absolute risk for miners who smoke and that for those who do not has been small, but the difference in the relative risk between the two groups is great [C4, R7]. As was true in some mining studies [C4, R7], data from the Japanese atomic bomb survivors fit additive and multiplicative models almost equally well [P7, K22].

470. The time from first exposure to lung cancer has commonly been about the same for smokers and non-smokers [C4, R7], implying that radiation, and not smoking, was responsible. Even in the Colorado miners, where an interaction was inferred, there was no evidence for an age of onset difference [W12]. This finding disagreed with earlier analyses of these data [W13], which seemed to show such a difference perhaps due to overestimation of the exposures [C4, R7, W12]. The latency period reported for Japanese non-smokers is longer than that for smokers. Although some of this difference could also be due to errors in the estimation of smoking and radiation exposures, some of it may reflect the dissimilarity between chronic mining exposures and the single exposures in Japan. There have been large differences in the exposure levels of the various mining cohorts, and dissimilar doses can have disparate effects (interactions not apparent in some situations may be detectable in others).

B. DIET

471. Stomach cancer is very common in Japan, and some dietary factors have been implicated (e.g., the high-temperature cooking of meat and fish and preservation methods for fish). Thus, radiation exposures in Japanese can be expected to have effects that are related to the high level of exposure to these other risk factors. In a multiple regression analysis of stomach cancer in Hiroshima and Nagasaki, Ikeda et al. examined the relative importance of various risk factors for stomach cancer [I8]. Their study, which had a total residual (unexplained) variance of less than 1%, showed a statistically significant association between stomach cancer risk and age, sex, consumption of milk and consumption of broiled (but not dried or pickled) fish. Radiation dose had a much smaller, non-significant effect [I8].

472. Stomach cancer in irradiated persons in Hiroshima and Nagasaki tends to occur more often in areas of intestinal metaplasia, and the frequency of the latter appears linearly related to dose [M15]. As noted earlier, intestinal metaplasia in the lower third of the stomach is a characteristic precursor of gastric carcinoma in Japan, suggesting that irradiation has interacted with predisposing dietary factors. Because gastric cancer rates are dropping in Japan as diet changes, it is imaginable that Japanese exposed to radiation at a future time would have fewer partially transformed cells and, hence, a lower risk of radiogenic cancer. Radiation may induce cancer by increasing the prevalence of the precursor state as well as by further transforming cells already in such a state.

C. INTERACTION BETWEEN THERAPEUTIC MODALITIES

473. The findings in patients given combined radiation and chemotherapy for cancers, especially adult cancers, were described earlier. Generally, the strongest effects were those of chemotherapy, and some studies found no specific radiogenic effect on solid tumours or on acute non-lymphocytic leukaemia (ANL), only a chemotherapeutic effect. Some applications of radiation have probably led to intense local irradiation and cell sterilization, which may actually weaken the combined effect of the two types of therapy. It is not known if either the presence of disease or the method of applying the therapies affects the nature of any interaction. As reviewed above, in several adult cancer series, the relative risk of persons who had not received radiotherapy was greater than 1.0, which shows how important it is to have proper reference groups when comparing the effects of different modalities of therapy. Even if those treated with combined therapy show greater cancer risks, if the patients do not represent the population at large, the inferences about the effects of therapy, including radiation, will not be precisely applicable to a general population of exposed individuals. In any case, chemotherapy is commonly part of the treatment in which radiotherapy is used, so that the potential effects of the latter alone cannot be readily assessed; this is particularly so in view of the constantly changing therapeutic schedules and agents.

474. One of the most interesting sets of subjects in which to examine the effects of combined radiation and chemotherapy is the set made up of patients who were treated for retinoblastoma. Since, as noted earlier, about 25% of patients with this childhood tumour have a genetic susceptibility to it and to other cancers also, this cohort provides an opportunity to examine the effects of the different therapies both inside and outside a well-delimited radiation field. For patients receiving no chemotherapy, there are good baseline data.

475. An analysis of British retinoblastoma patients has been reported by Draper [D15] (Table 43). The small sample sizes and the fact that most patients given chemotherapy were genetic cases limited the analysis to those with the genetic form of the disease.

The risk of a subsequent cancer among patients receiving both kinds of therapy was greater than for those receiving only one kind, both at 12 years and (especially) at 18 years after initial diagnosis. These differences were significant at the 5% level, although Draper noted that since the modes of radiotherapy may have been different for those also given chemotherapy, there could not be too much emphasis on the specific numbers. Thus, in genetically susceptible individuals, combined therapy adds to the risk of cancer; the excess risk is apparently experienced both inside and outside the radiation field. The fact that the effect of combined therapy seemed much greater after 18 than after 12 years suggests that an even greater effect may be revealed as more follow-up time accumulates.

476. In the data on Wilms' tumour [L3], combined chemo- and radiotherapy was given to four of the nine radiation-associated second tumour patients. Combined therapy did not increase the risk of cancer relative to radiation therapy alone, when all cancers were considered. The relative risk of chemotherapy, among irradiated patients, was 1.02. However, if only tumours arising in the field of irradiation were considered, the relative risk of chemotherapy was 1.50, significant at the 5% level. These patients received orthovoltage therapy.

D. STATISTICAL REFLECTION OF HIGH POPULATION RISKS

477. In the parallel analysis of cancer data from ankylosing spondylitics and the Japanese series, Darby et al. [D11] plotted both the relative risk and the excess risk of various cancers against the expected risk in the two populations. These are shown in Figure XIII. Most of the tumours cluster in a small area on such a graph ($RR < 5$; risk per 10^5 and year < 25). The points for stomach cancer, which is very prevalent in Japan, and for lung cancer, which is very prevalent in the United Kingdom, are among the few outliers on the respective graphs. Both exhibit very low relative risk contrasted to their population risks. It appears that the pattern observed by Darby et al. is, with the exceptions of leukaemia and CNS tumours, a linear one, with the relative risk roughly between 1.5 and 3 for all epithelial sites.

478. Central nervous system (spinal cord and nerve) tumours were much elevated, relative to their normally rare occurrence. This is probably because these tissues are seldom exposed to environmental mutagens (blood-CNS barrier), with almost no mix of spontaneous and radiogenic tumours in the data sets. For leukaemias, the relative risks were different in the two groups (about 3 in spondylitics and 9 in the Japanese survivors), but the population prevalences were similar. The relative risks for both sites (CNS and leukaemia) were different from the relative risks for most carcinomas. The explanation for this is not clear, but the discrepancy highlights the difference between haematopoietic and epithelial tissues and perhaps serves as indirect evidence for the importance of environmental risk factors in the epidemiology of radiogenic carcinomas.

E. GENERAL CONSIDERATIONS ABOUT INTERACTIONS

479. The many factors discussed in the previous sections indicate that there are numerous ways in which radiation could have, or could appear to have, an effect on the irradiated individual. Clearly, it is very important to ensure that the expected rates with which the risk in irradiated subjects are compared are representative of their population. The 1980 BEIR III Report [C4] attempted to derive summary risk coefficients of the excess cancers to be expected per 10^4 PYGy.

480. The BEIR III estimates [C4] were developed by considering all the data available, in an effort to synthesize the information from a variety of heterogeneous data sets. There are, however, pitfalls in such an approach. One reflection of the uncertainties surrounding the use of these estimates shows up in a comparison contained in one of the reports by the international group studying the risk of second cancer in cervical cancer patients [B12, D9]. This comparison showed a poor correspondence between the number of excess cancers (based on the expected number of cases in the referent populations of the eight collaborating tumour registries) and the number of excess cancers that was predicted by applying the BEIR III risk estimates [C4] to the doses and exposure times in the cervical cancer data. The comparison is given in Table 44. It should be remembered that the expected cases were based on risk coefficients per 10^4 PYGy derived largely from the Japanese T65 dose estimates, and the comparison in Table 44 is based on the cervical cancer data in [B12].

481. The biggest difference is in the leukaemias; the authors attribute this difference to cell sterilization in the pelvis and hence to an overestimate of the effective dose [B12], and which their case-control study, taking marrow-weighted doses and cell-sterilization into account, showed to be an artefact of assuming uniform dose to all marrow (i.e., when marrow-weighting is done, the discrepancy largely disappears [B36]. Dose-fractionation may also have reduced the apparent relative risk per unit dose relative to that found in other studies [B36]. However, the difference is too large to be attributed solely to that factor. In addition, more excesses of lung cancer have been observed than were predicted and fewer excesses of most other cancers, notably breast, kidney and bladder. These have plausible explanations which were reviewed earlier (paragraphs 269-284). In general, however, it must be emphasized that (a) cancer patients are not representative of the population at large in respect of many risk-factor exposures; (b) risk-factor exposures may be relevant to more than one type of cancer; and (c) radiation itself may have direct or indirect effects on the risk of cancer in other organs. Thus, to understand the true risk associated with radiation may be difficult, since good background cancer risks are not usually available for the special subset of individuals exposed to ionizing radiation.

482. These facts stress the importance of taking other environmental and host factors into account.

They also show that whole-population exposures may in many ways be more informative than exposures of selected population subsets, and that internal controls, rather than the whole population, may be the most appropriate comparison group. In the instance of the cervical cancer data, the appropriate comparison group is probably the benign gynaecologic disease group (to the extent that they in fact did not receive radiation therapy themselves). The data from Hiroshima and Nagasaki are as close to the ideal in this regard as any available.

VI. SUMMARIES OF RISK ESTIMATES IN MAJOR COHORTS

A. STUDIES PROVIDING SUMMARY RISK ESTIMATES

483. This chapter provides overall summaries of radiogenic cancer effects from the most comprehensive data sources currently available. Details from studies of tissue-specific exposures or susceptibilities were reviewed in chapter III. Here, results relevant to risk estimation and projection are given.

484. There are only three sets of data from which radiation effects can be estimated for a large variety of sites: those for the Japanese atomic bomb survivors, the ankylosing spondylitis patients and the cervical cancer patients. In all three, the sample was large, the individuals were followed for long time periods and an essentially similar kind of exposure was received by many parts of the body. Each set of data has its own characteristics. The Japanese data included internal controls, as did the cervical cancer data (i.e., patients treated without radiation). All the data are for short-term, low-LET exposures. In the spondylitics and the cervical cancer patients, groups of tissues receiving approximately the same level of dose were analysed jointly; the whole-body exposures experienced in Japan could not, of course, be included in this analysis. Only from Japan do we have effective comparisons of the exposure effects in males and females. The Japanese cohorts also provide the most comprehensive data from which to estimate dose-response patterns.

485. The most commonly used measure of the effect of exposure on a given site is the number of excess cancer cases per 10,000 persons exposed to 1 Gy after one year (10^4 PYGy), although some estimates count experience only after a five-year or 10-year latency period. The methods by which this number has been computed were discussed in chapter II.

486. Summary estimates of site-specific risk coefficients are available for the Life Span Study in Japan [K7], the Nagasaki tumour registry [W5], the ankylosing spondylitis patients [S31], the BEIR III Report [C4] and an older report from the ICRP [I9]. Land [L11] has collated some additional data. These risk estimates can now be revised in the light of newer dose estimates and longer follow-up times. In this chapter, the latest reports available are summarized.

B. PROJECTION OF RELATIVE RISK IN THE MAJOR STUDIES

1. Results from exposure to treat cervical cancer

487. For most sites, the international study of cervical cancer patients [B12, D9] found that the number of excess cancer cases was smaller, except for the lung, than would have been predicted based on: (a) the number of person-years at risk; (b) the expected number of cases in the appropriate registry populations; and (c) the BEIR Committee estimates [C4] of the excess number per 10^4 PYGy for the same sites. This difference has already been set forth in Table 44, at which point the question was raised of how well the irradiated subjects typified their larger populations.

488. *Pooled heavily irradiated sites.* To summarize the general effects of heavy irradiation such as was

received to treat cervical cancer, the authors have analysed the joint manifestation of second primary cancers occurring in heavily irradiated sites; that is, sites close to the irradiation and likely to have received more than 1 Gy (stomach, small and large intestine, liver, gallbladder, pancreas, uterine corpus, ovary, other genital organs, kidney, bladder, bone and connective tissue). These will be referred to as heavily irradiated sites. In general, the pattern observed agrees with what has been found in Japan and in the ankylosing spondylitics [D11]. The details of the separate registries and site-by-site analysis may be found in [D9]; the results are summarized in [B12], from which the following is taken.

489. The minimum latency period for the heavily irradiated sites after cervical cancer was about 10 years; the excess risk thereafter did not diminish for at least 30 years. Figure XV compares these exposed patients
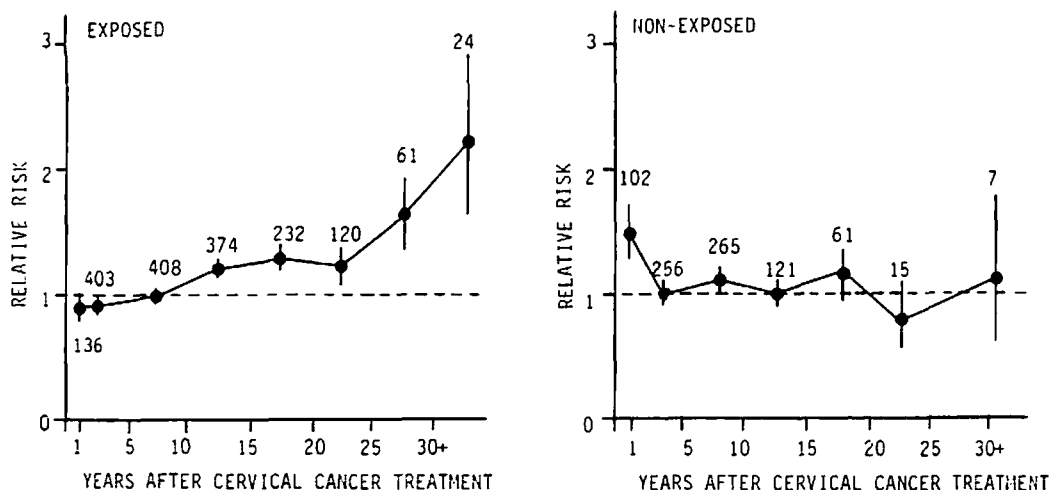
Figure XV. Risk of a second primary cancer occurring in or near the pelvis (close and intermediate sites), related to time of diagnosis of cervical cancer, for patients treated with and without radiation. The number of cancers are given above the 80% confidence bars.
[B12]
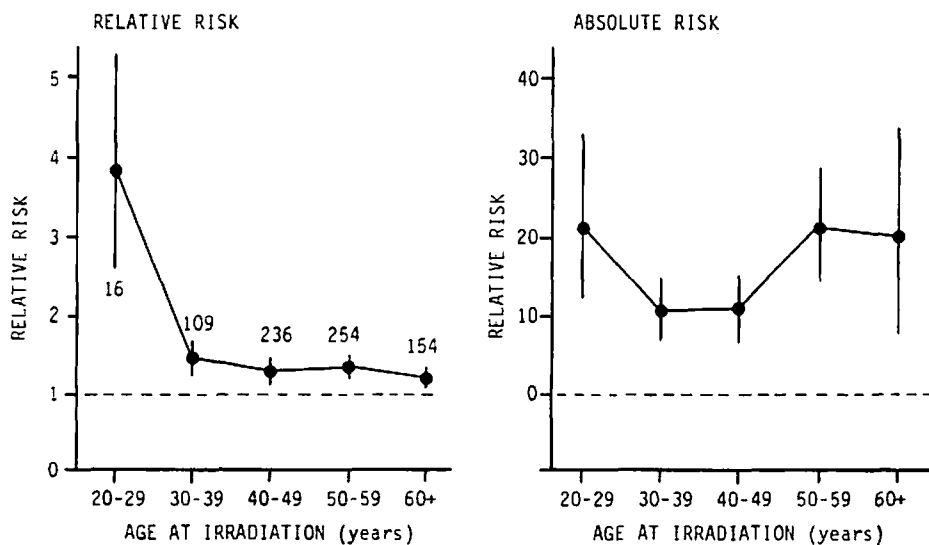
Figure XVI. Relative and absolute risks for second primary cancers occurring in or near the radiation field (close and intermediate sites), related to age at exposure, exclusive of the first 10 years of observation, for women treated with radiation. The number of cancers are given above the 80% confidence intervals.
[B12]
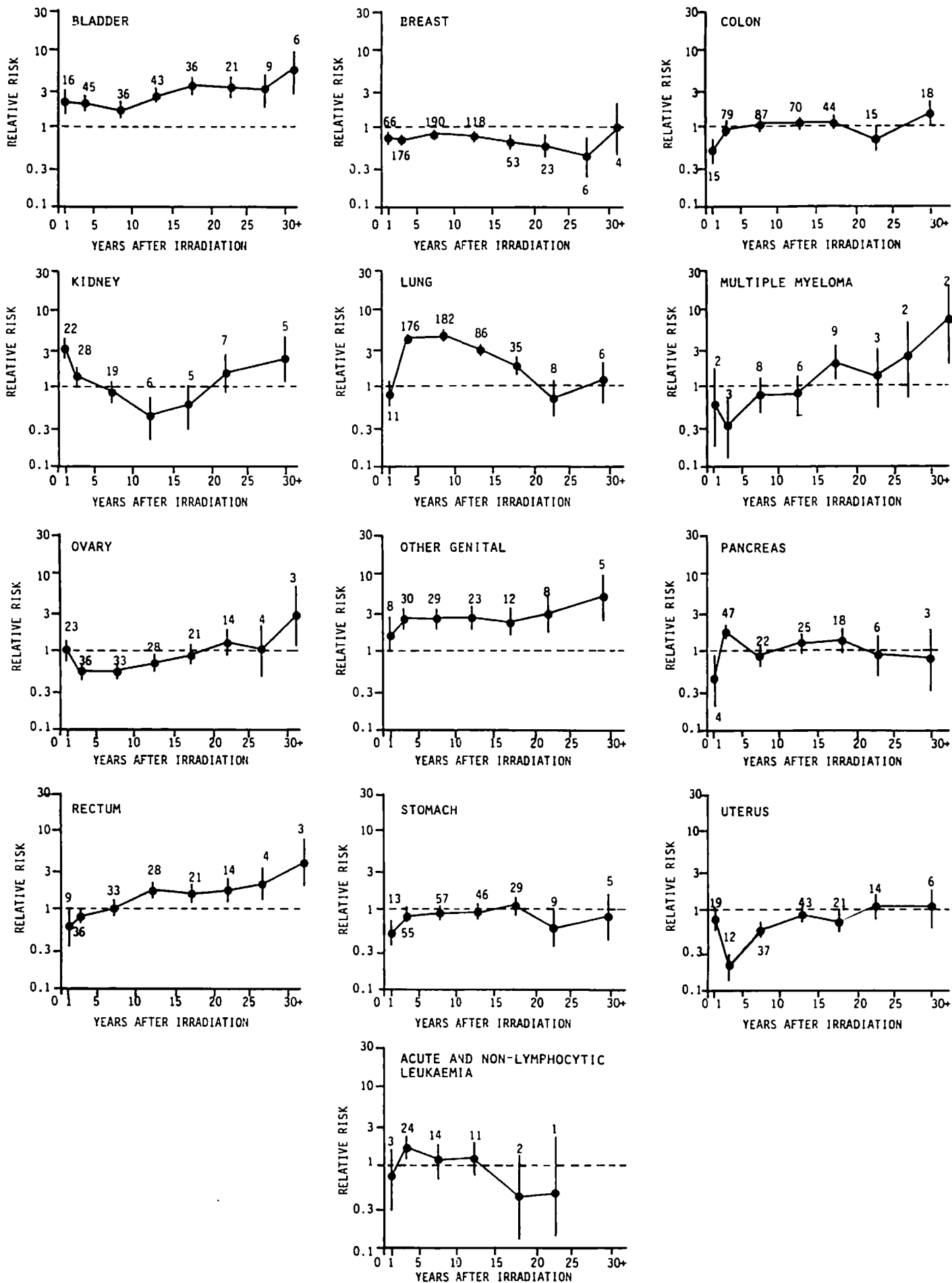
Figure XVII.   Relative risks of second cancers in women irradiated to treat cervical cancer.
[B12]

with non-exposed cervical cancer patients, who manifested no increased risk when all the heavily irradiated sites were aggregated. Many of these women were followed for the rest of their lives (some lived into their nineties) and it was seen that risk apparently continues to remain elevated during all post-irradiation life [B12].

490. In terms of relative risk, women are more sensitive if irradiated under the age of 30, but thereafter age at irradiation appears to have little effect for these pooled sites. Since the background risk of cancer at these heavily irradiated sites increases with age, the absolute risk rises with age at exposure. This is shown in Figure XVI. The Japanese data have typically showed high sensitivity among those who were young at the time of the bombings.

491. *Individual heavily irradiated sites.* These same data have been analysed separately for each site [B12, D9]. Some of these findings are important enough to warrant review here. The patterns of relative risk following exposure at some of these sites are given in Figure XVII. Table 26 gives the most recent relative risk values for these projection effects, pooling data on all ages at exposure, based on a subset of the cervical cancer patients and a control group for comparison.

492. Figure XVII shows that bladder cancer increased gradually with time, with a relative risk of about 3.0. The projection effect appears to be radiogenic. As noted earlier, however, bladder cancer was among the smoking-related sites with similar patterns in the non-irradiated; but in the non-irradiated it decreased with time. While it is curious that rectal, but not colon, cancer was elevated, the projection pattern of rectal cancer is clearly the kind of pattern to be expected for radiation-related malignancies, and it obtained only among irradiated patients [B12]. Endometrial cancer (corpus uteri) had a relative risk of less than 1.0; this may be due, at least in part, to a high prevalence of hysterectomy. The increase in the relative risk 10 years after irradiation, with a levelling off afterwards, suggests a radiation effect. The marked and significant increase in "other genital cancers" refers mainly to an increase at the vulva, vagina, and unspecified sites; these sites probably share risk factors (e.g., HPV susceptibility) and may not reflect a radiogenic effect; they were at elevated risk in all groups in the study.

493. The bladder cancer projection is typical of a radiogenic epithelial cancer, except that it appeared in the first 10 years after irradiation. Boice et al. [B12] attributed this to mis-classified cervical metastases. After a 15-year latent period, there was no association between risk and age at exposure. The high level of risk and the increase over time suggest that more than the confounding effects of smoking are involved [B12].

494. In terms of sites remote from the source of exposure, an increase in smoking-related cancers was found, most dramatically in the lung. The incidence pattern (relative risk highest five to 10 years after irradiation and no excess cases after 20 years) is not typical of radiogenic lung cancer. The deficit of breast cancer is attributed to ovarian ablation by the radiation, which indirectly has a protective effect.

495. *Haematopoietic tissue.* Figure XVII shows the overall pattern of relative risk of leukaemias following irradiation. Pelvic marrow in these women received 3-15 Gy. While there was a marked deficit in leukaemias, relative to the BEIR III estimates (see Table 44), the pattern of excess leukaemias matches the pattern, with regard to projection effects, that is expected for radiogenic leukaemias (an excess beginning two to five years after exposure and diminishing after about 20 years). The relative deficit in excess cases is attributed to local cell killing [B36]; the dose received by the peripheral marrow is estimated to have been < 1 Gy, a dose which is leukaemogenic. The figure also shows the small excess of multiple myeloma and its persistent increase.

2. Results from exposure to treat ankylosing spondylitis

496. Results have recently become available that summarize some of the effects seen in the patients exposed to treat ankylosing spondylitis. The analysis presented here pertains only to the effects of single courses of x-ray treatment [D21, S28, S31]. The expected numbers were derived from British national mortality statistics. Table 45 presents the relative risks for major groups of sites as a function of time since irradiation [D21]. In these data the relative risk for leukaemia can be seen to rise rapidly and to persist beyond 25 years after exposure. The relative risks for the other sites remained approximately constant for the first 25 years after exposure, with values between 1.5 and 2.5, but then tended to disappear. Little effect, overall, was seen in lightly irradiated sites.

497. The site-specific projection effects are given in more detail in Table 46, also from [D21]. The authors found that for several sites the relative risk was elevated as early as up to two years after exposure as well as from three to nine years after exposure. They attributed this unexpectedly early appearance of excess relative risk to the possibility that tumours that had existed had been mistaken for ankylosing spondylitis, and they suggested that the relative risk at six to eight years' post-exposure was only slightly different from 1.0 [S31]. In their view, these data are consistent with the Japanese and other results for solid adult tumours in terms of the first appearance of excess risk, though not in terms of the disappearance of excess risk after 25 years.

498. Table 47 gives the relative risk values for the same series of patients as a function of their age at exposure, for leukaemia and for the heavily irradiated sites. The relative risk for leukaemia appeared to be slightly lower among those exposed at under age 25 and roughly constant afterwards, but none of the differences were significant. Also, the differences were not significant for all heavily irradiated sites combined.

499. A recent study has improved the dose estimates for the spondylitis patients [L16]. Earlier estimates, in

particular the BEIR III estimates, were very different from these new values, so that summary tables of the new values are included here for reference (Tables 48 and 49). This study was based on a sample of 934 patients (1/15 of the total series), for 903 of whom organ dose estimates are reported in the tables. Estimates were based on an Oak Ridge Laboratory program [W19] that models the process based on a mathematically defined human phantom. It is clear from the tables that there was great inter-individual variation in dose; thus, dose-response patterns from the entire series of over 14,000 patients are not based on precise individual exposure estimates. The new dose estimates are about 19% higher than prior estimates and very different from BEIR III [C4], although they are close to recent estimates by Drexler and Williams [D22].

3. Joint analysis of Japanese (T65D) and ankylosing spondylitis data

500. The detailed analyses of the risk effects from Hiroshima and Nagasaki, based on the revised (DS86) dose estimates, constitute the most important single data set on risk effects in existence. However, to augment the information from this and the large series of ankylosing spondylitis patients, Darby et al. [D11] analysed the Japanese and spondylitis data jointly. A summary of their results and of some of the basic data are presented. However, it should be noted that (a) the data from Japan apply to the old dosimetry (T65DR); (b) the spondylitis doses have been revised [L16]; and (c) the spondylitis risks have been revised [D21] since this joint analysis was prepared. Therefore, the joint analysis must be considered only rough and qualita-

tive in nature, and it is to be read carefully in regard to carcinoma risks more than 25 years after exposure.

501. With these cautions in mind, Table 40 gives joint, summary relative and absolute risk values for the Life Span Study [W5] and the spondylitis patients [S28]. This paper [D11] provided some summary statistics on projection effects, with regard to a series of selected sites for which results between the two data sets could be meaningfully compared.

502. In the spondylitics, absolute risk standardized for time since exposure increased rapidly with age at exposure; in the Life Span Study, there was less evidence of such a trend. The result was similar for absolute risk by time since exposure standardized for age at exposure: a trend in the spondylitics but not in the Japanese. For the studies to be compared more directly, the observed Japanese risks were standardized to the same exposure-time distributions seen in the spondylitics, and this produced clear trends in the data from Japan for age at exposure and time since exposure. The joint estimate was an absolute risk of 31.7 per 10^5 PY (SE = 8.5) for every 10-year increase in age at exposure, and the studies did not differ significantly. In Japan, but not in the spondylitics, there was a statistically significant (p < 0.05) trend in time since exposure. The combined analysis showed no significant difference (p > 0.10), and the joint estimate was an average increase in absolute risk with time since exposure of 34.0 per 10^5 PY (SE = 15.7) for each six-year time period. This was significant at the 5% level.

503. Relative risk results are summarized in Figure XVIII, which shows that in the ankylosing spondylitis
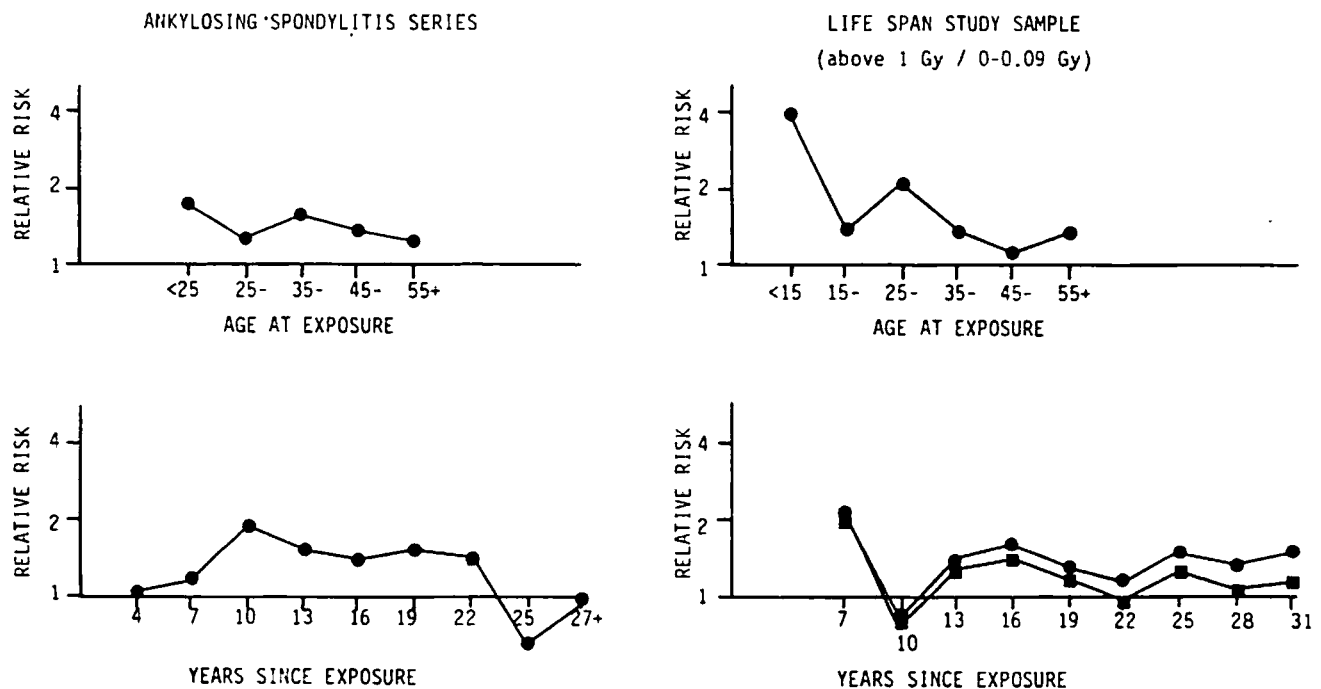
Figure XVIII. Relative risk of cancer in selected sites combined in relation to age at exposure and time since exposure for the ankylosing spondylitis series and for the Life Span Study sample (T65DR doses).
[D11]

patients there were no trends in relative risk for age at exposure, and only before 10 and after 22 years did relative risk fall below its generally flat projection pattern; there was no evidence that these two factors interacted [D11]. The data from Hiroshima and Nagasaki showed significant linear and quadratic trends in relative risk with age at exposure (declining with increasing age), and a log-linear trend in relative risk could be fitted to the data. The trend in relative risk with time since exposure was roughly level, both before and after incorporating a log-linear trend in relative risk with age at exposure. In analysing these jointly, Darby et al. found no trend in the relative risk in time since exposure; for five to 30 years after exposure, the relative risk remained about constant. Jointly there was a significant log-linear trend in relative risk for age at exposure, with the joint estimate of the trend in log (RR) with exposure age of −0.5 (SE = 0.13).

4. Recent results from studies of the Japanese exposed to the atomic bombings

504. The Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, have at various times used a variety of measures of individual exposures to the atomic bombings of Hiroshima and Nagasaki. These included distance from the hypocentre [M38]; the presence or absence of the symptoms associated with acute radiation illness [N10]; and, now, no fewer than three separate physical dosimetries, namely, the T57 [R19, A17], (for an application of these doses, see [I10]), the T65 [M24], and the new Dosimetry System 1986, or DS86 [M39, N11, R20]. Each successive method of expressing doses has necessitated a re-estimation of the risk coefficients associated with the various known effects of ionizing radiation and a re-examination of the dose-response relationships. With these changes there has emerged a better ability to estimate the risk coefficients in terms of organ absorbed doses or organ dose equivalents rather than in terms of kerma, whether free-in-air or in-house (shielded).

505. The newest system of dosimetry is an outgrowth of a series of events. In 1975, Preeg of the Los Alamos National Laboratory (United States) re-examined the gamma-ray and neutron spectra from the Hiroshima and Nagasaki atomic bombs using a one-dimensional model and discovered that they differed considerably from the spectra used in calculating the T65 doses. Simple calculations based on these spectra suggested that the T65 neutron dose was markedly overestimated for Hiroshima. Subsequently, Loewe and Mendelsohn at the Lawrence Livermore National Laboratory (United States) and Kerr and Pace at Oak Ridge National Laboratory (United States) independently calculated the air doses at Hiroshima and Nagasaki and reported that both the neutron and the gamma doses differed substantially from the T65 estimates. These findings prompted a complete re-evaluation of the atomic bomb radiation dosimetry (for a fuller account of the events that preceded this reassessment, see [R20]). The reassessment, begun jointly by the Governments of Japan and the United States, culmi-

nated in March 1986 in a consensus system known as the Dosimetry System 1986 (DS86). The principal differences between this system and the T65 dosimetry, the heretofore most commonly used system (see Table 50), are as follows [R20]:

(a) the yield of the Hiroshima weapon is now presumed to have been approximately 20% greater than had earlier been thought; that is, 15 rather than 12.5 kilotons;

(b) although the free-in-air (FIA) gamma doses are somewhat greater at distances of 1.4 km or more in Hiroshima, neutron exposures are less in both cities, and substantially so in Hiroshima, about 10% of their previously estimated value (30% in Nagasaki). Since delayed radiation from the fireball makes a relatively greater contribution to the total DS86 dose, the loss or gain of shielding as a result of the blast effect, particularly in the first several seconds following the detonation of a bomb, could substantially influence kerma in shielded areas and, ultimately, organ absorbed dose. Time-dose dependencies have not, however, been taken into account either in this new system of dosimetry or the old;

(c) attenuation of the FIA gamma kerma by wooden Japanese structures, houses and tenements is approximately twice as great under the DS86 than under the T65 dosimetry (the average transmission factors under the two systems are 0.90 (T65) versus 0.46 (DS86) in Hiroshima and 0.80 versus 0.48 in Nagasaki). However, attenuation of the neutron kerma by such structures differs much less strikingly (the average transmission factors are 0.36 (T65) versus 0.31 (DS86) in Hiroshima and 0.41 versus 0.35 in Nagasaki);

(d) transmission of gamma rays through tissue is significantly higher, at least for the deeply situated organs, than had previously been estimated [K14]. It must be borne in mind, however, that in the T65 system each specific organ transmission factor is a constant averaged over all postures, orientations and ages; whereas in the DS86 system, fixed values are not used for the proximally or "heavily" exposed (defined as those survivors within 1,600 m in Hiroshima and 2,000 m in Nagasaki), where detailed exposure histories are generally available. Their organ doses reflect the circumstances of their individual exposures, including posture, orientation and age at the time of the bombing. The increased tissue transmission for most organs tends to offset, wholly or largely, the changes in the shielding transmission factors;

(e) finally, for some 18% or so of the exposed members of the Life Span Study cohort (largely individuals surviving in concrete buildings or factories), doses cannot as yet be computed, and the new dosimetry improves but does not clarify all of the implausibly high exposures seen with the T65 system. There remain a number of survivors whose estimated whole-body shielded kerma exposures exceed 4 Gy or, in some cases, 6 Gy. These are doses at or above the recently estimated LD95 in these cities [F13]; given the virtual obliteration of the immune system at doses in excess of 7 or 8 Gy, survival under the

circumstances that obtained in these cities would be most unlikely. Better means are needed to address these incongruities than the simple truncation of dose, since their inclusion in analyses can affect the shape of the dose-response relationship as well as estimates of its parameters [G13, G18, J6].

506. As previously seen with the T65 doses, a statistically significant increase in the frequency of deaths with increasing dose is observed for leukaemia, cancers of the oesophagus, stomach. colon, lung, breast, ovary and urinary bladder and multiple myeloma. No significant increase is as yet observed for cancers of the gallbladder, pancreas, uterus and prostate or for malignant lymphoma. The most recent report was extended to include other sites of cancer, such as bone, pharynx, nose and larynx, and skin except melanoma. but none of these sites showed a significant dose-response relationship [S49]; however, mortality from tumours of the central nervous system other than the brain tends to increase with dose $(0.10 > p > 0.05)$ (mortality from brain tumours alone does not).

507. While the excess in leukaemia mortality has declined with time, it none the less remained significantly elevated as late as 1981-1985, showing that the period of risk is at least 40 years rather than the commonly supposed 25. For cancers other than leukaemia, excess deaths continue to increase with time in proportion to the natural cancer rate for the attained age, and the relative risk remains unchanged over time for all specific age cohorts except the youngest, i.e., 0-9 years at the time of the bombings. For the latter cohort, unlike the older ones, the time from exposure to death is shortened with increasing dose for all cancers except leukaemia, and the relative risk decreases with time (Tables 51 and 52).

508. Tables 51 and 52 show the time course of excess risk in the DS86 subcohort data as a function of age at and time since exposure, for relative and absolute excess risk, in 10-year groups. The relative risk at 1 Gy changes significantly with time after exposure. The magnitude of this change is known only over a limited time period (about 40 years) since exposure.

509. Tables 53 and 54 give three summary measures of risk, namely, the excess relative risk at 1 Gy, excess deaths per 10^4 PYGy and the attributable risk. for all malignant neoplasms, leukaemia, all cancers except leukaemia, and eight specific sites of solid tumours based on the T65 and DS86 systems. These risks were derived by fitting a linear dose-response model to the data from both cities, both sexes and all ages at exposure within that subset of individuals in the Life Span Study sample for whom both T65 and DS86 doses are presently available (some 82% of all exposed individuals in the sample). Note that in so far as shielded kerma is concerned (Table 53), under the DS86 system, the excess relative risks are increased from 35% (stomach cancer) to as much as 53% (cancer of the ovary and other uterine adnexa). For excess deaths, the corresponding figures are 31% (multiple myeloma) and 61% (cancer of the ovary and other uterine adnexa). However, for no site or group of sites does the attributable risk change as much as

10%. For organ absorbed dose (Table 54), with the exceptions of cancer of the female breast or the ovary and other uterine adnexa, the risks are invariably lower with the DS86 doses and as much as 30% lower in the case of cancers of the stomach (excess relative risk).

510. Over the range of doses from 0 to 6 Gy, there is no clearly significant evidence of non-linearity (although other forms of response fit the data), so from a purely statistical point of view linear risk estimates are a reasonable summary of the dose-response. Moreover, when linear. quadratic, and linear-quadratic models (with or without provision for cell-killing) are fitted to the data on all cancers except leukaemia and on those five sites where a clear dose-response curve had previously been obtained (i.e., leukaemia, and cancers of the stomach, colon, lung and female breast), a simple linear model fits the data on leukaemia, cancers of the stomach, lung and female breast, and all cancers except leukaemia better than the quadratic model and as well as the linear-quadratic model, as judged by the deviance (that is, twice the difference in the log likelihoods under the full model, which exactly fits the data, and under the model based on the parameters that have been estimated). Inclusion of cell-killing does not significantly improve the fit, except in one instance where leukaemia mortality under either the linear or linear-quadratic model fits somewhat better with a cell-killing term. These findings hold true both for organ absorbed doses and shielded kerma.

511. Under the DS86 system, the neutron doses, although not wholly negligible, are so small that meaningful estimation of the neutron RBE is difficult, if not impossible. Reasonable RBE estimates cannot be derived directly through maximum likelihood estimation; however, some insight is possible if it is assumed that the small inter-city differences that still obtain reflect differences in neutron exposures. With the DS86 organ doses, assuming an equality of excess relative risk between Hiroshima and Nagasaki, the neutron RBE for leukaemia is 20-30; for all cancers except leukaemia, 30 or more; and for cancers of the stomach, lung and female breast, less than 1. Based on an equality of excess deaths between the cities, the neutron RBE for leukaemia or all cancers except leukaemia is 30 or more; for lung cancer, 10-20; and for cancers of the stomach and female breast, less than 1. The disparity between these estimates attests further to the difficulty of deriving meaningful estimates of the RBE with the new dose estimates for the survivors.

512. The differences between the cities are smaller under the new system than under the old for all sites of cancer, including leukaemia, and are no longer statistically significant. However, at face value, mortality in Hiroshima remains higher at most doses than in Nagasaki, for leukaemia as well as all cancers except leukaemia. This fact. when coupled with a similar consistent tendency for other indices of radiation damage (such as the frequency of chromosomal aberrations, lens opacities, and epilation), suggests that some explanation for the small inter-city difference in dose response is still necessary.

C. UNCERTAINTIES ASSOCIATED WITH RISK ESTIMATES

513. Even after many decades of study, the uncertainties that surround estimates of the carcinogenic effects of radiation are many and fundamental. Indeed, there is still no model of the underlying process that is clearly the correct one. The importance of a good theoretical model is greatest where the data are weakest, at low doses of low-LET radiation, so that our ability to estimate these risks is severely limited.

514. Because the majority of all cancers appear to have an environmental origin in the sense that avoidable exposure to environmental risk factors is involved [D13], much of this Annex has dealt with the problems in risk evaluation caused by the existence of multiple risk factors. In addition to environmental risk factors, there are also many host factors, such as genes, age, hormonal status, sex and the like, that affect risk.

515. It is probable that in any population exposed to ionizing radiation there is variation in the exposure to other risk factors. At low levels of radiation, this variation may be greater, perhaps much greater, than the risk produced by the radiation itself. It is not surprising that it is difficult to estimate risk at low doses or that different results are often obtained. The methods used to estimate confidence intervals tacitly assume that all exposed individuals in a given category (e.g., age, sex or dose) have equal risk, which seems unlikely to be true.

516. The most important documented other risk factor is smoking. Another source of bias is the "healthy worker effect": in occupational cohorts, workers are often healthier than the general population so that their baseline cancer rates may differ from the rates of the larger population, complicating the problem of determining the expected number of cases in these cohorts unless control groups from within the cohort are used.

517. The twentieth century has been a period of rapid change in levels of exposure to cancer-causing agents in all populations in which radiation exposure data are available. This is reflected in changing cancer rates within populations over time. All of the major cohorts used in radiation biology to estimate cancer risks have experienced changing exposure levels, though it has not been possible to account for this well in any study. Estimates of risk derived from cohorts that have been followed for the past half-century to the present will have inexact application to cohorts exposed now or in the future, and the degree of the inexactness is not known.

518. There is substantial variation in general mortality rates in different countries. Exposed individuals may be expected to experience somewhat different lifetime risks in a developing country as compared with an industrialized one. However, much of this difference in overall mortality occurs during childhood and would have little effect. Also, cancer rates for most sites are lower in developing countries, so that the absolute excess, and perhaps even the relative risks for the same dose, may be different. Most large population exposures studied to date have occurred in industrialized nations; there are few data and perhaps less exposure in the developing countries.

519. In addition to changing baseline cancer risks and the effects of other exposures, there is uncertainty over the dose-response pattern. Most current studies use a linear model for breast and thyroid cancer and a linear-quadratic model for other sites; these are the best-available models only, for the data do not really permit the validation of a specific model with confidence. It is unfortunately true that most estimates of low-LET, low-dose effects are based on extrapolations from high-dose data.

D. UNCERTAINTIES ASSOCIATED WITH RISK PROJECTIONS

520. The many uncertainties involved in the estimation of risk from observations on exposed cohorts have been reviewed in this Annex. The main limitations may be stated as follows: (a) no single large cohort has as yet been followed throughout its entire lifetime, so that the lifetime effects of exposure cannot be empirically determined; (b) the data that are available are most incomplete for those who were young at exposure: these individuals have not reached an advanced enough age for the bulk of their risk to be expressed, yet their lifetime risks may be the greatest; and (c) there are not now, and for the foreseeable future will not be, sufficient data on low doses to allow useful risk estimation.

521. In the face of these limitations, there are formidable problems in determining what model(s) to use in projecting risk forward into the unobserved future lifetimes of potential cohorts. Once the current cohorts have been completely observed, risk projection will have a sounder empirical basis.

522. The work of Muirhead and Darby [M36, M37], cited earlier, as well as models applied by the Radiation Effects Research Foundation (RERF) [S49], shows clearly that, depending on what covariates are considered and on how their effects are modelled, one can obtain strikingly comparable degrees of fit even to the best available data on the major exposed cohorts. In the Muirhead and Darby models, the parameter γ expressed, at values of 0 and 1, the 'pure' multiplicative and additive projection effects; however, the most likely value of this parameter was sometimes statistically indistinguishable from either of these models under certain combinations of covariates. With an intermediate value of γ, the intuitive biological meaning of the model becomes unclear, and the model is probably best thought of as an empirical one only. Given this, it is clear, as noted in Muirhead and Darby [M37] that a variety of models could be constructed with approximately equivalent goodness-of-fit.

523. Although the goodness-of-fit of several projection models to the empirical data may be comparable,

their projected lifetime risks may not be as close. Being, therefore, currently unable to make lifetime projections with much confidence, alternative models have to be presented, which, hopefully, bracket the true risks. Even so, there is no way of specifying quantitatively the degree of uncertainty in these alternatives.

524. Until very recently, it had appeared from experimental animal data and empirical data on humans that the relative risk projection model was the more appropriate of the two models for most solid carcinomas. However, if the excess risk of these tumours eventually declines with advancing time since exposure, as some data now suggest, then neither simple additive nor simple multiplicative projection effects will pertain, and none of the models, even hybrid models such as those of Muirhead and Darby, which describe the effects of time since exposure in a monotonic way, will be applicable.

525. These are fundamental problems, for it does not currently appear possible to discriminate among the various projection models based on their fit to empirical data. The only practicable solution to this problem may be to wait until the experience of the Japanese, the spondylitics and the other cohorts is more fully expressed than at present and to derive empirical projection models. Even so, changes in baseline risks, as well as confounding cancer risk factors, may make such projections inaccurate for future cohort experiences.

VII. RISK PROJECTIONS

A. GENERAL CONSIDERATIONS

526. In chapter II of this Annex, the various concepts related to risk projection, the kinds of data required, and past efforts to estimate lifetime risk from exposure to ionizing radiation were discussed. In this chapter, the most appropriate existing data will be used to compute estimates of lifetime risk for those cancer sites for which sufficient information exists to make meaningful projections. The purpose is to derive approximate estimates of the risk of exposure to low-LET radiation, taking into account sex, age at exposure and time since exposure for the lifetime of an entire exposed population.

527. Radiation-induced mortality in a population may be represented in a number of ways, most commonly as either the expected lifetime number of excess cancer deaths in the exposed population or the number of person-years of life lost because of cancer deaths, both per unit collective dose. Estimation of these expressions of risk remains formidable, as does a meaningful synthesis of the estimates that are already available. The task is complicated by one or more of the following main difficulties: (a) the unique nature of some of the samples from which risk coefficients have been derived; (b) the differences between studies in sample sizes and in the periods of follow-up; (c) the methods of case ascertainment that have been employed;

(d) the poor knowledge of the doses received and their distribution over sites; and (e) the nature of the comparison groups used.

1. Whole-body risk coefficients

528. Some of the numerous studies described elsewhere in this Annex, although important in their own right, are of limited value for projection purposes; they provide the relative frequency of occurrence of cancer in an exposed group, as contrasted with a non-exposed referent one, but often at only one of the many sites of interest, and the dosimetric uncertainties make estimates of the risk of cancer per unit dose difficult. Commonly, doses in these particular cohorts have been concentrated in one part of the informative range for estimating dose-response patterns, making it difficult to estimate effects at low or intermediate doses. Three studies, namely, those of the ankylosing spondylitis patients [D11, D21], the women treated with radiotherapy for cervical cancers [B12] and the survivors of the atomic bombings of Hiroshima and Nagasaki [S48, S49], have been the bases for estimating the frequency of occurrence of cancer, per unit dose, at multiple sites of malignancy. But, even here, however, derivation of a combined risk coefficient is difficult and has not been attempted.

529. While these three studies agree generally in identifying the sites at which the frequency of cancer is elevated following exposure to ionizing radiation, the study-specific estimates of the excess relative risk for specific malignancies per unit dose, based on the information currently published vary, particularly in so far as the cervical cancer series is concerned. There are numerous reasons why this should be so, but especially pertinent are the conditions of exposure, the nature of the dose data presently available, differences in the age or sex distribution of the exposed individuals in the study samples, the dissimilar periods of follow-up, and the background rates used to compute the expected number of cases. Table 55 summarizes the main characteristics of these three studies and illustrates the differences between them in the respects just enumerated. These points were reviewed in chapters III and IV.

530. Exposure of the patients with cervical disorders or ankylosing spondylitis occurred because of illness; this was not the case among the Japanese survivors. The reasons why these patients may not be representative of the general population were discussed in chapter IV. In the two patient series, exposure was to either x rays or gamma rays, whereas the atomic bomb survivors received a mixed dose of gamma rays and neutrons, albeit primarily the former. The Japanese sample alone includes a full representation of sexes and ages; the other two studies are restricted either wholly or largely to one sex, and they do not include a sufficient number of individuals below the age of 25 at the time of exposure, when the excess relative risk appears to be larger, to provide an estimate applicable to a general population. Individual estimates of dose are not available for all (or even the majority) of the patients with cervical disorders or ankylosing spondyl-

itis. Risk coefficients have been derived from the mean dose among a 7% random sample of the spondylitis patients, and dose-response estimates, based on the individual doses received by the cervical cancer patients in that series, encompass only a subset of the patients. However, mean doses are often poor descriptors of the dose distribution, notably among cancer patients, because of the highly skewed nature of the individual doses and their wide range. As to the periods of follow-up, the maximum length of follow-up of the first sample members is similar in the three studies, but since enrolment proceeded over a longer period of time in the two patient series, the mean years of surveillance for them is substantially shorter than for the atomic bomb survivors. In terms of sample size, the atomic bomb survivors and the cervical cancer series are approximately equivalent, but the number of the person-years at risk in the study on the atomic bomb survivors is much larger. In the cervical cancer and spondylitis series, unlike the atomic bomb survivors, the variation in doses among exposed organs is very different, because the treatment was concentrated on one part of the body. This makes whole-body equivalent dose estimation difficult. There have also been marked changes in the nature of x-ray equipment and in therapeutic methods. Finally, there are differences in the nature of the referent groups in the three studies; these were thoroughly discussed earlier in this Annex (see chapters I and III). A summary of the excess relative risks per gray obtained in these three studies is provided in Table 56.

531. A special feature of the atomic bomb survivors is that they received exposure from low-LET radiation and from neutrons simultaneously. It is important therefore to consider how the projections to follow would be affected by the assignment of either a fixed or a dose-variable RBE for neutrons, relative to gamma rays. Figure XIX provides, in graphical form, the change in the estimated number of excess deaths
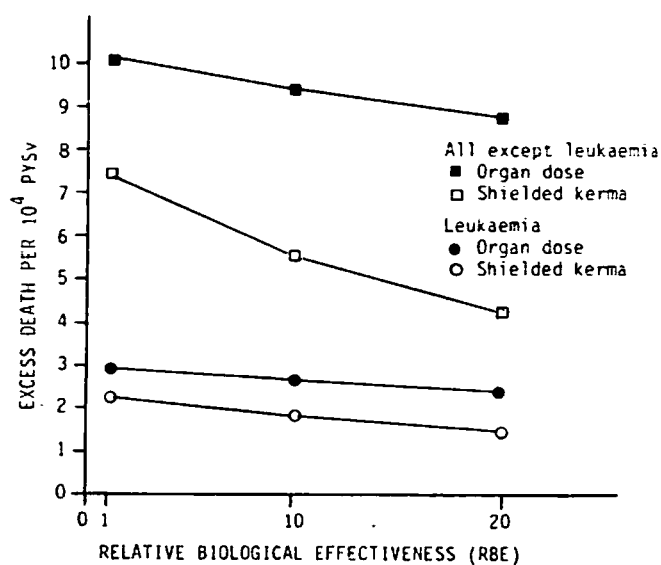
Figure XIX. Changes In risk coefficients for varying values of the RBE of neutrons, relative to gamma rays, based on Japanese DS86 data.
[S48]

with fixed values of RBE varying from 1 to 20. It will be noted that the risk coefficients for both leukaemia and all cancers other than leukaemia become smaller as the assigned RBE increases. Over the range of 1 to 20, the risk estimates based on shielded kerma diminish by about 54-72%; however, the estimates based on organ dose equivalent diminish by only 15-20%, reflecting the higher transmission values associated with gamma- and neutron-radiation under the DS86 system of dosimetry. Elsewhere, Shimizu et al. [S48] have shown that the use of a variable RBE, one changing as a multiple of the inverse of the square root of the neutron dose, would have an approximately equivalent effect on the projections. Thus, for example, the estimate of the excess deaths from leukaemia, using an RBE equal to $1/\sqrt{D_N}$, where D_N is the neutron dose in gray, is 2.93; whereas that based on an RBE equal to $20/\sqrt{D_N}$ is 2.47. Similar changes occur for excess deaths attributable to cancers other than leukaemia; the risk coefficient changes from 10.08 to 8.86 excess deaths per 10^4 PYGy, or slightly less than 20%.

2. Site-specific risk coefficients

532. In addition to the three studies that involved (albeit under different conditions of exposure) the simultaneous irradiation of many tissues in the body and from which risk estimates could be extracted and their relationships analysed, there are a large number of other studies in which single tissues were exposed to radiation for a variety of purposes and from which risk estimates to individual tissues have been derived, as reviewed in detail in chapter III. The risk coefficients resulting from these studies are summarized in this section.

533. Since the UNSCEAR 1977 Report [U2], in which radiation carcinogenesis in humans was last reviewed, several organizations have estimated summary risk coefficients (absolute or relative) for a variety of major organ sites. These include studies by BEIR III [C4] in 1980 and by the United States Nuclear Regulatory Commission in 1985 [G11], and the United States National Institutes of Health, also in 1985, in the radioepidemiological tables [U3]. Their reports attempted to combine the literature available at the time. The BEIR III Report synthesized individual studies along with the most recent Japanese data then available: Gilbert [G11] and the radioepidemiological tables relied heavily on BEIR III, modifying their estimates according to a few other reports but mainly basing them on the then-latest data from the patients treated for ankylosing spondylitis and the atomic bomb survivors. Each of these studies, to which the reader is referred, discussed the reasoning behind its respective site-specific coefficients. For comparison purposes only (because the information on which they are based is now out of date), the summary risk coefficients for each study are given in Tables 4 and 8 [C4, G11].

534. Because these studies appeared in the period 1980-1985, they could not include the results of the latest data and dose revisions in Japan [R20, S49] and

in the spondylitis series [D21, L16], nor could they include the recently published risk coefficients from the cervical cancer series [B36, B38]. Site-specific risk information from the most recent studies is given here in Tables 26, 46, 51, 52, 53 and 54. These tables provide the current estimates of risk from the three largest studies based on age at exposure, time since exposure and sex. The scientific details of these studies were discussed earlier, along with the limitations and specific characteristics of each study population.

535. Chapter III of this Annex reviewed many other studies in which site-specific risk coefficients were estimated. While they vary greatly in their particulars, e.g., sample size and the like, it is worth summarizing the risk coefficients from these studies. For each site, reference will be made to the tables and figures, discussed in chapter III, that provided the best data on risks. Also, the principal bibliographic references for each site will be given, as will be the general range of risk estimates from other studies not already included. Note that the estimates in the following summary that are derived from the Japanese or spondylitics are based on the old dosimetry and do not include the most recent data reports (these values are given in Table 56).

536. *Leukaemia.* While many studies of different types of exposure have found an excess of leukaemia, the best risk coefficients come from the spondylitis patients [D21, L16, S31], the Japanese data [S48, S49], and, very recently, from the marrow-weighted study of cervical cancer patients [B36]. These individuals received exposures to external low-LET radiation. The risk coefficients are included in Table 56. Some other dose-response data, from gynaecologic patients, were summarized in Table 31. The BEIR III Committee estimated the absolute risk coefficient for brief exposure in childhood to be about 0.01-2.2 excess cases per 10^4 PYGy [C4; see Tables V-17 and V-18], and Ron and Modan [R1] estimated absolute risk to be 0.60 male and 0.87 female cases for the same unit of exposure, although this difference was not statistically significant.

537. *Multiple myeloma.* Risk coefficients for multiple myeloma are summarized in Table 32. The most important reference for these data is [C10]. A recent estimate from Japan gives 0.48 incident cases per 10^4 PYGy bone marrow dose [H5, I2]; however, the latter estimate is based on the T65 dosimetry.

538. *Bone.* Table 33 provides a summary of risk coefficients for bone cancer based on an analysis by BEIR III [C4]. Figure VIII presents dose-response data. Other estimates for gamma-emitting radionuclides are 2.4 excess cases per 10^4 PYμCi for long-half-life isotopes (absolute); 1.8 (children) and 1 (adults) for short-half-life isotopes; and for alpha-emitting radionuclides (absolute) 200 per 10^4 PYGy [T11]. There are many cases of bone cancer in exposed children, but dose-response estimates are unreliable relative to a general population since most of the children, exposed during treatment of retinoblastoma, are genetically susceptible to osteosarcoma even in the absence of irradiation (see section III.B).

539. *Breast.* There are no data on breast cancer in males. Tables 36, 37 and 38 summarize the details of risk coefficients from a variety of studies. For adult exposures, the range of absolute risk coefficients is 3-10 per 10^4 PYGy, and that of relative risk coefficients is 2-5. For juvenile exposures the data are less reliable, but absolute risk coefficients are 3-8 per 10^4 PYGy [B6, T6] and the excess relative risk at 1 Gy, based on death certificates, is about 0.69 in the most recent T65D data from Japan [P15].

540. *Thyroid.* Thyroid cancer risks (incidence) are summarized in Tables 20, 21, 22 and 39 and in Figure I. Other estimates are 1-4 per 10^4 PYGy [C4, Z3] for adults and 1.5-9.5 for children [S13, S38], as judged by a variety of studies, including those of exposure to fallout. A major recent report discusses thyroid cancer induction in detail [N5]. There is about a 3:1 sex ratio of cases, with females predominating, and it has been estimated that only about 10% of all cases become fatal; many benign tumours also arise. The latency period for fatal cancers appears, however, to be very long (even up to 40 years or more), so that the current data may still be incomplete.

541. *Skin.* Satisfactory summary risk estimates for skin cancer incidence do not exist. The BEIR III estimates (see [C4], Table A-32) of between 0.44 and 1.02 cases per 10^4 PYGy, based on scalp and thymus irradiation, are not consistent with the chest fluoroscopy data. In uranium miners, Sevc [S51] has estimated one excess case of basal cell carcinoma of the skin per 10^4 PYSv. Information is not yet available from Japan.

542. *Lung.* Other than the Japanese and spondylitis patients, the best data on lung cancer are derived from individuals who inhale alpha-emitting radionuclides. Most data come from males, except in Japan, and the occurrence of this cancer is seriously affected by smoking interactions; there is as yet no consensus on whether the effects of smoking are more additive in nature or more multiplicative. Thomas and McNeill's [T11, T20] summary of these risks is provided in Table 10. These absolute risk coefficients are in units of million person-years per working level month (WLM); as discussed earlier, an approximate factor for converting from cases per 10^6 PY WLM to cases per 10^4 PYGy is 1.67 (with 1 WLM corresponding to 6 mGy absorbed dose in the bronchial tree). The absolute estimates range between 5 and 50 cases per 10^4 PYGy. As noted in chapter III, even when they are based on the same data, the estimates do not always agree, and they must be treated as uncertain. Most estimates of relative risk from brief external exposures to doses of less than 10 Gy are 1.2-2.0. Full treatments of risks to the lung will be found in [C20, I11].

543. *Digestive system.* The estimates presented from Japan and the spondylitis patients (see Table 56) constitute the best information available on most digestive system cancers. As previously discussed, the data from the spondylitis patients are not reliable in regard to colo-rectal cancer because of their high spontaneous rates of colo-rectal disease, and the results from studies of pelvic irradiation to treat gynaecological disorders are inconsistent and appear

to be affected by cell sterilization and other biological or environmental effects. Most liver cancer data come from internal emitters, particularly the Thorotrast patients. The Japanese and the spondylitis patients show uncertain results, and neither the studies by themselves nor their joint analysis has found an excess sufficient to derive useful risk coefficients (the BEIR III best estimate is given in Table 4). The liver is a site of frequent metastasis, and risk estimates may confound primary and secondary hepatic cancers.

544. *Salivary glands.* Detailed risk coefficients for salivary gland cancers, based on results of many studies, are given in Table 42. These were derived by Land [L11] in a summary analysis of this site. Land estimated the best overall absolute risk coefficient for this site to be 0.26 ± 0.06 cases per 10^4 PYGy. A recent estimate from Japan, based on T65 dosimetry, is 0.056 ± 0.036 per 10^4 PYGy [O4, T15].

545. As has been noted, the inter-study spread of values observed for single tissues is large, sometimes very large, presumably owing to the differences mentioned in paragraph 527. There is no fully satisfactory way to make suitable allowance for these differences in generating a combined estimate. Thus, there are only two options: either to combine the data without regard to the important differences enumerated above, a step that does not appear defensible; or to select the best possible set of estimates from among the various studies. Therefore, the Committee compares in the section to follow the data from the atomic bomb survivors, the ankylosing spondylitis series and the series of patients irradiated for cervical cancer.

B. SUMMARY OF RISK PROJECTION METHODS AND RISK ESTIMATES

546. The projections by the Committee will consider the induction of leukaemia and other cancers separately, drawing from the atomic bomb survivors and the ankylosing spondylitis and cervical cancer patients. Estimates are computed at 1 Gy of high dose rate exposure based on a linear dose-response model in the case of solid cancer. Data on leukaemia in the spondylitis and cervical cancer series take account of cell killing. The Committee has adjusted for this fact in the estimate it used to project the lifetime risk among the spondylitis patients, but could not do so in the case of the cervical cancer series. Separate estimates are computed from an additive projection model and a multiplicative projection model, using the life-table methods and minimum latency periods described below. These methods are similar in concept to those used by the BEIR III Committee [C4] and by the Nuclear Regulatory Commission of the United States [G11], although the details differ, largely to accommodate new data. It has generally been presumed that the additive and multiplicative models encompass the range of reasonable projections; however, Muirhead and Darby [M36, M37] have questioned whether this is true. As was seen in chapter II, they contend that it is difficult, given current data, statistical methods and biological theory, to choose between the additive and multiplicative models, or to determine some intermediate ones.

547. In addition to excess cases per 1,000 persons exposed to 1 Gy, estimates will be provided of lost life expectancy in person-years per 1,000 persons.

1. The basic projection model

548. The lifetime risk coefficients estimated in this chapter have been computed using an interactive, parametric demographic projection model developed by the Centre d'Etude sur l'Evaluation de la Protection dans le Domaine Nucléaire (CEPN, France) in 1985. It employs classical double-decrement life-table techniques and is not dependent on the data nor assumptions used in the present calculations. The model is sufficiently general to permit a wide range of choice of demographic, epidemiological and biological data or assumptions. Several kinds of computations can be made, including: (a) the effect of a single exposure on a cohort of a given age and sex, and (b) the effect of a single exposure to a given population of mixed ages and sexes.

2. Analytical expression of the model

549. The analytical formulation for calculating lifetime risk is the following: at age a and for a dose D, the absolute excess mortality rate $V(a,D)$ is considered. If an exposure at age a_0 is assumed, the corresponding lifetime risk $U(a_0,D)$ is

$$U(a_0,D) = \int_{a_0}^{100} V(a,D)[N(a,D)/N(a_0)]da$$

where $N(a,D)/N(a_0)$ is the probability of survival to age a for an individual alive at age a_0, taking into account the risk of mortality both from radiation-induced cancer, and from all other causes.

550. To compute this lifetime risk, the studies on irradiated populations provide the following risk coefficients: (a) the absolute excess mortality rate, $I(D)$, and (b) the excess relative risk per Gy, that is $K(D)$.

551. The following two expressions for $V(a,D)$ are associated with the additive (absolute) and multiplicative (relative) projection models, respectively:

$$V(a,D) = I(D)$$

$$V(a,D) = K(D)C(a)$$

where $C(a)$ is the baseline cancer mortality rate in the population for the sites under consideration.

552. Thus, the lifetime risk estimates can be expressed as follows:

Additive risk projection model

$$U_a(a_0,D) = I(D) \int_{a_0+L}^{a_0+L+P} [N(a,D)/N(a_0)]da$$

Multiplicative risk projection model

$$U_m(a_0,D) = K(D) \int_{a_0+L}^{a_0+L+P} C(a)[N(a,D)/N(a_0)]da$$

where L is the minimum latency time and P the plateau period (i.e., the period of time following exposure during which manifestation occurs, and over which the risk is presumed to be constant). It should be noted that this method of estimating lifetime risks is essentially the same as that employed in the BEIR III Report [C4] and in the NUREG Report [G1]. An alternative approach would be to calculate separately the total number of cancers occurring in a lifetime in an exposed and a non-exposed population, and to take as the excess number of cancers the difference between these totals. The latter method would result in a smaller number of excess cases, for it excludes from the excess that fraction of cases which would have developed cancer for non-radiation related reasons at a later date.

3. Calculation of the loss of life expectancy

553. Using the same notation as in paragraph 549, the life expectancy at age a_0 (i.e., the average survival time for individuals alive at age a_0) is given by

$$\int_{a_0}^{100} [N(a,D)]/[N(a_0)]da$$

If this is computed both assuming no radiation exposure and assuming exposure at dose D, the difference between the two quantities is the loss of life expectancy due to exposure.

4. Demographic and background epidemiological data required

554. The characteristics that must be known for the population under study are the following: age and sex structure, overall mortality rate and cancer mortality rate by site. Since the model uses a year as the time-scale of interest, annual values are obtained by linear interpolation from the published information (which is generally presented in age intervals of 5 or 10 years). The survival rates are computed from current mortality rates and the projections assume that these will not change in the future.

5. The computational process

555. The principle of the model is to compute, by a discrete time analog of the basic demographic equation, for every year, i, the numbers of alternative outcomes possible for survivors through the previous year, i − 1, (that is, the numbers of fatal cancers at each site under observation, of deaths related to all other causes and of survivors to the next year). The first value is calculated and serves to increment the cumulated number of cancer cases already computed for the previous years and then to modify the baseline life-table. This calculation is limited to the assumed period of expression of excess cancer risk after the exposure. This period depends on the site or tissue under consideration: the minimum latency period has been taken to be 2 years for leukaemia and 10 years for all solid cancers. The plateau durations are

assumed to be 40 years and lifetime for all cancers except leukaemia and 40 years for leukaemia. The number of survivors at age i + 1, N(i + 1), is equal to the number of survivors at age i, N(i), minus the number of those who die from baseline mortality, minus the number of those who die from radiation exposure.

6. Reference population

556. The reference populations considered here as the bases for the lifetime projections are the current general Japanese population for the atomic bomb survivors, the current adult male population of the United Kingdom for the spondylitis patients and the current adult female population in the United Kingdom for the cervical cancer series. The first two populations were selected since the studies were carried out in these two countries. The adult female population of the United Kingdom has been assumed to be representative of the other populations among which the cervical cancer study was conducted. The validity of extrapolation to other populations will be considered later.

7. Risk coefficients

557. The excess risk coefficients for the atomic bomb survivors are those based on the DS86 subcohort, as given in Table 54. These coefficients were derived by the authors [S48, S49] on a linear relative risk model, using organ absorbed doses from the explosions, and are restricted to mortality. The RBE of neutrons was assumed to be 1 in their estimation procedure. The coefficients represent mean values for both cities, both sexes (except for the breast and ovary), and all ages at the time of the bombings combined. The sites of cancer that have been selected for risk projection are those for which a statistically significantly increased mortality with increasing dose has been shown; namely, the bladder, breast, colon, leukaemia, multiple myeloma, oesophagus, ovary and stomach. Thyroid, lung and bone will be discussed later. For the spondylitis and cervical cancer series, the risk coefficients are given in Table 56. It is important to note, first, that in all three instances the risk coefficients that are used have been obtained from published reports and do not take into account the underreporting of cancer deaths on death certificates. BEIR III [C4], in its projections, increased these coefficients by 23% to take account of underreporting. A comparable action here would increase the Committee's projections of excess lifetime mortality by 20-25%. Second, and specifically with respect to the risk coefficients derived from the atomic bomb survivors, there is a levelling off, or a plateauing of the risk at shielded kerma of approximately 4 Gy and higher, and thus a linear relative risk model fitted to the full array of observed doses may underestimate the risk at doses below 4 Gy (approximately 3 Gy in organ absorbed dose). When the risk is estimated based on shielded kerma of less than 4 Gy, the excess deaths per 10^4 PYGy are approximately 5% higher for leukaemia,

485

and 15% higher for all cancers except leukaemia [S48].

558. Two kinds of coefficients are used as input, as in Table 54; these vary with the type of model chosen for the lifetime projection: the excess relative risk per Gy is used for the multiplicative projection model (constant relative risk) and the excess mortality per 10^4 PYGy is used for the additive projection model (constant absolute risk). In all cases, both the multiplicative and the additive projection models have been used, for comparative purposes (even though, as discussed earlier, for some sites one model appears to be more realistic than the other). Use of the two models in this context is not meant to imply any description of causative biological processes; the models are simply used to derive lifetime risk projections.

8. Indexes of harm

559. The indexes of harm have been restricted to different expressions of the effects of excess mortality associated with radiation-induced cancers in a lifetime after exposure. Two indexes are presented. The first is the lifetime excess number of fatal cancers, and the second is the loss of life expectancy in a population of 1,000 persons exposed at various ages to a single dose of 1 Gy of low-LET radiation at a high dose rate to each tissue.

560. Although the values of the indexes are calculated by the Committee at 1 Gy, values may be computed at other doses, provided the shape of the basic dose-risk relationship (linear, linear-quadratic, etc.) is known.

9. Treatment of uncertainty

561. The risk coefficients given in Tables 54 and 56 are accompanied by their 90% confidence intervals, when available. The upper and lower 90% statistical confidence intervals of these coefficients have been used to calculate the uncertainty inherent in the indexes of harm. It must be emphasized that this does not encompass the total uncertainty associated with the projections but only the statistical one attributable to the risk coefficients used as inputs. Uncertainties on dose and on demographic variables are not considered explicitly.

10. Fractionated and low-dose-rate exposure

562. The risk coefficients derived from the Life Span Study and given in Table 54 relate to instantaneous exposures to moderate to high doses and in principle represent only such exposure conditions. As shown in Table 55, irradiation of the cervical cancer patients was protracted over a few days or weeks, and that of the spondylitis patients was fractionated over a few weeks. For low-dose rates, an appropriate correction factor should be used if the indexes of harm are to reflect the experience coming from such epidemiological and experimental conditions.

C. RESULTS OF PROJECTIONS

563. The projections that follow should be prefaced by some statements about the approximations inherent in the model adopted. First, the Committee's lifetime projections are based on a simple modelling procedure, and deliberately so. More complex models could have been used and more effort to adjust for the known shortcomings in the data could have been made, but with each such *ad hoc* adjustment the results would have become progressively more particular and less and less applicable to the broad community of countries to which the Committee's deliberations are directed. As an illustration, the risk coefficients the Committee has employed are based on deaths reported to be due to the presence of a malignancy. Death certificates, however, are known to underreport the deaths that actually are attributable to cancer. An adjustment could have been made to account for this underreporting, but the Committee has not done so, for the degree of underreporting will undoubtedly vary from country to country.

564. The Committee has used other simplifications. Among these are age-constant risk coefficients (absolute or relative) that do not change with time following exposure (after the minimal latency period) or with age at exposure, as well as stable age-specific rates of mortality ascribable to cancer and other causes. The Committee has also ignored possible differences in mean survival time after the diagnosis of a malignancy as a consequence of different medical standards in different countries and their evolution with time. Again, while the model used could accommodate other assumptions, the data are still too sparse or contradictory to provide alternatives confidently. For example, the observations on the patients with ankylosing spondylitis suggest that the relative risk coefficient for all cancers other than leukaemia declines with time after exposure [D21], but this has not been seen, at least as yet, among the atomic bomb survivors of Hiroshima and Nagasaki [S49], except for those exposed as children. If the relative risk does in fact decline, then the Committee's projections will over-estimate the lifetime risk. Similarly, if mean survival time of cancer cases increased, the loss of life expectancy would decline, although the total number of cancers would not change much (some diminution would be expected, however, as a result of the increased mortality from competing causes).

565. The coefficients assumed for the computations have been derived by linear regression analysis in the case of the atomic bomb survivors, the ankylosing spondylitis patients, and the cervical cancer series with cell-killing correction for leukaemia in the latter case. The model used by the Committee to project lifetime risks of cancer mortality or life span shortening at 1 Gy of low-LET irradiation administered at a high dose rate does not require selection of any given function of the dose-response relationship and therefore the Committee has not imposed any pre-selected function on the original data in order to derive its two projections.

566. For reasons of convenience, the Committee will consider separately the projections for the adult

population (males and females over 25 years of age), where comparisons among the three studies cited in paragraph 528 are possible; and the young population (below 25 years of age), for which the only reliable risk estimates are those that come from the atomic bomb survivors.

1. The adult population

567. The Committee's projections were carried out according to the assumptions given in Table 57. To allow a comparison of the results of the three studies cited in paragraph 528, the basic assumptions need to be adapted somewhat. First, the atomic bomb survivors study comprises individuals of both sexes and all ages, which the other two studies do not (see Table 55). Consequently, for a meaningful comparison, it has been necessary to examine only the adult population in the Japanese series. This means that the basic risk coefficients shown in Table 56 had to be modified to take into account the subtraction of the young cohorts. It is these modified figures for the absolute excess death per 10^4 PYGy, shown in Table 58, that have been used in the computations that will follow. Of necessity, since the requisite risk coefficients have not been published for the adult population only (nor for the working population, defined as aged 25-64), the Committee has been obliged to use excess risk coefficients based on averaging the sex-specific risks within the age groups 20-29, 30-39 and above 40, and weighting these averages by the proportion of the population within each of the age groups. To estimate lifetime risks in the working population, the Committee has used the risk coefficients derived from all ages and both sexes. Figures of the ankylosing spondylitis and cervical cancer series, which were not corrected, are also shown in Table 58. Second, the cervical cancer series refers only to females, so a female population (that of the United Kingdom) has been taken as the reference; similarly, the spondylitis cohorts are mostly males and therefore the male population of the United Kingdom has been adopted as a referent. Thus, the results of the extrapolations from the Japanese and cervical cancer series should be compared only in the female population, and the results from Japan and the spondylitis series should be compared only in the male population. Third, for cancers other than leukaemia, a comparison is only possible among two of the series, because no appropriate risk coefficient can be derived from the cervical cancer series. The spread of doses between the heavily irradiated pelvic organs (where cell sterilization could be important) and the organs in the upper part of the body (which received very low doses) is so large that risk coefficients based on averaged absorbed doses would have no meaning. These reservations also apply, though to a lesser extent, to the spondylitis series; however, since the authors [L16] provided an average whole-body dose (in addition to excess relative risk [D21]), the computations were made using these summary figures.

(a) Excess lifetime mortality: leukaemia

568. Table 59 shows the results of the Committee's projections, based on the model and assumptions

described, in respect to excess lifetime mortality for leukaemia using the risk coefficients for each of the three major series (Table 58). Under the multiplicative risk projection model, the risk estimates range from 2.8 to 8.1 for females and 9.0 to 14 for males, and under the additive risk projection model from 1.4 to 7.0 for females and 4.4 to 13 for males (excess cases per 1,000 persons at 1 Gy of high dose rate low-LET exposure). Even considering the problems with the risk coefficients in these series, discussed earlier, these values are all well within an order of magnitude of each other.

(b) Excess lifetime mortality: all cancers other than leukaemia

569. Only two of the three general series the Committee has cited give usable estimates of the excess risk of cancers other than leukaemia, namely, the atomic bomb survivors and the patients with ankylosing spondylitis. For the assumption of a lifetime plateau (lower half of Table 59), the estimates of these two series are within a factor of about 2 to 4, the figures being lower for the series on the ankylosing spondylitis patients as compared to the Japanese atomic bomb survivors. It is tempting to speculate that this difference in risk relates to the modality of irradiation being instantaneous for the atomic bomb survivors and fractionated over a few weeks for the ankylosing spondylitis patients. Although this phenomenon is suggested by the data and by no means demonstrated, it is in the same direction that would be in agreement with a large body of radiobiological literature, reviewed most recently in the UNSCEAR 1986 Report and in reference [N1]. This shows that dilution in time of the dose yields generally lower effects than for the same dose delivered at high dose rate and/or without fractionation.

570. When the mortality from leukaemia is combined with that from all other cancers, assuming a plateau of 40 years for leukaemia and a lifetime plateau for all other malignancies (after the minimum latency), between 46 and 56 additional cancers would be expected in a population of 1,000 adults (500 males and 500 females), based on the Japanese risk coefficients, under the additive and multiplicative projection models, respectively.

(c) Loss of life expectancy: leukaemia

571. Table 60 shows the results of the projections in regard to loss of life expectancy attributable to the additional cases of leukaemia. The results are quite similar to those for excess lifetime mortality; namely, all three series provide estimates in generally good agreement. The spondylitis patients and the Japanese-based estimates under the multiplicative model are in fact very similar. Even the greatest discrepancies, between the cervical cancer and the other series, are within a factor of about 5.

(d) Loss of life expectancy: all cancers other than leukaemia

572. Taking the figures in the lower half of Table 60 as the most conservative ones, the projections derived from atomic bomb survivors are two to about four

times as great as those based on the ankylosing spondylitis patients. Life lost calculated by the additive risk projection model is higher than that calculated by the multiplicative risk projection model, but not by much.

573. As Table 60 shows, the expected number of person-years of life lost from all cancers would be about 840 for the additive model and about 620 for the multiplicative model for irradiation of 1,000 adults (500 males and 500 females), based on the Japanese risk coefficients, under the conditions described in Table 57.

574. It warrants reiteration that the absolute values given so far for irradiation of an adult (over 25 years) population apply to 1,000 persons of both sexes when a constant risk coefficient is used.

2. The population of children as a part of the population

575. The epidemiological evidence accumulated to date strongly suggests that the initial relative risk of subsequent malignancy following exposure to ionizing radiation is appreciably higher when exposure occurs early in life (within the first two decades after birth). From what is so far known about the biological aspects of cancer induction, this finding is not unexpected. However, apart from the data on the youngest age at the time of the bombings cohorts in the Japanese Life Span Study, there are few data from which specific risk coefficients can be derived, and even among the Japanese survivors the coefficients available are based on small case numbers and have relatively large sampling errors. These cohorts, furthermore, are those with the largest expected numbers of years still to live, and it is far from clear whether the high excess relative risks presently seen will persist. It is true that the Japanese data suggest a declining risk, both for leukaemia and all cancers except leukaemia, notably among survivors exposed before the age of 10 (the trends seen in Tables 51 and 52 for the 0-9 age group are statistically significant). These cohorts have only recently entered those years of life when the background rates for virtually all solid tumours, as well as for the chronic forms of leukaemia, increase markedly. Thus, it will be several decades before their cancer experience as middle- and older-aged individuals is clear. This poses a dilemma for the projection of lifetime risks. On the one hand, it would be unwise to assume that the risks will decline, for if they did not, the indices of harm could be grossly underestimated. On the other hand, to assume that these excess relative risks will persist throughout life, if in fact they do not, will project a harm that is much too high for these cohorts. It is largely for these reasons that the Committee has elected to examine the childhood population separately.

576. There are two separate aspects of the irradiation of young cohorts: first, their apparently greater susceptibility to the carcinogenic effect of radiation (this aspect can be studied by a discussion of the declining risk coefficient as a function of age) and second, their longer life expectancies relative to adults

and the correspondingly longer time during which the consequences of exposure may be expressed.

577. The first aspect has already been considered in Tables 51 and 52. These Tables present excess relative risks and excess deaths for the atomic bomb survivors (which is the only series for which such estimates, although preliminary, are so far available) as a function of age at exposure and age at time of death, separately for leukaemia and all other cancers. The limited experience does not warrant analysing this phenomenon site-specifically.

578. The second aspect, as it applies to the population of Japan, is illustrated in Table 61. Since the risk coefficient has been presumed to remain constant over all ages, the impact of the demographic component introduced by the younger cohorts may be perceived from this Table.

579. The main difficulties in assessing the impact of exposure on the young arise when one attempts to evaluate the interaction between these two aspects for the purpose of calculating an overall measure of risk for the whole population, considering each age class separately. In fact, each age class will be characterized by its own coefficient of risk and its own demographic future. Since it appears from Tables 51 and 52 that the excess relative risk does not systematically change for ages above 20, and certainly not for ages above 30 (at least for solid cancer), the Committee has not attempted to calculate the whole extent of these changes. It should be pointed out that the observed values at the younger ages, based as they are on a relatively small number of cases, have large and unequal sampling errors. Previous attempts to take age-related coefficients into account have relied solely upon a statistical smoothing of the observed values. The Committee believes, however, that the observed changes in susceptibility as a function of age are not related to time alone, but also to the biological stages in development that are unique to certain ages, such as puberty and its associated hormonal changes.

580. Under these circumstances the Committee decided to make two separate sets of projections, using the multiplicative and the additive projection models: (a) the lifetime excess mortality and loss of life expectancy as it applies to a population for which the same risk coefficient is taken for all ages and (b) the lifetime excess mortality and loss of life expectancy as it applies to a population at ages 0-9 and 10-19, with coefficients specific for these age groups. These latter coefficients are as follows:

	Age at irradiation	
	0-9	*10-19*
Leukaemia		
Excess relative risk	19.1	4.5
Excess deaths	3.42	1.52
Other malignancies		
Excess relative risk	1.56	0.96
Excess death	2.77	6.16

These values have been taken from [S49] (Appendix Tables 5a and 5b), averaging over the two sexes.

581. For the multiplicative model and for excess lifetime mortality, the difference in the final effect introduced by using a measure of risk related to the specific age at exposure rather than a constant risk, that is a risk averaged over all ages and exposure, can be substantial. The computations show that one obtains three to four times more deaths due to leukaemia and all other cancers for the ages 0-9 at the time of exposure by using the age-specific risk. For the ages 10-19 at the time of exposure this difference in risk tends to reduce to 1-2. In both cases this difference will be expected to decline further as the average age in the cohorts increases and the coefficient of risk adopted approaches the coefficient for the whole population. This phenomenon is repeated in the projections for loss of life expectancy.

582. For the additive, rather than the multiplicative, model, the difference between the excess mortalities calculated using the constant coefficient and the age-related coefficient is very small for leukaemia, and it even tends to reverse for the age cohort 10-19. This accords with the fact that the risk coefficient for this particular age group happens to be lower than the average value adopted for computations on the whole population. As is true for the multiplicative model, these effects are almost repeated in the projections for loss of life expectancy.

583. To provide estimates of risk to be applied to the whole population, computations have been made using the various age-at-exposure classes, attributing to each of them the coefficient that applies to that particular class, projecting the risk of that class over the appropriate period of time (40 years or lifetime) and summing up the overall effects over all age-at-exposure classes. This was done for both the multiplicative and the additive projection models and for excess lifetime mortality and loss of life expectancy, separately. The final results of these summations are given in Table 62.

584. Considering the number of fatalities from leukaemia and other malignancies together (upper part of Table 62), it is seen that between about 42 and about 107 deaths would be predicted by the additive and the multiplicative model, respectively. The lower half of the Table shows that between about 950 and 1,370 person-years can be expected to be lost if the whole population is exposed to 1 Gy under the conditions specified.

585. There is a different way of arriving at similar projections; namely, to use a single risk coefficient which does not take age at exposure into account explicitly. It should be noted that this method of projection has its own shortcomings, for a risk coefficient so estimated is essentially a weighted average of the age-specific relative risks with weights proportional to the numbers of cancer deaths in the specific age groups. Thus most of the weight will be given to the older age groups whose actual relative risks are smaller. Nevertheless, to provide a comparison, this has been done in Table 63 in respect to the population of Japan. The values in parentheses provide the corresponding numbers when the upper

and lower 90% bounds of the risk estimate are used (see Table 54). It shows that, under the conditions specified above, one would expect to observe a total of about 71 extra fatal cases under the assumption of a multiplicative projection, compared with about 45 cases for an additive projection model.

586. The first method (Table 62) may overestimate the lifetime excess mortality under the multiplicative model as the excess relative risk in the younger age-at-exposure groups has been falling with increasing time since exposure (see Table 51). On the other hand, this method may well underestimate the lifetime excess mortality using the additive model, as the excess risks have been increasing with time since exposure in the younger age-at-exposure groups (see Table 52). Conversely, under the second method (Table 63) the multiplicative model may underestimate the lifetime harm for the younger age-at-exposure groups, but the harm for these groups under the additive model may be overestimated. With the multiplicative risk projection model there is about a 30% decrease in estimated lifetime mortality from all malignancies using the second method compared with the first, while with the additive model the second method leads to about a 50% increase.

3. Extrapolation to other populations

587. Risk coefficients are always estimated, and lifetime risks projected, in the context of a particular population. Each exposed population from which risk coefficients are estimated has its own background mortality rates from all causes of death, and its own age- and sex-specific cancer rates. Indeed, not all individuals within any given population are at the same risk. Considering this, it is fair to ask what use can be made of risk coefficients obtained from one population for predicting lifetime risks in any other population. The projections given in this chapter have been derived by applying the closest possible expected rates of death (from cancer and from all other causes); namely, those from the same country as the exposed. Even so, baseline risks in the Japanese exposed to the atomic bombs, a wartime and post-war environment, were not the same as those of current Japanese, nor even precisely of those of Hiroshima and Nagasaki today. It is known that there are changes occurring in Japan in regard to baseline mortality rates and that there are also regional differences in Japan, as in every other country. Similarly, the all-United Kingdom mortality patterns are certainly not exactly those of the ankylosing spondylitis or the cervical cancer patients.

588. Because baseline mortality is always changing in every population, and this includes major changes in a variety of cancer risk factors, it is difficult to know how accurate lifetime risk projections might be. One way to place outer limits on this error would be to compare the lifetime risk estimates based on the same risk coefficients and different baseline mortality patterns. For this Annex three populations have been chosen to compare projected risks. To do this, the absolute and excess relative risk coefficients derived

from the experiences of the atomic bomb survivors have been applied to (a) the Japanese population using the Japanese 1980 national mortality patterns, representing the nearest available representative rates for those coefficients; (b) the United Kingdom, representing a rather typical older industrialized nation; and (c) Puerto Rico, representing (as best as worldwide data will permit) a population with high infant and infectious disease mortality, and low cancer rates.

589. The populations are compared in Table 64, and the results of this comparison for leukaemia, other cancers and all malignancies are given in Tables 65 and 66. The latter Tables show that across these three populations there is virtually no difference in risks projected by the additive model. Even for the multiplicative model, the maximum difference, using Japan as the basis of comparison, is a factor of $71/58 = 1.2$. This clearly shows that the lifetime risk projections are very insensitive to differences in overall, and cancer-specific mortality differences within the range of contemporary large national populations, and for leukaemia or all cancers pooled. Thus, the risk projections derived here would seem to have rather broad generality and applicability. Much larger proportional differences may apply to site-specific cancer with large international variation in risk, such as female breast, stomach, large bowel and lung.

590. It should be pointed out, however, that this conclusion applies to only one of the uncertainties in the extrapolation of risk projections to other populations. It is not yet known how much the risk coefficients themselves might vary between different ethnic groups or populations with differing exposures to other carcinogens which could act synergistically; the range of today's knowledge is limited essentially to data from Japan and from a variety of industrialized populations. Within this context, and given the statistical problems in estimation, the range of risk coefficients is rather small, well below a full order of magnitude.

4. Comparisons with previous studies

591. The Committee made its last previous estimates of lifetime risk in the UNSCEAR 1977 Report [U2]. This Report gave values for all cancers of $1.0 \ 10^{-2} \ Gy^{-1}$ (range 0.75-1.75, Annex G, paragraph 318) for low dose low-LET radiation and $2.5 \ 10^{-2} \ Gy^{-1}$ (Annex G, paragraph 317) for high dose low-LET radiation. Leukaemia was about one fifth of the total. The projection was carried out by assessing the leukaemia risk and projecting a ratio of 5-7 for all cancers to leukaemia ultimately, thus obtaining the total cancer risk.

592. Additional epidemiological and other information has accumulated since 1977. This includes extensions and changes in the data for the Japanese atomic bomb survivors, in the ankylosing spondylitis series in the United Kingdom and in various other specific tumour sites such as lung (radon), thyroid and breast. A new study of patients surviving treatment for carcinoma of the cervix has provided additional

information on second cancers at selected sites. Most of these studies make some contribution to quantitative risk estimates.

593. The atomic bomb survivors are especially important and provide the largest single data set over a range of doses. In this population the data have now accumulated over three additional time periods since the 1977 Report was written, viz. 1975-1978, 1979-1982 and 1983-1985. These are important time periods for the expression of solid tumours, 30-40 years after exposure to the bombs. Not only has the total amount of data on excess cancers increased by approximately threefold, but the extension of the data in time and the increasing information for all age cohorts, especially the young, provide further tests of models and thus aid in methods of projection and in knowledge of age dependence. Furthermore, the dosimetry of the survivors has been evaluated (and measured in the survivor range by thermoluminescent methods) and tends to increase risk by factors, when expressed in terms of shielded kerma, between 1 and 2 depending on the cancer site. Some improvements have also been made in statistical methods.

594. The atomic bomb survivors have been used in this report as the main source of risk estimates, while the Committee notes that other sources of data such as the ankylosing spondylitis patients are in general terms consistent with these estimates, especially when the mode of delivery of the exposure is taken into account. The Committee has not itself made primary estimates of risk in the Japanese atomic bomb survivors, but has relied on risk estimates developed in recent publications for the appropriate period of observation. These risk estimates have then been projected to a lifetime separately by the additive and multiplicative models and for both an age-structured population and for risks averaged over one intermediate age range. Lifetime risks have been estimated separately for an adult population alone and an entire population of all ages.

595. In this Annex the risk estimates for a population of all ages for mortality from all cancers at 1 Gy of high dose rate low-LET radiation range from 4 to 11 $10^{-2} Gy^{-1}$ (Table 62), whereas for an adult population alone the range is from 5 to 6 $10^{-2} Gy^{-1}$ (Table 59) (the ranges reflecting the additive and multiplicative models of projection, respectively). Leukaemia accounts for one quarter to one tenth of the total. The Committee has also provided estimates of the years of life lost as determined by the two projection methods. It may also be noted that while the age dependence has become more evident than in the UNSCEAR 1977 Report, sex differences have become smaller.

596. General appraisals of risk estimates have been made by various other groups since the UNSCEAR 1977 Report. The BEIR III Committee of the National Academy of Sciences in the United States produced a comprehensive report in 1980 [C4] which provided a range of from 0.1 to 5 $10^{-2} Gy^{-1}$ for all cancers using additive and multiplicative models for projection and quadratic, linear-quadratic and linear models for dose response. The preferred values of risk at the time the

report was issued were based on the linear-quadratic model and on additive projection and were quite similar to the values in the UNSCEAR 1977 Report (see [C4], Table V-25).

597. Later, for a report of the Nuclear Regulatory Commission in the United States, Gilbert [G11] developed risk estimates based on a linear-quadratic dose-response model (together with upper and lower bounds, roughly a factor of 3 above and below) and both additive and multiplicative projection models and years of life lost (Tables 8 and 9). The lifetime risk estimates ranged from about 0.3 to 6 10^{-2} Gy^{-1} with a central value of about 2 10^{-2} Gy^{-1} for low doses of low-LET radiation.

598. A group constituted by the National Institutes of Health in the United States assembled risk information for the purpose of developing tables of probability of causation (i.e., risk estimates for specific cancer sites at nominal ages as a function of time after exposure [U3]). The input used risk information updated from the BEIR III report similar to that of Gilbert. Lifetime risk estimates can be derived from the basic input using an additive projection model and again values of about 2 10^{-2} Gy^{-1} for low doses would be found.

599. These two recent groups had access to data from the Japanese atomic bomb survivors up to 1978 but were too early to obtain the full benefit of recent risk estimates from Japan utilizing the additional time periods and revised dosimetry now available to this Committee and included in this analysis.

D. RISKS AT LOW DOSES AND LOW DOSE RATES

600. At doses and dose rates defined by the Committee as low (less than 0.2 Gy and less than 0.05 mGy/min for low-LET radiation) radiation-related carcinogenic effects in an exposed population will almost always be masked by the larger carcinogenic effects of other factors. Moreover, in an exposed study population there will always be some level of dose below which no statistically significant excess of cancer occurs compared with the control population. In the dose range below this point, the excess cancer risk cannot be observed and cannot therefore be directly determined. In this dose range the Committee has to use a model to interpolate between the certainly zero excess risk at zero dose and the observed excess risk at doses of the order of 1 Gy. This may require the use of a correction factor if the projections based on high doses and high dose rates are to be applicable to exposures to low doses and low dose rates.

601. In the risk estimates derived above, no correction was made for the possible reduction of effects under conditions of low dose or low dose rate. The experimental literature contains a wealth of data showing that there are such effects. This has been recently reviewed by UNSCEAR [U1] and earlier by the National Council on Radiation Protection [N1]. The former report concludes that for low-LET radia-

tion most dose-response curves for tumours induced in animals are concave upward and may be fitted by linear-quadratic or quadratic models, although in some cases linearity may apply. Moreover, dose rate studies with low-LET radiation almost invariably show a decreased incidence of tumours with decreasing dose rate in animal populations.

602. The human data on this subject are sparse, but are reviewed in the UNSCEAR 1986 Report [U1] which concludes that extrapolation linearly down to zero dose would overestimate the risk by a factor up to 5 in typical situations. The study by Howe [H6] and the very recent study by Holm [H28] are not considered in the UNSCEAR 1986 Report but are discussed earlier in the present Annex.

603. Since 1986 new data on human populations relevant to the effects of low doses have emerged from the revision of the experience in atomic bomb survivors [S49]. Table 67 shows the excess relative risk per 1 Gy of organ absorbed dose for doses above and below 0.5 Gy, using the entire 0-6 Gy dose range, and for progressively lower dose ranges below 1 Gy [S49]. Considering first leukaemia, a significant difference in the excess relative risk exists among survivors exposed to 0.5 Gy or more, as opposed to those exposed to lower doses (5.53 versus 2.44, respectively). This suggests persistence of a curvilinear dose-effect relationship for haematopoietic malignancies. In so far as all cancers except leukaemia are concerned, the excess relative risk associated with the higher doses does not differ significantly from that at the lower doses (0.41 versus 0.37, respectively). At doses below 0.20 Gy, the Japanese data have not revealed a significant excess of malignant tumours, and the nature of the dose-response relationship at these doses is uncertain. The expected numbers of additional cancer deaths at these lower doses are still small, relative to the background rate, even under the linear dose-response model, and the scatter of the data points is such that they can be fitted almost equally well by a quadratic, linear-quadratic or linear dose-response relationship [S48].

604. Epidemiologic studies of continuous internal irradiation of the thyroid gland by ^{131}I represent one source of information on the effect of low dose rates in human populations. A preliminary study of 10,000 patients who received doses to the thyroid gland in the range of 0.5 to 1.5 Gy found no excess of thyroid cancer after a mean follow-up of 17 years although 16 excess cases would have been expected based on external low-LET irradiation of the thyroid [H27]. An analysis of this study by the National Council on Radiation Protection of the United States concluded that ^{131}I should be considered no more than one-third as effective as external irradiation at high dose rates probably due to factors related to dose rate and dose distribution. An expanded study of 35,000 patients receiving diagnostic examinations has been published [H28]. These studies are discussed in paragraph 398. Both conclude that doses received from internal ^{131}I irradiation are less carcinogenic than similar doses from external acute irradiation. A factor of at least 3 has been proposed [N5], and possibly even 4 [H28]. Although the reduction of dose rate is held by some to

be a major contributor to the evident reduction in effectiveness, others contend that non-uniformity of dose distribution in the gland from ^{131}I may occur and contribute too [N5].

605. Epidemiologic studies of highly fractionated exposures to external low-LET radiation represent a second source of information on a low dose or low dose rate factor. As discussed in paragraph 367, there appears to be a non-linear dose response in the Canadian study of breast cancer following multiple fluoroscopic examinations [H6]. This appears to be related to the much smaller dose per examination received by the breasts of women who were irradiated posteriorly rather than anteriorly. A fractionation effect was not demonstrated in the similar but much smaller Massachusetts study [B3]. However, in this study it was not possible to distinguish a low dose cohort irradiated posteriorly. There appears to be a low dose or low dose rate factor of at least 3 in the Canadian study [H6].

606. Previous attempts to estimate lifetime risk for humans, such as BEIR III [C4], the Nuclear Regulatory Commission [G11], and the National Institutes of Health [U3] have handled the problem posed by low doses and low dose rates differently. BEIR III used a linear-quadratic dose-response function as one of their tested models, but the BEIR III Committee felt unable to recommend a specific general reduction for low dose rates. The other reports [G11, U3] both relied on the NCRP summary of the experimental literature [N1]. This was done by using a quadratic term in the dose-response function only for modelling exposure at low-dose rates. In the central estimates by Gilbert [G11], for which the results are given in Table 8, the linear coefficient was reduced by a factor of 3.3, and in the lower bound estimates by a factor of 10, for all organs except breast and thyroid.

607. From examination of both experimental and human data the Committee concludes that the carcinogenic effects of low-LET radiation are generally smaller at low doses and at low dose rates compared with those at high doses and dose rates. The reduction factors will vary with dose and dose rate and with organ system but will generally fall within the range 2 to 10.

E. LIFETIME RISK ESTIMATES FOR SPECIAL TISSUES

1. Lung

608. The computations provided in this Annex, based on DS86 risk coefficients, include low-LET, high-dose-rate exposure to the lung, based on the atomic bomb survivor experience. However, it is important to also estimate risk coefficients and lifetime risks for the alpha-irradiation experienced in connection with radon daughter exposure in the home and work-place. Thomas et al. [T20], ICRP [I11], and BEIR IV [C20] have reviewed the literature on radon (and related) exposures and have estimated lifetime risk. The Committee has reviewed these findings, along with other recent reports, in chapters III and IV.

609. Life-table methods essentially identical to those used in this Annex have been used by ICRP [I11] to derive lifetime risk estimates for continuous exposure to radon progeny, the high-LET exposure. Since the Committee believes that those estimates are reasonable in the light of the available data, it simply presents them in Table 68.

610. Thomas et al. [T20] have provided risk estimates for two types of exposure: (a) occupational exposure at 4 WLM up to a maximum of 200 WLM and (b) lifetime exposure of 0.02 WL 17 hours per day, 7 days per week as an upper tolerable limit for exposure that might be experienced in homes. The risk figures were adjusted for active breathing (occupational exposure) and quiescent breathing (home exposure), but they were not adjusted for age to account for varying susceptibility. The authors suggest, however, that since recent dosimetric studies indicate that breathing rate corrections may be inappropriate, their lifetime natural risk estimates might be doubled. Thomas et al. [T20] used eight risk models; namely, all combinations of additive and multiplicative projections: constant and age-varying risk coefficients; exposure times over which exposure is effective in incrementing risk. The projections were based on the Canadian life-table and lung cancer risks. Table 10 provides their risk coefficients and the lifetime excess risks.

611. The ICRP used similar assumptions and essentially the same demographic method of projection [I11]. Their publication reviews the entire literature, biological and physical, on radon daughter exposure, including the available studies on mining, in-home exposures and the relationship of risk to smoking, age, sex, and latency period. Their results are given in Table 68. For details and the methods of deriving the risk coefficients see the ICRP study [I11]. The ICRP concludes that the multiplicative risk projection model gives a better "best" fit for the data and provides a more realistic way of extrapolating from the higher mining doses to lower in-home doses than the additive model. It cites several published estimates, ranging from 0.10% to 1.0% excess cases at a constant annual exposure of 0.19 WLM.

612. Risk estimates for adult male uranium miners have been reviewed in [C20, I11, I12, U2]. More recent publications and papers prepared for publication have been noted by the Secretariat. Some of these data suggest that the minimum latency period to initial appearance of excess lung cancers after first exposure to high concentrations of radon progeny is five years, rather than the 10 years previously assumed [K28, M40, S51]. The interaction between cigarette smoking and exposure to radon progeny was closer to additive than to multiplicative for the Czech miners [S51]. These data have not yet been analysed in depth by the Committee. The preliminary analysis available does not suggest any reason for a major change in the previous risk estimates [I12, U2] of 1.5-4.5 10^{-4} fatal lung cancers per WLM. More detailed consideration of epidemiological data relating to lifetime risk estimates for cancer induction by inhalation of radon and radon progeny is anticipated in future UNSCEAR Reports.

2. Bone

613. The Committee is unable to provide reasonable lifetime risk estimates for exposure to low- or high-LET irradiation for bone cancer. The data from Japan do not provide statistically meaningful risk coefficients, and there are problems with using the available literature on adults (e.g., the radium dial painters and patients injected with radium isotopes) to assess lifetime risk with demographic projection methods. The literature is summarized in chapter III.

614. While exposed children are probably sensitive to bone cancer induction, the genetically atypical nature of the available cohorts, relative to whole-body exposure, precludes a useful estimation of risk from their data, other than as discussed in chapter III.

3. Thyroid

615. The best estimates of thyroid cancer are available from [N5], and were given in Table 39. This was based on the most recent data yet available. There are no published data from Japan from which to make projections beyond those already given in this Table. Recent data from Holm [H28] have been noted earlier.

F. RISK ASSESSMENT BY CANCER TYPE

616. In section VII.C, the Committee calculates the projected risk of induction of malignancies for two broad classes of malignancy: leukaemia and other solid cancers. The reason for considering only these two classes is that in the patient series reported there are not enough observations to allow separate computations for all cancer sites and all ages in order to obtain an overall estimate. The only series in which there appears to be enough information for at least an exploratory site-specific analysis is that on the atomic bomb survivors from Hiroshima and Nagasaki. Therefore, simply to show what type of data the model used could generate—given the appropriate background information—the Committee has refined its analysis of the Japanese series to compute the risk of radiation-induced cancers by anatomical site, on the basis of multiplicative and additive risk projection models and for the two indices of radiation harm described earlier. These computations were performed using the risk coefficients and the assumptions specified in Tables 56 and 57; the results are given in Tables 69 and 70.

617. It should be borne in mind that the final results of the computations are no better than the original data from which they were derived. Although the atomic bomb survivor study is the only study that allows these projections, the number of cancers observed for each site and each age class is often small. Consequently, the projected values carry large uncertainties. It should also be pointed out that these computations apply strictly to the Japanese population and could not be transferred easily to other populations having different demographic and epidemiological characteristics.

618. The Tables are computed on the assumption of an age-constant risk coefficient, since there was not enough information for most sites (particularly in young cohorts) to allow meaningful analysis of the radiosusceptibility of young cohorts exposed below 20 years of age separately for each site. Taking this factor into account would, of course, increase the risk attributable to younger ages and, since these ages dominate the overall risk projection, they would increase the expected risk substantially. The Committee considers that taking an average risk coefficient overestimates to some extent the risk of the age classes that are old at the time of exposure and underestimates the risk of the younger cohorts. The data available at present do not allow quantification of this statement on a site-by-site basis.

619. Table 69 presents the expected additional cancer cases at nine specific sites, including the marrow, and for all other sites collectively, designated as the remainder, under the two risk projection models. It should be noted that the number of excess cancers at sites not specifically identified, i.e., the remainder, has been computed, first, through subtraction of the excess cancers at the identified sites from the total projected excess number at all sites and, second, through the actual computation of the risk coefficient associated with this collection of sites, and projecting the excess number from the estimated risk coefficient. The difference between these two methods of estimating the expected number is small. Table 70 summarizes the loss of life expectancy per person after exposure to 1 Gy, under the same assumptions as in Table 69.

G. SUMMARY AND CONCLUSIONS

620. The Committee had available to it certain additional data that made it desirable to reconsider the assessment of the risk of radiation-induced cancer. These additional data were the result of: (a) a re-evaluation of the doses of the Japanese atomic bomb survivors; (b) an extension of the observation periods for several cohorts during which radiation-induced cancers continued to occur; (c) the availability of data from several new cohorts; and (d) the introduction into the analysis of both the additive and the multiplicative risk projection models for lifetime cancers and loss of life expectancy, taking into account competing causes of mortality.

621. In its projections, summarized in Table 71, some of the risk coefficients used by the Committee were derived by the authors of the reports from which they were taken using a linear dose-response relationship. However, there is no direct epidemiological evidence that substantiates this at low doses and/or low dose rates, and there is in addition some epidemiological evidence of non-linearity. Based primarily on the experience of the atomic bomb survivors who received uniform whole-body irradiation at high doses and dose rates and low-LET, the Committee derived excess absolute and relative risk coefficients. Using these risk coefficients, the Committee estimated lifetime risks of mortality in the range of 4 to 11 10^{-2} Gy^{-1}. The Committee considered that these risk estimates apply to a dose range of 0.5-6 Gy and noted that they are

strongly influenced by the finding that children are considerably more sensitive to radiation effects than adults.

622. The above estimates are qualified by the facts that (a) the estimates have been derived using Japanese data and the extent to which they apply to other populations is not clear; (b) although the multiplicative model leads to higher estimates of projected mortality than the additive model, the projected estimates of the expected years of life lost are similar under the two models. This is because under the multiplicative model a large proportion of the projected deaths occur in very old people when the years of life lost are few; and (c) there are two other major cohorts, those of patients irradiated for ankylosing spondylitis and cervical cancer, which give rise to somewhat lower estimates of lifetime risk.

623. The Committee agreed that there was a need for a correction factor to modify the risks given above for low doses and low dose rates. The Committee considered that such a factor certainly varies widely with individual tumour type and with dose rate. However, the appropriate value to be applied to total risk for low dose and low dose rate should lie between 2 and 10. The Committee intends to study this matter in detail in the future.

624. The Committee has not presented risk estimates for high-LET radiation in general in this Annex except for the exposure to radon of uranium miners. For low doses of external high-LET radiation it would be necessary to multiply the risks for low-LET radiation by an appropriate quality factor. No dose or dose rate reduction factor is considered necessary for high-LET radiation at low doses.

T a b l e   1

Population groups exposed to ionizing radiation
used in risk evaluation studies

Populations	Study population size
Atomic bombings	
Residents of Hiroshima and Nagasaki	91,000
Nuclear weapons testing	
Military test observers	10,000
Populations near test sites	500,000
Marshall Islanders	250
Medical therapeutic exposures	
Ankylosing spondylitis patients	14,000
Cervical cancer patients	180,000
Patients receiving chest irradiation	10,000
Patients receiving Thorotrast injections	2,000
Patients receiving head and thymus irradiation	20,000
Hodgkin's disease patients	10,000
Patients irradiated for immunosuppression	
Hemangioma patients	
Childhood cancer patients b/	10,000
Fetus receiving pre-natal examination	1,000
Occupational exposure	
Nuclear shipyard workers	24,000
Reactor and processing plant personnel	30,000
Underground miners	22,000
Radium dial painters	4,000
Radiologists	10,000
Natural background	
Persons with elevated exposure due to geography	
Persons living in houses with high radon levels	
Nuclear accidents	
Individuals in public, workers, emergency crews	

T a b l e   2

Epidemiological studies used to assess radiation carcinogenesis in man

```
Cohort studies
  Prospective follow-up
    Survivors of atomic bombings
    Marshall Islanders
  Retrospective/prospective follow-up
    Individuals identified from medical records
      Patients irradiated therapeutically
      Radiological workers and radiologists
    Individuals identified through employment records
      Occupationally exposed individuals
      Military test observers
    Individuals identified through geographic data
      Populations in high natural background areas
      Individuals living in local fallout areas

Case-control studies
  Retrospective ascertainment
    Pre-natal exposures

Opportunistic or ad hoc studies
  Nuclear accident victims
```

T a b l e   3

Mortality to incidence ratios for transforming risk estimates
[C4]

| Site of cancer | Expectation of cancer (per cent) | | | | Mortality/ Incidence ratio | |
| | Males | | Females | | | |
	Mortality	Incidence	Mortality	Incidence	Males	Females
Oesophagus	0.4	0.4	0.2	0.2	1.00	1.00
Stomach	0.9	1.2	0.7	0.9	0.75	0.78
Intestine	2.3	4.4	2.8	5.1	0.52	0.55
Pancreas	1.0	1.1	0.9	1.0	0.91	0.90
Lung	4.9	5.9	1.2	1.6	0.83	0.75
Urinary	1.0	2.7	0.6	1.3	0.37	0.46
Lymphoma	1.1	1.5	0.9	1.2	0.73	0.75
Breast	0	0	3.0	7.7	-	0.39
Thyroid	0.03	0.17	0.09	0.46	0.18	0.20
Liver	0.20	0.20	0.18	0.18	1.00	1.00

T a b l e   4

Excess cancer incidence (excluding leukaemia and bone cancer)
per 10^4 person years and Gy, 11-30 years after exposure,
estimated in the BEIR 1980 Report
[C4]

| Site | Age at exposure (years) | | | | | Age-weighted average a/ |
	0-9	10-19	20-34	35-40	>50	
Males						
Thyroid	2.20	2.20	2.20	2.20	2.20	2.20
Lung	0.00	0.54	2.45	5.10	6.79	3.64
Oesophagus	0.07	0.07	0.13	0.21	0.56	0.26
Stomach	0.40	0.40	0.77	1.27	3.35	1.53
Intestine	0.26	0.26	0.52	0.84	2.23	1.02
Liver	0.70	0.70	0.70	0.70	0.70	0.70
Pancreas	0.24	0.24	0.45	0.75	1.97	0.90
Urinary	0.04	0.23	0.50	0.92	1.62	0.81
Lymphoma	0.27	0.27	0.27	0.27	0.27	0.27
Other	0.62	0.38	1.12	1.40	2.90	1.52
All sites	4.80	5.29	9.11	13.66	22.59	12.85
Females						
Thyroid	5.80	5.80	5.80	5.80	5.80	5.80
Breast	0.00	7.30	6.60	6.60	6.60	5.82
Lung	0.00	0.54	2.45	5.10	6.79	3.94
Oesophagus	0.07	0.07	0.13	0.21	0.56	0.28
Stomach	0.40	0.40	0.77	1.27	3.35	1.68
Intestine	0.26	0.26	0.52	0.84	2.23	1.12
Liver	0.70	0.70	0.70	0.70	0.70	0.70
Pancreas	0.24	0.24	0.45	0.75	1.97	0.99
Urinary	0.04	0.23	0.50	0.92	1.62	0.88
Lymphoma	0.27	0.27	0.27	0.27	0.27	0.27
Other	0.62	0.38	1.12	1.40	2.90	1.64
All sites	8.40	16.19	19.31	23.86	32.79	23.10

a/ Average of the age-specific coefficients, weighted according to
the age distribution of the population of the United States.

Table 5

Excess mortality from all cancers per 10^4 persons exposed to low-LET radiation estimated in the BEIR 1980 Report
[C4]

Dose-response model applied	Excess deaths	
	Absolute risk projection model	Relative risk projection model
Single exposure to 0.1 Gy a/		
Linear-quadratic	7.66	22.55
Linear	16.71	50.14
Quadratic	0.95	2.76
Continuous exposure to 0.01 Gy per year b/		
Linear-quadratic	47.51	119.70
Linear	112.60	286.90

a/ Normal expectation of deaths from cancer in follow-up period: 1638.
b/ Normal expectation of deaths from cancer in follow-up period: 1673.

Table 6

Lifetime risk of cancer mortality from low-LET radiation estimated in the BEIR 1980 Report
[C4]

Dose-response model applied	Excess deaths per 10^4 per Gy	
	Absolute risk projection model	Relative risk projection model
Single exposure to 0.1 Gy		
Linear-quadratic	77	226
Linear	167	501
Quadratic	10	28
Continuous exposure to 0.01 Gy per year		
Linear-quadratic	67	169
Linear	158	403

T a b l e   7

Ratios of excess deaths from radiation-induced cancers
other than leukaemia and bone cancer
to excess deaths from radiation-induced leukaemia and bone cancer
[C4]

Duration of exposure and dose rate	Dose-response model	Absolute risk projection model	Relative risk projection model
Lifetime (0.01 Gy/year)	Linear-quadratic	2.4	7.5
	Linear	2.6	8.1
Between ages 20-65 (0.01 Gy/year)	Linear-quadratic	3.0	5.7
	Linear	3.3	6.2

T a b l e   8

Models and assumptions for cancer risk estimates
used in the United States Nuclear Regulatory Commission study
[G11]

Effect	Type of model	Latency (Years)	Plateau (Years)	Mortality risk coefficient Absolute per 10^4 per Gy	Mortality risk coefficient Relative per cent per Gy
Leukaemia	Absolute, linear-quadratic	2	25	2.2	n/a
Bone cancer	Absolute, linear-quadratic	2	25	0.1	n/a
Breast cancer	Relative, linear, non-age-specific	10	-	3.5, 2.3 a/	103, 42
Lung cancer	Relative, linear-quadratic	10	-	2.0	37
GI cancer b/	Relative, linear-quadratic	10	-	2.7	39
Thyroid cancer	Absolute, linear, age- and sex-specific age < 18	5	-	0.25, 0.125 a/	
Other cancers c/	Relative, linear-quadratic	10	-	1.5	20
	Absolute, linear	0	10	28	n/a

a/ First coefficient is for exposure under, second for exposure over age 20.
b/ Including cancers of the oesophagus, stomach, colon, rectum, pancreas, and
other unspecified gastointestinal cancers.
c/ Including all cancers except leukaemia.

Table 9

Lifetime risks of cancer mortality
from low-LET radiation at low dose rates (<0.05 Gy per day)
estimated in the United States Nuclear Regulatory Commission study
[G11]

	Number of deaths (per 10^4 per Gy)			Years of life lost (per 10^4 per Gy)		
	Lower bound	Central estimate	Upper bound	Lower bound	Central estimate	Upper bound
Leukaemia	5	14	48	168	505	1682
Bone	0.2	1	2	7	22	75
Breast	4	60	87	97	955	1452
Lung	5	20	138	100	288	1971
Gastrointestinal	9	57	189	222	661	2202
Thyroid	7	1	7	20	203	203
Other	5	29	96	124	378	1260
Leukaemia a/	1.2	1.2	3	80	80	200
Other a/	1.2	1.2	3	80	80	200

a/ Due to in utero exposure.

Table 10

Estimated risks of lung cancer in uranium and non-uranium miners
[T11]

Location of mine	Type of mine	Mean dose (WLM)	Lung cancer deaths		Excess cases per 10^6 PY WLM a/	Relative risk per 10^2 WLM a/	Ref.
			Observed	Expected			
Canada							
Ontario	Uranium	36	62	25.54	9.59 (2.07)	4.97 (0.86)	[H17]
Ontario	Uranium	40-90	119	65.78	2-5	1.5-2.3	[M19]
Ontario	Gold		279	230.85	3-15	1.25-1.75	[M19]
Newfoundland	Fluorspar	204	65	3.76	17.82 (2.35)	3.30 (0.34)	[D14]
Czechoslovakia	Uranium	313	198	28.24	16.82 (1.40)	2.92 (0.16)	[S19]
Sweden							
Kiruna	Iron	110	13	4.47	2.72 (1.15)	2.74 (0.73)	[J3]
Zinkgruven	Lead,zinc	270	20	2.32	30.40 (7.69)	3.82 (0.71)	[A13]
Malmberget	Iron	170	14	2.95	5.53 (0.63)	3.21 (0.75)	[R14]
National survey		163	36	6.07	3.43 (0.69)	4.03 (0.61)	[S32]
United Kingdom	Iron	260	36	20.58		1.29 (0.11)	[B25]
United States	Metal	620	47	16.1	1.99 (0.44)	1.33 (0.07)	[W15]
Colorado plateau	Uranium	1180	159	25.24	3.52 (0.33)	1.45 (0.04)	[A12]

a/ Values in parentheses are standard errors.

Goodness of fit of different lifetime projection models
for all cancers other than leukaemia in the population of England and Wales
[M37]

(Single exposure to 0.1 Gy with gamma and neutron components
in the same proportion as at Hiroshima;
The models that fit the data well are underlined.)

Covariate of risk	Minimum deviance a/	γ b/	Deviance a/ at γ = 0 (Multiplicative risk model)	Deviance a/ at γ = 1 (Additive risk model)
None (constant risk)	42.02	0.43	57.54	58.87
Sex	38.87	0.40	49.78	55.15
Age	34.34	0.01	34.34	53.92
Time since exposure	26.06	0.57	50.31	31.64
Sex, age	27.01	-0.19	28.48	50.73
Sex, time since exposure	23.03	0.55	42.23	28.90
Age, time since exposure	24.11	1.35	32.31	24.34
Sex, age, time since exposure	22.49	0.91	24.94	22.51

a/ For ease of presentation, a value of 400 has been subtracted
from these deviances. In comparing the difference in deviance
resulting from the inclusion of an extra variable in the model,
a reduction in deviance of 3.84 is significant at the 5% level
and a reduction of 6.63 is significant at the 1% level.
b/ γ denotes the value of the parameter that minimizes the
deviance.

T a b l e   12

Application of a generalized risk model to data on mortality
from all cancers other than leukaemia
in the Hiroshima atomic bomb survivors
[M37]

(A 10-year minimal latent period is assumed.)

Covariates of risk	Risk model	Number of deaths per 10^4	Years of life lost per 10^4
Sex, age	Multiplicative	225	2940
	Additive a/	28	535
Time since exposure	γ = 0.57 b/	1460	14800
Sex, age, time since exposure	Multiplicative	983	10300
	Addivive	816	7350
Sex, age, log (time since exposure)	Multiplicative	104	1760
	Additive	87	1310

a/ This model does not fit the Hiroshima data well.
b/ γ denotes the value of the parameter that minimizes the
deviance.

Stage in carcinogenesis possibly affected by radiation in various organs
as deduced from theoretical multi-stage models

Stage affected and tumour site	Population studied	Exposure type	Ref.
Early stage possibly affected			
All cancers except leukaemia	Atomic bomb survivors	Single	[D1]
All cancers except leukaemia	Ankylosing spondylitis patients	Brief chronic irradiation	[S2]
All heavily irradiated sites	Metropathic hemorrhagica patients	Brief chronic irradiation	[S3]
Breast	Atomic bomb survivors	Single	[D1]
Breast	Atomic bomb survivors	Single	[M5]
Breast	Chest fluoroscopy patients	Brief chronic irradiation	[B3]
Breast	Post-partum mastitis patients	Brief chronic irradiation	[S1]
Thyroid	Infant patients	Brief chronic irradiation	[H1]
Lung	Underground miners	Long chronic exposure to radon	[W12]
Late stage possibly affected			
Leukaemia	Ankylosing spondylitis patients	Brief chronic irradiation	[C2]
Leukaemia	Radiologists	Long chronic exposure to x rays	[S4]
All stages possibly affected			
Osteosarcoma	Radium dial painters	Long chronic exposure to radium-226	[M3]
Uncertain stages affected			
Leukaemia	Atomic bomb survivors	Single	[B4]

T a b l e   14

Relative risk of leukaemia in pre-natally exposed children

Study location	Years of incidence	Relative risk	Ref.
UNSCEAR (weighted mean)	1940-1957	1.58 a/	[U1]
United States	1947-1960	1.52 a/	[M8]
United States			
White	1947-1967	2.88	[D3]
Black	1947-1967	0.00 b/	[D3]
United Kingdom	1943-1965	1.48 a/	[S5]
Finland	1959-1968	1.90	[S7]
Hiroshima-Nagasaki	1945-1979	2.15	[I1]
English twins	1943-1965	2.20 a/	[M7]
United States twins	1930-1969	1.60 c/	[H11]

a/ Significant at 0.05 level or better. UNSCEAR value is
sample-size weighted value of studies done before
1964, including nine sets of data with a total of
1,626 cases contrasted with 2,706 controls. Relative
risk from Japan was calculated from the dose-specific
risk rate data in [I1] and is not significant (see
text). Most cases and excess risk reported here
occurred before the age of 10.
b/ No cases observed.
c/ In this series, relative risk of solid tumours was
3.2, not significant; other series have found values
less than the RR for leukaemia.

Table 15

Second primary cancer in children treated for a primary cancer
[M28]

Type of second cancer	Number of second cancers			
	Total	Radio- therapy group	Chemo- therapy group	Other non-radio- therapy
Bone	67	52	8	7
Soft-tissue sarcomas	59	43	6	10
Haematopoietic	59	36	12	11
Skin	30	19	5	6
Brain	28	13	11	4
Thyroid	26	24	1	1
Breast	13	9	0	4
All others	24	12	6	6

Table 16

Development of second primary cancers in children
[T4]

Primary cancer	Number of children	Percentage with second cancer
Wilms' tumour	1248	2.2 a/
Hodgkin's disease	1036	2.5
Retinoblastoma	319	6.3
Neuroblastoma	790	2.4
Ewing's sarcoma	213	5.2 b/
Rhabdomyosarcoma	385	2.9
Brain (excluding medulloblastoma)	764	1.4
Medulloblastoma	285	2.4
Soft-tissue sarcoma	550	1.3
Non-Hodgkin's lymphoma	423	1.2
Acute lymphocytic leukaemia	1530	0.3
Osteosarcoma	271	1.5

a/ In other studies, occurrence of second cancers in Wilms' tumour patients is about 2.5% [L3, S10].
b/ Involved about 5 years of follow-up; in another study [S11] of 10 years of follow-up it has been estimated to be 35%.

T a b l e   17

Cancer risk in children irradiated to treat tumours
having a substantial heritable fraction

Disease	Site irradiated	Dose range (Gy)	Increased second cancer risk (%) 10 years	Increased second cancer risk (%) 30 years	Second cancer type	Ref.
Retinoblastoma	Head	>100 a/ 35-50 b/	2-3	9-14	80% osteosarcomas 20% other sarcomas	[A3,A8, D15,F2, S26,V1]
Ewing's sarcoma	Bones	54-65 b/	35		80% osteosarcomas	[S11]
Wilms' tumour	Abdomen	25-30 a/	1-2	15	Various carcinomas	[L3]

a/ Orthovoltage therapy.
b/ Megavoltage therapy.

T a b l e   18

Occurrence of second non-ocular tumours in patients with retinoblastomas
[A3]

Primary tumours and type of treatment	Number of cases	Number of second tumours	Number in treatment field	Number outside treatment field
Bilateral	693	89	58	31
Unilateral	18	5 a/	2	3
Radiation	688	89	62	27 b/
No radiation	23	5	1	4

a/ Includes three patients without family history of retinoblastoma.
b/ Includes one case with cobalt plaque who developed tumour in the humerus.

T a b l e   19

Cumulative incidence of second primary cancers
in patients with genetic retinoblastoma
[D15]

Site of second cancer	Number of patients	Type of second cancer	Number of second cancers	Cumulative incidence (per cent) at 12 years	Cumulative incidence (per cent) at 18 years
All sites	384	All cancers	26	4.3	8.4
		Osteosarcomas	17	3.6	6.0
In radiation field	314	All cancers	14	3.4	6.6
		Osteosarcomas	8	2.4	3.7
Outside radiation field	384	All cancers	12	1.6	3.0
		Osteosarcomas	9	1.6	3.0

Table 20

Risk of thyroid and other cancer in children receiving head and neck irradiation

Site or cause of irradiation	Number in study	Dose (Gy)	Tumour type	Increased risk at 30 years	Excess risk per 10^4 PYGy	Reference
Tinea capitis	10842	0.09	Thyroid	0.15		[R1, S27]
		3.8	Leukaemia	0.13		
	2226	3-6	Basal cell	<1.0		
Thymus	2651	1-10	Thyroid	1.0	3.5	[S13, H1
			Leukaemia	<0.5	1.0	
Tonsils	2578	7.8	Thyroid	8.0	3.6	[L9]
Marshall Islanders	250	7-20	Thyroid	7.3	1.8	[C6,C10,L9]
Atomic bomb survivors		0-6	Thyroid		7.1	[U2]
Local fallout (USA)	2945	0.3-2.4	Thyroid	?		[C4]

Table 21

Dose-response relationships for thyroid cancer in children irradiated for enlarged thymus
[S38]

	Control	Dose range (Gy)				
		0.01-0.49	0.50-1.99	2.00-3.99	4.00-5.99	>6.00
Person-years	118157	33449	6020	11456	6382	1727
Mean dose	0	0.17	1.2	2.5	4.5	7.5
Cancers	1	4	1	6	11	5
Rate (/10^5 PY)	0.7	12.3	18.8	51.0	128	154
Expected cases a/	1.43	0.31	0.07	0.13	0.08	0.03
Relative risk	0.7	12.9	13.6	45	130	196
Excess/10^4 PYGy	-	6.9	1.5	2.0	2.8	2.0

a/ Expected based on age and sex-specific thyroid cancer rates for New York state 1969-1971.

Table 22

Dose fractionation and risk in thymus-irradiated children
[S38]

	Mean dose (Gy)	Person-years	Cancers	Expected cancers	Excess per 10^4 PYGy
Dose per fraction					
0.01-0.49 Gy	0.18	33268	4	1.0	6.1
0.50-1.99 Gy	2.2	8622	6	6.8	2.2
>2 Gy	3.1	14340	12	14.2	2.3
Number of fractions					
1	0.74	29414	7	5.1	2.9
2	1.5	22417	6	9.7	1.5
3	2.5	5445	9	7.3	3.8

T a b l e 23

Risk of breast cancer in atomic bomb survivors under 10 years of age
at the time of the bombings
[T7]

	Dose range (Gy) (T65DR)				
	0	0.01-0.09	0.10-0.49	0.50-0.99	>1.00
	Mean dose (Gy)				
	0	0.026	0.17	0.55	1.9
Observed	6	5	5	5	3
Expected	13.2	5.45	3.56	0.85	0.93
Relative risk	0.45	0.92	1.40	5.88	3.23

T a b l e 24

Risks of leukaemia and other cancers
in patients treated for Hodgkin's disease

	Relative risk a/					Risk rates b/			
Treatment	All cancers			Leukaemia		All cancers		Leukaemia	
	[B11]	[B11]	[G4]	[G4]	[B9]	[B11]	[C7]	[B11]	[C7]
X rays only	1.6	15.0	-	-	1.0 c/	0.0034	0.015	0.0010	0.000
Chemotherapy only	4.0	9.3	2.60	147	1.0 c/	0.0075	0.029	0.0040	0.062
Combined	14.5	20.0	4.27	118	261.0	0.0093	0.030	0.0070	0.064

a/ Relative risks are observed/expected.
b/ Risk rate data are cases/person-year except for the last, which is a
   cumulative (actuarial) risk after 7 years post-exposure.
c/ No second cancers were observed in these groups, so baseline value
   (relative risk) may be set to 1.0.

Relative risk of second cancer following radiotherapy
for benign gynaecologic disorders and for cervical cancer
[W6, B12]

(Cancer patients followed for at least 10 years; other patients
followed for a variable length of time, but generally more than 10 years.
Risks significant at the 0.05 or better level are underlined.)

Organ dose level and site of second cancer	Relative risk		
	Radiotherapy treatment		No radiotherapy treatment
	Cancer patients	Non-cancer patients	
High doses a/			
Colon	1.1	1.1	1.3
Rectum	1.8	1.2	1.4
Uterine corpus	1.0	2.8	0.1
Ovary	0.9		0.5
Bladder	3.5	2.1	1.2
Other genital	3.2		2.8
Intermediate doses b/			
Stomach	1.0	0.8	0.6
Pancreas	1.2	0.5	0.9
Kidney	0.8	2.1	2.1
Oesophagus	1.1		0.0
Small bowel	2.4	1.3	5.0
Gallbladder	0.8	0.9	1.5
Low doses (remote sites) c/			
Lung	2.3	0.9	2.2
Breast	0.7	0.9	0.9
Thyroid	1.4		0.6
Oral cavity	1.7	1.9	1.7
Salivary gland	1.7		0.0
Brain	0.6		2.0
General systemic cancer of unknown original site			
Leukaemia	0.9	2.3	0.6
Multiple myeloma	1.4		0.0
Lymphoma	1.3	2.3	0.3
Hodgkin's disease	1.0		1.1

a/ For cancer patients around 10 Gy; for non-cancer patients 1-10 Gy.
b/ For cancer patients 1-10 Gy; for non-cancer patients comparatively
smaller.
c/ For cancer patients around 0.1 Gy; for non-cancer patients
comparatively smaller.

Relative risk and excess cases of cancer
following irradiation to treat cervical cancer
[B38]

(90% confidence intervals in parentheses.)

Second cancers	Relative risk at 1 Gy a/	Excess cases per 10⁴ PYGy
Colon	1.00 (0.00-1.02)	0.01 (-0.03- 0.18)
Cecum	1.02 (0.99-1.09)	-
Rectum	1.02 (1.00-1.04)	0.06 (0.00- 0.16)
All female genital	1.01 (1.00-1.02)	0.05 (-0.01- 0.17)
Ovary	1.01 (0.98-1.14)	0.05 (-0.03- 0.60)
Vagina	1.03 (1.00-1.08)	-
Other genital	0.98 (0.95-1.07)	-0.01 (-0.02- 0.03)
Bladder	1.07 (1.02-1.17)	0.12 (0.01- 0.30)
Connective tissue	0.95 (0.89-1.13)	-0.01 (-0.03- 0.03)
Stomach	1.69 (1.01-3.25)	3.16 (0.05-10.40)
Pancreas	1.00 (0.72-1.62)	0.00 (-0.65- 1.43)
Kidney	1.71 (1.03-3.24)	1.10 (0.06- 3.50)
Breast	1.03 (0.13-2.29)	0.54 (-14.6-21.7)
Thyroid	13.30 (0.00-77.0)	6.87 (-2.04-39.2)
Leukaemia		
CLL	1.00 (0.90-1.43)	0.00 (0.00- 0.17)
AL and CML	1.14 (1.00-1.45)	0.10 (0.00- 0.31)

a/ See original publication for details of the calculations.

T a b l e   27

Relative risk of second cancers in patients treated for ovarian cancer
[R11]

(Risks significant at the 0.05 or better level are underlined.)

Site of second cancer	Relative risk		
	Non-irradiated patients		Irradiated patients
	N = 6713 a/	N = 5455 b/	N = 6596 a/
All sites	1.1	1.5	2.1
Bladder	0.4	2.8	c/
Breast	1.0	1.1	2.2
Colon	1.3	1.9	2.8
Connective tissue	0.9	3.3	c/
Endometrium	2.9	4.5	5.9
Leukaemia	0.3	1.3	9.3
Lung	2.0	0.7	0.8
Lymphoma	1.6	2.7	3.6
Myeloma	2.8	0.0	c/
Rectum	1.1	0.3	1.1
Stomach	0.8	0.5	c/

a/ Study group from United States National Cancer Institute
End Results Program.
b/ Study of a survey of 70 United States medical centers
using chemotherapy.
c/ Less than 2 patients observed.

Table 28

Relative risk of second cancers in patients treated for breast cancer
[H20]

Site of second cancer	Relative risk	
	Irradiated patients	Non-irradiated patients
Kidney	1.9	0.7
Oesophagus	1.7	0.7
Non-Hodgkin's lymphoma	1.7	0.7
Chronic lymphocytic leukaemia	1.2	0.4
Acute non-lymphocytic leukaemia	2.5	1.2
Lung, 10-19 years after irradiation	2.3	1.5
Lung, 20-29 years after irradiation	4.8	1.8

Table 29

Relative risk of leukaemia following treatment
of other primary cancers in adults
[C8]

(Sites not listed produced no cases of subsequent leukaemia and therefore
the relative risk is not estimable (or is 0.0).
Risks significant at the 0.05 or better level are underlined.)

Site of primary cancer	Surgery only		Radiation only		Chemotherapy only	
	Number	Risk	Number	Risk	Number	Risk
Oral/buccal	5634	1.1	6663	1.3	768	0.0
Oesophagus	675	0.0	2464	0.0	503	0.0
Stomach	5279	0.0	617	5.0	2882	2.5
Colon	31109	0.9	798	0.0	5490	1.4
Rectum	13493	1.1	2286	1.5	2197	1.0
Larynx	1817	0.7	3636	1.2	122	0.0
Lung/bronchus	11527	0.7	22113	0.5	13215	0.9
Connective	1420	1.0	527	3.3	528	0.0
Melanoma	8078	1.3	142	0.0	455	0.0
Breast	39416	1.0	10854	1.7	6040	_3.8_
Endometrium	8855	0.4	10276	_2.1_	523	0.0
Ovary	2864	0.8	1283	_10.0_	4407	_9.0_
Prostate	22322	0.9	7035	1.4	539	0.0
Testis	883	0.0	1147	3.3	674	17.9
Bladder	14824	1.1	2878	1.2	855	1.4
Kidney/renal	5118	_2.5_	1056	2.0	870	0.0
Thyroid	4154	2.1	925	0.0	103	45.3
Multiple myeloma	39	25.0	332	5.0	3603	_4.0_
All other	8710	1.5	8896	1.1	20863	1.7
All sites	192754	1.0	93651	_1.4_	70674	_2.3_

T a b l e 30

Relative risk of leukaemia in ankylosing spondylitis patients
and in atomic bomb survivors
[C11]

Population	Relative risk	Excess cases per 10^4 PY
Ankylosing spondylitis patients	4.79 (3.4- 6.6)	1.96 (1.24-2.88)
Atomic bomb survivors	9.38 (7.0-12.6) a/	3.95 (3.04-4.86)

a/ Individuals exposed to >1 Gy compared to those exposed to <0.1 Gy (T65DR).

T a b l e 31

Relative risk of leukaemia (incidence)
in women treated for gynaecological disorders
[W6]

Dose (Gy)	Condition treated	Cases	Relative risk
Mean marrow dose a/			
0.4-1.3	Benign and malignant disorders	9	3.5
1.0-3.0	Benign and malignant disorders	3	1.2
3.0-15	Benign and malignant disorders	9	1.1
Total		21	1.5
Mean pelvic marrow dose			
1.6-3.2	Benign disorders	10 b/	2.8
1.6-5.0	Benign disorders	9	3.5
2.2-5.2	Metropathia haemorrhagica	6 b/	4.6
3.0-9.0	Benign disorders	3	1.2
9.0-45	Uterine malignancies	9	1.1

a/ Includes cases treated for benign as well as malignant disorders.
b/ Based on leukaemia deaths.

T a b l e 32

Relative risk of multiple myeloma following various radiation exposures
[C10]

(Risks significant at the 0.01 or better level are underlined,
the others are significant at the 0.05 level.
90% confidence intervals in parentheses.)

Group and exposure type	Number of cases	Relative risk
Uterine cancer	3	0.28 (0.1-0.7)
All cohorts receiving appreciable alpha-radiation	14	4.32 (2.6-6.8)
All other cohorts receiving gamma- or x-ray therapy or diagnostic exposure	13	2.05 (1.2-3.3)
All cohorts receiving only x rays	11	2.02 (1.1-3.3)
All cohorts except uterine cancer	50	2.25 (1.7-2.8)
All cohorts	53	1.61 (1.3-2.0)

Table 33

Risk coefficients for radiation-induced bone sarcomas
estimated in the BEIR 1980 Report
[C4]

Type of radiation and model	Cumulative risk coefficient per 10^4 PGy	Risk rate coefficient per 10^4 PYGy
Alpha particles (high-LET)		
Linear	27	1
Dose-squared	3.7 a/	980 b/
Beta, gamma, and x rays (low-LET)		
Linear	1.4	0.05
Dose-squared	9200 a/	24000 b/

a/ Per 10^4 PGy^2.
b/ Per 10^4 PYGy^2.
Provisional coefficients for endosteal doses up to a few Gy.
The risk-rate coefficient is determined by dividing the
cumulative risk by 27 years, the total risk period, for
alpha particle exposure.

Table 34

Relative risk of skin cancer in patients who received scalp irradiation
to treat tinea capitis
[C4]

Age or time (years)	Number of skin cancers	Relative risk
Age at exposure		
1-19	0	0
20-24	0	0
25-29	4	2.9
30-34	8	4.5
35-39	12	5.2
40-44	5	3.1
>45	0	0
Time since exposure		
1- 9	0	0
10-14	0	0
15-19	1	0.9
20-24	7	3.8
25-29	14	4.7
30-34	9	4.8

Table 35

Relative risk of breast cancer by dose and age at exposure,
Hiroshima and Nagasaki incidence data, 1950-1980
[T14]

Age at the time of bombing	Kerma (Gy) a/							
	0.0	0.01-0.09	0.10-0.49	0.50-0.99	1.00-1.99	2.00-2.99	3.00-3.99	>4.00
	Average tissue dose (Gy) a/							
	0	0.026	0.168	0.55	1.10	1.89	2.65	4.03
0- 9	1.0	2.01	3.10	13.03	8.98	0	25.4	0
10-19	1.0	0.91	1.73	2.27	3.45	5.80	4.86	12.7
20-29	1.0	0.90	1.42	1.58	2.57	2.80	4.02	5.95
30-39	1.0	1.09	0.68	0.93	2.96	4.30	2.21	7.61
40-49	1.0	0.81	1.35	0.25	0.84	2.43	2.06	0
>50	1.0	0.97	1.08	0.52	3.53	2.77	0	0
Total b/	1.0	1.0	1.3	1.4	2.7	4.5		

a/ Based on T65DR.
b/ Totals obtained from [T6].

Table 36

Relative risk of breast cancer in four different studies
(Modified from [H6], based on data from [B3, H6, L6, S1, T14])

Age at exposure	Atomic bomb survivors (T65DR)	New York mastitis	Massachusetts fluoroscopy	Canadian fluoroscopy
10-19	5.6	a/	4.8	4.6
20-29	2.8	2.2	1.5	4.0
30-39	4.0	1.6	1.4	1.7
40-49	0.6	5.2	2.0	0.8
>50	a/	a/	0.0	

Rates compare disease in women exposed to more than 1 Gy with cases expected in unexposed women.
a/ Insufficient data.

Breast cancer incidence in women
[L6]

Study series	Age at exposure	Number of breast cancers	Relative risk at age					
			20-29	30-39	40-49	50-59	60-69	>70
Rochester mastitis patients	20-29	18		3.0	1.9	2.5		
	30-39	13			1.7	3.1	2.8	
Massachusetts fluoroscopy patients	10-19	15	9.0	4.1	3.1	3.1		
	20-39	24		1.1	1.7	1.2	2.1	
LSS patients, 1950-1974 (T65DR doses)	10-19	40 a/	8.8	4.9	3.1			
	20-29	31		2.0	1.9	3.4		
	30-39	19			0.3	2.4	1.2	
	40-49	12			2.2	0.8	1.0	0.7
	>50	11				0	1.8	1.6

a/ Exposure of 0.1 Gy or more.

T a b l e   38

Breast cancer incidence in irradiated relative to unexposed women
[H6], based on [B3, H6, L6, S1])

Breast tissue dose (Gy)	Atomic bomb survivors a/	New York mastitis	Massachusetts fluoroscopy	Canadian fluoroscopy
0	1.0	1.0	1.0	1.0
0.01-0.99	1.2	0.7	1.2	1.1
1.00-1.99	3.3	1.9	2.0	2.0
2.00-2.99	2.3	1.8	2.3	3.5
3.00-3.99	3.0	3.0	1.5	3.0
>4.00	8.1	2.3	5.2	14.6

Data given are relative rates of breast cancer excluding the first five years of post-operation observation in all except the Canadian series, to exclude non-radiogenic cases.
a/ Based on T65DR.

Estimate of excess thyroid cancer cases (incidence)
per 10⁴ individuals exposed to 0.06-15 Gy
[N5]

Source of irradiation	Exposed under age 18		Exposed over age 18	
	Male	Female	Male	Female
Annual excess				
Internal a/	0.28	0.56	0.56	1.12
External b/	0.84	1.68	1.68	3.36
Lifetime excess				
Internal a/	2.74	6.80	4.83	10.50
External b/	8.22	20.40	14.50	31.50

a/ Internal doses include exposure to iodine isotopes 125, 131.
b/ External doses include exposure to x or gamma radiation
   or to iodine isotopes 132, 133, 135.
Mortality can be assumed to be 1/10 the incidence values given in
the Table. Assumes excess risk = 2.5 cases per 10⁴ PYGy, based on
data derived from North American children, both sexes pooled.

T a b l e   40

Relative risk of cancer in heavily irradiated sites
for combined data of
ankylosing spondylitis patients and the Japanese Life Span Study
[D11]

(Risks significant at the 0.05 or better level are underlined.
90% confidence intervals in parentheses.)

Site of second cancer	Relative risk	Excess cases per 10⁴ PY
Pharynx	1.76 (0.73-4.22)	0.02 (-0.10-0.14)
Oesophagus	1.82 (1.29-2.57)	0.45 (0.11-0.80)
Stomach	1.24 (1.09-1.41)	1.14 (0.31-1.96)
Pancreas	1.24 (0.87-1.76)	0.15 (-0.18-0.47)
Larynx	1.35 (0.70-2.59)	0.07 (-0.11-0.25)
Lung	1.54 (1.36-1.76)	2.30 (1.49-3.12)
Ovaries	2.39 (1.54-3.72)	0.93 (0.28-1.57)
Skin	0.61 (0.19-1.98)	-0.03 (-0.16-0.10)
Bones (excluding jaw and nose)	2.40 (1.08-5.34)	0.09 (-0.05-0.23)
Multiple myeloma	2.16 (1.11-4.20)	0.16 (-0.02-0.34)
Other lymphomas	1.58 (1.07-2.33)	0.20 (0.10-0.49)
CNS tumours (spinal cord and nerves)	9.31 (4.72-18.4)	0.23 (0.07-0.40)
Others	1.62 (1.28-2.03)	0.93 (0.41-1.46)
All heavily irradiated sites	1.46 (1.35-1.57)	6.56 (4.98-8.15)
Selected sites	1.41 (1.30-1.53)	4.99 (3.55-6.42)

Sex differences in cancer mortality risks
in atomic bomb survivors (T65DR doses)
[P15]

Site	Relative risk at 1 Gy exposure		P a/	Excess risk per 10^4 PYGy		P a/	Background mortality sex ratio (F/M)
	Male	Female		Male	Female		
Leukaemia	3.84	4.08	0.96	1.95	1.20	0.03	0.54
All cancers except leukaemia	1.11	1.25	0.007	3.29	4.42	0.3	0.57
Bladder, kidney	1.41	1.77	0.5	0.27	0.23	0.8	0.47
Colon	1.18	1.60	0.8	0.19	0.37	0.5	0.55
Oesophagus	1.09	2.23	0.03	0.14	0.22	0.8	0.12
Liver b/	1.31	1.46	0.8	0.11	0.06	0.6	0.33
Lung c/	1.19	1.67	0.03	0.78	0.92	0.95	0.32
Multiple myeloma	1.64	1.43	0.8	0.07	0.06	0.7	1.27
Stomach	1.07	1.19	0.15	0.90	1.07	0.8	0.46

a/ Significance is two-sided test of sex difference.
b/ Includes intra-hepatic bile ducts.
c/ Includes trachea and bronchial tree.

T a b l e   42

Risk of salivary gland cancer incidence in medically irradiated populations
[L11]

Mean age at exposure	Number irradia- ted	Mean follow-up (years)	Mean dose (Gy)	Number of cancers	Excess cases per 10^4 PYGy a/	Ref.
0-15	1644	18.2	2.0	2	0.43±0.32	[S24]
0-1	2872	23.3	1.4	2 b/	0.40±0.28	[H1]
5.1	554	21.5	5.0	3	0.65±0.38	[M11]
5	466	27.7	2.4	1 b/	0.21±0.37	[J4]
5.5	1922	29.9	7.9	8	0.21±0.07	[S15]
				19 b/	0.48±0.12	
7.9	2215	20.5	0.4	1	0.67±0.75	[S16]
				3 b/	1.90±1.30	
>15	10902	16.8	0.4	4	0.72±0.40	[M13]
				3 b/	0.47±0.37	
57	1005	19.1	5.3	2	0.26±0.28	[H21]

a/ After a five-year latency.
b/ Benign cases.

T a b l e   43

Effect of type of treatment on cumulative incidence
of second primary cancers in patients with genetic retinoblastoma
[D15]

Type of treatment	Site of second cancer	Number of patients	Number of second cancers	Cumulative incidence (per cent) at	
				12 years	18 years
Radiotherapy	All sites	140	4	4.2	4.2
	In radiation field	140	3	2.9	2.9
	Outside radiation field	188	1	1.0	1.0
Radiotherapy with chemotherapy	All sites	62	8	6.6	14.2
	In radiation field	62	4	4.2	9.9
	Outside radiation field	65	5	4.6	7.5
Chemotherapy	All sites	3	1	100	100
No radiotherapy, no chemotherapy	All sites	48	0	0	0

T a b l e   44

Comparison of predicted and observed excess second cancers
in women irradiated to treat cervical cancer
[B12]

Second primary cancers	Risk coefficient (cases per 10^4 PYGy) [C4]	Organ dose (Gy)		Predicted excess cancers	Observed excess cancers a/
Stomach	1.68	2.0 (0.5-3.5)		60	+3
Colon	1.12	5.0		100	+15
Liver	0.70	1.5 (0.5-2.5)		20	0
Pancreas	0.99	1.5 (0.3-3.0)		25	+9
Lung	3.94	0.3 (0.1-0.6)		25	+77
Breast	5.82	0.3 (0.1-0.6)		37	-101
Kidney	0.88	2.0 (0.6-3.5)		30	-6
Bladder	0.88	30		475	+82
Thyroid	5.80	0.1 (0.0-0.3)		15	+4
Lymphoma	0.27	~10 (3.0-13)		50	+15
Acute and NL leukaemia	2.70	7.5 (3.0-13)	b/	1000	+13
		2.5 (0.8-3.3)	c/	350	+13
		0.3 (0.1-0.4)	d/	45	+13

a/ In women, except those with leukaemia, living more than 10 years; for women with leukaemia, values are for 1-20 years after irradiation.
b/ Averaged over entire bone marrow.
c/ Excluding pelvis contribution.
d/ Excluding pelvis, lumbar spine, and upper femur contributions.

Relative risk of cancer mortality
in ankylosing spondylitis patients
[021]

Site	Time since first treatment (years)							Total
	0-2.5	2.5-4.9	5-9.9	10-14.9	15-19.9	20-24.9	>25	
All neoplasms	1.77	1.53	1.48	1.61	1.51	1.15	1.08	1.33
Leukaemia	5.45	12.51	4.67	2.41	2.19	1.46	1.94	3.17
Colon cancer	2.40	0.54	2.41	1.38	1.87	0.46	1.02	1.30
All other a/	1.57	1.28	1.30	1.60	1.47	1.19	1.07	1.28

a/ All neoplasms other than leukaemia and cancer of the colon.

T a b l e   46

Relative risk of cancer mortality at specific sites
in ankylosing spondylitis patients
[021]

(Risks significant at the 0.05 or better level are underlined.
Relative risk computed as observed/expected ratio.)

Site	Time since first treatment (years)			Total >5 a/
	<5	5-25	>25	
Mouth	0.00	1.68	1.41	1.58
Pharynx	0.00	1.77	1.14	1.56
Oesophagus	0.84	2.05	2.41	2.20
Stomach	1.01	1.20	0.62	1.01
Rectum	0.94	1.14	0.96	1.07
Liver	2.71	0.58	2.01	1.10
Pancreas	3.24	1.13	0.86	1.02
Larynx	2.84	1.37	1.85	1.54
Lung	1.22	1.37	0.97	1.21
Breast	1.58	1.88	1.02	1.62
Uterus	0.00	1.15	0.65	1.02
Ovary	1.17	1.07	0.62	0.93
Prostate	3.04	1.24	1.07	1.16
Kidney	1.11	1.61	1.36	1.52
Bladder	1.96	0.91	1.62	1.20
Skin	0.00	1.23	1.52	1.33
Spinal cord	96.6	6.77	0.00	4.72
Other CNS	0.67	1.60	1.49	1.57
Bone	1.88	2.95	2.96	2.95
Hodgkin's disease	2.42	1.66	0.00	1.32
Other lymphoma	2.03	2.89	1.13	2.24
Multiple myeloma	0.00	1.52	1.97	1.72
Other	1.90	1.35	1.10	1.25
Total	1.44	1.38	1.07	1.26

a/ At least five years have elapsed since treatment.

Table 47

Relative risk of cancer mortality in age groups of
ankylosing spondylitis patients
[D21]

| Age at first treatment | Time since first treatments (years) | | | | | |
| | All but colon and leukaemia | | | Leukaemia | | |
	5-25	>25	Total >5 a/	5-25	>25	Total >1 b/
<25	1.97	1.06	1.38	2.98	0.00	1.10
25-34	1.50	0.98	1.22	4.98	2.21	3.06
35-44	1.37	1.10	1.26	6.66	1.44	3.02
45-54	1.35	1.25	1.33	3.90	3.34	3.57
>55	1.16	0.78	1.15	4.85	0.00	3.28
Total	1.38	1.07	1.26	5.01	1.87	3.03

a/ At least five years elapsed since treatment.
b/ At least one year elapsed since treatment.

Table 48

Organ dose estimates (Gy) for ankylosing spondylitis patients
calculated using the Monte Carlo technique
[L16]

Organ	Mean of estimated doses	Median of estimated doses	Standard deviation	Range	10-90% range
Adrenals	7.3	6.6	5.8	0-38.1	0.08-14.4
Bladder	1.5	1.1	1.7	0-17.2	0.05- 3.3
Brain	0.14	0.11	0.20	0- 4.8	0- 0.3
Gastrointestinal tract					
Stomach	2.5	2.4	1.7	0-12.8	0.18- 4.5
Upper large intestine	3.0	3.1	1.8	0-11.6	0.43- 5.4
Lower large intestine	2.6	2.1	2.7	0-25.7	0.15- 5.4
Small intestine	4.3	4.4	2.6	0-16.1	0.59- 7.3
Oesophagus	4.2	4.3	3.2	0-27.2	0.05- 8.1
Genitalia					
Testes	0.23	0.08	0.60	0- 6.6	0- 0.5
Ovaries	3.8	3.3	3.7	0-21.0	0.02- 8.2
Other than above	0.24	0.09	0.74	0-13.0	0- 0.4
Heart	2.5	2.6	1.9	0-17.3	0.04- 4.8
Kidneys	4.6	4.3	3.6	0-30.8	0.24- 9.0
Liver	1.6	1.6	1.3	0-11.5	0.11- 3.0
Nasal region	0.47	0.44	0.44	0- 3.1	0- 1.1
Pancreas	3.5	3.5	2.4	0-17.0	0.15- 6.3
Pulmonary region					
Lungs	1.8	1.6	1.6	0-13.3	0.05- 3.5
Main bronchi	6.8	6.5	5.4	0-59.9	0.19-13.9
Trachea	3.6	3.6	3.0	0-14.3	0- 7.6
Skeleton					
Pelvis	9.4	10.0	6.1	0-35.3	0.48-16.1
Ribs	4.4	4.2	3.4	0-28.7	0.15- 8.3
Spine	14.4	14.5	9.7	0-65.9	1.2 -27.0
Other than above a/	0.48	0.36	0.61	0- 6.3	0.06- 0.9
Skin					
Trunk skin	1.8	1.7	1.1	0- 9.7	0.47- 3.0
Skin excluding trunk a/	0.19	0.17	0.20	0- 2.3	0.01- 0.4
Spleen	1.6	1.2	1.9	0-21.6	0.12- 2.7
Thyroid	0.99	0.97	0.89	0-10.5	0- 2.1
Uterus	3.5	3.1	3.5	0-18.1	0.04- 7.0
Totals					
Trunk	2.9	2.9	1.7	0-12.5	0.78- 5.0
Legs	0.08	0.03	0.22	0- 4.0	0- 0.1
Head	1.5	1.5	1.3	0- 7.6	0- 3.2
Total body	1.9	1.9	1.1	0- 8.1	0.51- 3.3

a/ Indirect calculation.

Table 49

Red bone marrow dose estimates (Gy) for ankylosing spondylitis patients
calculated using the Monte Carlo technique
[L16]

Marrow site	Proportion of total red bone marrow mass (%)	Mean of estimated doses	Median of estimated doses	Standard deviation	Range	10-90% range
Arms	1.9	0.43	0.17	1.4	0-15.4	0-0.41
Legs	3.8	0.09	0.03	0.25	0- 4.2	0-0.15
Cranium	11.9	0.32	0.23	0.36	0- 4.0	0-0.78
Mandible	1.2	0.26	0.20	0.27	0- 1.8	0-0.66
Clavicles	1.6	0.41	0.31	0.64	0- 8.5	0-0.80
Scapulae	4.8	0.65	0.38	1.4	0-20.6	0.01-0.93
Ribs	10.2	1.9	1.9	1.4	0-11.3	0.05-3.6
Pelvis	36.2	4.3	4.6	2.8	0-16.7	0.16-7.7
Upper spine	3.4	4.7	5.2	4.0	0-20.8	0-9.9
Mid spine	14.1	6.9	7.1	5.0	0-37.6	0.06-13.1
Lower spine	10.9	7.8	8.1	5.0	0-31.3	0.35-13.8
Total marrow	100.0	3.8	3.7	2.2	0-13.1	0.89-6.7

Table 50

Comparison of the mean shielded kerma and organ absorbed dose (mGy)
in atomic bomb survivors exposed to 0.01 Gy and over under the T65DR and DS86 dosimetries
[S48]

Organ dose	Dose system	Both cities				Hiroshima				Nagasaki			
		Number	Total	Gamma	Neu-tron	Number	Total	Gamma	Neu-tron	Number	Total	Gamma	Neu-tron
Shielded kerma	DS86	41719	295	287	8	31044	304	295	10	10675	267	265	3
	T65DR	41316	414	350	64	26146	442	344	99	15170	366	362	4
Bone marrow	DS86	40701	242	239	3	30569	247	243	3	10132	228	227	1
	T65DR	41316	219	201	18	26146	227	199	28	15170	204	203	1
Large intestine	DS86	39859	223	222	1	30083	226	225	2	9776	215	215	1
	T65DR	31958	198	186	12	21873	189	173	16	10085	217	216	1
Lung	DS86	40382	240	238	2	30469	244	242	3	9913	228	227	1
	T65DR	41316	194	180	14	26146	200	179	22	15170	182	181	1
Stomach	DS86	39961	228	226	2	30136	232	229	2	9825	218	217	1
	T65DR	41316	181	169	12	26146	187	169	18	15170	171	171	1
Female breast	DS86	25252	240	236	4	18803	248	243	5	6449	217	216	1
	T65DR	25211	309	276	33	15937	321	270	51	9274	288	286	2
Bladder	DS86	40060	231	229	1	30240	235	233	2	9820	220	219	1
	T65DR	41316	174	162	12	26146	180	162	18	15170	164	164	1
Ovary	DS86	24581	211	210	1	18439	215	214	1	6142	198	198	0
	T65DR	19563	190	181	9	13214	182	168	13	6349	208	207	1

**Relative risk at 1 Gy by age at the time of the bombings (ATB)
and age at death based on DS86 shielded kerma**
[S49]

(Risk before the assumed minimum latency period of 10 years
indicated in parentheses.)

Age ATB	Age at time of death						
	0-20	20-29	30-39	40-49	50-59	60-69	>70
Leukaemia							
0-10	44.16	3.41	8.64	0.95			
10-19	54.74	-	2.45	1.02	0.82		
20-29		5.33	3.54	43.09	1.02	0.82	
30-39			0	24.05	10.58	1.47	3.89
40-49				0.83	3.82	0.82	3.10
>50					15.63	5.18	6.90
Total	46.47	9.81	4.75	5.68	3.98	1.70	4.40
All cancers except leukaemia							
0-10	(70.07)	5.89	1.96	1.86			
10-19	(40.90)	(0.82)	1.66	1.59	1.68		
20-29			(1.38)	2.09	1.74	1.37	
30-39			(0.84)	(1.12)	1.11	1.23	1.48
40-49				(1.25)	(1.12)	1.13	1.33
>50					(2.58)	(0.95)	1.15
Total	75.32	2.22	1.60	1.58	1.39	1.13	1.29
Stomach cancer							
0-10	(0)	7.22	1.30	1.54			
10-19	(0)	(0.82)	1.26	1.21	2.88		
20-29			(0.82)	2.66	1.93	1.77	
30-39			(76.88)	(1.00)	0.97	1.18	1.48
40-49				(1.60)	(1.17)	1.05	1.24
>50					(3.30)	(0.92)	1.12
Total	0	1.30	1.26	1.70	1.40	1.06	1.22
Lung cancer							
0-10	(0)	0.84	0.82	0.83			
10-19	(0)	(0)	0.81	5.56	1.50		
20-29			(0)	0.83	1.75	1.03	
30-39			(0)	(0.81)	1.49	1.50	1.26
40-49				(0)	(1.58)	1.34	1.40
>50					(0.85)	(2.29)	1.44
Total	0	0.84	0.82	2.32	1.57	1.44	1.39
Breast cancer							
0-10	(0)	0	0.92	3.04			
10-19	(0)	(0)	10.48	2.16	4.21		
20-29			(2.10)	0.81	2.05	5.78	
30-39			(0.83)	(0.80)	2.86	2.28	1.03
40-49				(0)	(0.82)	1.13	0.82
>50					(8.16)	(0.82)	1.37
Total	0	0	3.72	1.63	2.57	1.61	1.01

Excess deaths per 10⁴ PYGy by age at the time of the bombings (ATB) and age at death based on DS86 shielded kerma
[S49]

(Risk before the assumed minimum latency period of 10 years
indicated in parentheses.)

Age ATB	Age at death						
	0-20	20-29	30-39	40-49	50-59	60-69	>70
Leukaemia							
0-10	6.71	0.93	1.27	-0.01			
10-19	3.95	-	0.56	0.02	-0.06		
20-29		3.93	1.52	4.84	0.01	-0.28	
30-39			0	3.18	2.26	1.09	3.89
40-49				-0.35	3.07	-0.24	3.50
>50					4.31	3.84	5.12
Total	6.48	2.17	1.16	1.88	1.54	1.09	4.24
All cancers except leukaemia							
0-10	(0.43)	1.32	2.85	5.16			
10-19	(3.96)	(-0.12)	2.00	5.84	13.91		
20-29			(1.39)	9.40	15.71	14.33	
30-39			(-1.32)	(1.33)	3.16	11.00	41.01
40-49				(2.48)	(3.37)	7.31	37.30
>50					(35.29)	(-2.88)	17.21
Total	0.79	0.54	1.98	5.35	9.62	6.85	30.53
Stomach cancer							
0-10	(0)	0.43	0.43	1.24			
10-19	(0)	(-0.06)	0.23	0.58	6.61		
20-29			(-0.29)	5.40	5.46	8.21	
30-39			(4.77)	(0.01)	-0.35	2.82	11.93
40-49				(2.62)	(2.24)	1.15	8.52
>50					(15.79)	(-2.34)	5.56
Total	0	0.06	0.31	2.10	3.41	1.19	8.20
Lung cancer							
0-10	(0)	-0.01	-0.02	0.10			
10-19	(0)	(-0)	0.03	1.75	1.15		
20-29			(0)	-0.06	1.71	0.19	
30-39			(0)	(0.10)	-1.10	3.82	3.11
40-49				(0)	(0.68)	2.19	7.26
>50					(-0.15)	(3.11)	4.74
Total	0	-0.00	-0.02	0.56	1.11	2.62	5.50
Breast cancer							
0-10	(0)	-0	-0.03	1.18			
10-19	(0)	(-0)	2.99	2.39	4.55		
20-29			(0.37)	-0.16	1.90	4.14	
30-39			(-0.16)	(-0.18)	-3.83	0.66	0.05
40-49				(0)	(-0.41)	0.20	-0.23
>50					(11.27)	(-0.12)	0.87
Total	0	0	1.09	0.76	2.88	0.61	0.02

Table   53

Comparison of DS86 and T65DR risk coefficients for mortality based on shielded kerma in the Japanese DS86 subcohort
[S48]

(Both cities, both sexes and all ages ATB combined.
90% confidence intervals in parentheses.)

Site of cancer	Dose system a/	Excess relative risk per Gy	Ratio DS86/ T65DR	Excess deaths per 10^4 PYGy	Ratio DS86/ T65DR
All malignant neoplasms	DS86	0.39 (0.32-0.46)	1.39	10.0 (8.56-11.8)	1.43
	T65DR	0.28 (0.23-0.33)		7.00 (5.87-8.19)	
	T65DRf	0.25 (0.21-0.30)		6.21 (5.24-7.22)	
Leukaemia	DS86	3.92 (2.89-5.40)	1.37	2.29 (1.88-2.73)	1.43
	T65DR	2.87 (2.10-3.89)		1.60 (1.30-1.91)	
	T65DRf	2.62 (1.95-3.48)		1.40 (1.16-1.65)	
All except leukaemia	DS86	0.29 (0.23-0.36)	1.32	7.41 (5.23-9.08)	1.41
	T65DR	0.22 (0.17-0.27)		5.25 (4.17-6.37)	
	T65DRf	0.19 (0.15-0.23)		4.62 (3.70-5.58)	
Oesophagus	DS86	0.43 (0.09-0.91)	1.43	0.34 (0.08-0.67)	1.55
	T65DR	0.30 (0.06-0.65)		0.22 (0.05-0.45)	
	T65DRf	0.18 (-0.01-0.45)		0.14 (-0.01-0.32)	
Stomach	DS86	0.23 (0.13-0.34)	1.35	2.07 (1.19-3.05)	1.46
	T65DR	0.17 (0.09-0.25)		1.42 (0.83-2.07)	
	T65DRf	0.13 (0.07-0.20)		1.13 (0.63-1.67)	
Large intestine except rectum	DS86	0.56 (0.25-0.98)	1.37	0.56 (0.26-0.91)	1.47
	T65DR	0.41 (0.18-0.71)		0.38 (0.18-0.63)	
	T65DRf	0.41 (0.20-0.69)		0.37 (0.19-0.58)	
Trachea, bronchus and lung	DS86	0.46 (0.25-0.72)	1.39	1.25 (0.70-1.89)	1.44
	T65DR	0.33 (0.18-0.51)		0.87 (0.49-1.29)	
	T65DRf	0.30 (0.17-0.44)		0.83 (0.50-1.20)	
Female breast	DS86	1.00 (0.48-1.75)	1.41	1.02 (0.53-1.60)	1.46
	T65DR	0.71 (0.34-1.21)		0.70 (0.36-1.10)	
	T65DRf	0.83 (0.46-1.32)		0.80 (0.48-1.17)	
Ovary and other uterine adnexa	DS86	0.81 (0.16-1.89)	1.53	0.45 (0.10-0.90)	1.61
	T65DR	0.53 (0.07-1.24)		0.28 (0.04-0.58)	
	T65DRf	0.50 (0.09-1.10)		0.28 (0.06-0.55)	
Bladder, other unspecified urinary	DS86	1.02 (0.45-1.07)	1.44	0.55 (0.26-0.89)	1.53
	T65DR	0.71 (0.30-1.30)		0.36 (0.17-0.60)	
	T65DRf	0.61 (0.25-1.12)		0.29 (0.13-0.48)	
Multiple myeloma	DS86	1.86 (0.55-4.45)	1.43	0.21 (0.07-0.39)	1.31
	T65DR	1.30 (0.40-2.99)		0.16 (0.06-0.28)	
	T65DRf	0.70 (0.15-1.72)		0.10 (0.02-0.20)	

a/ T65DRf = T65DR-full, meaning that risk coefficients were calculated by using TR65DR dose on the full T65DR cohort.

Comparison of DS86 and T65DR risk coefficients for mortality
based on absorbed dose in the Japanese DS86 subcohort
[S48]

(Both cities, both sexes and all ages ATB combined.
90% confidence intervals in parentheses.)

Site of cancer	Dose system	Excess relative risk per Gy	Ratio DS86/ T65DR	Excess deaths per 10^4 PYGy	Ratio DS86/ T65DR
Leukaemia	DS86	5.21 (3.83-7.12)	0.90	2.94 (2.43-3.49)	0.95
	T65DR	5.76 (4.24-7.86)		3.11 (2.56-3.71)	
All except leukaemia	DS86	0.41 (0.32-0.51)	0.71	10.13 (7.96-12.44)	0.73
	T65DR	0.58 (0.46-0.72)		13.97 (11.11-17.04)	
Oesophagus	DS86	0.58 (0.13-1.24)	0.87	0.45 (0.10-0.88)	0.92
	T65DR	0.67 (0.12-1.47)		0.49 (0.09-1.00)	
Stomach	DS86	0.27 (0.14-0.43)	0.69	2.42 (1.26-3.72)	0.72
	T65DR	0.39 (0.23-0.58)		3.34 (1.95-4.83)	
Large intestine except rectum	DS86	0.85 (0.39-1.45)	0.82	0.81 (0.40-1.30)	0.83
	T65DR	1.04 (0.43-1.85)		0.98 (0.42-1.63)	
Lung	DS86	0.63 (0.35-0.97)	0.88	1.68 (0.97-2.49)	0.89
	T65DR	0.72 (0.41-1.11)		1.89 (1.10-2.79)	
Female breast	DS86	1.19 (0.56-2.09)	1.31	1.20 (0.61-1.91)	1.33
	T65DR	0.91 (0.43-1.57)		0.90 (0.46-1.42)	
Ovary	DS86	1.33 (0.37-2.86)	1.10	0.71 (0.22-1.32)	1.11
	T65DR	1.21 (0.11-3.06)		0.64 (0.06-1.43)	
Bladder	DS86	1.27 (0.53-2.37)	0.80	0.66 (0.31-1.12)	0.81
	T65DR	1.59 (0.63-3.03)		0.81 (0.34-1.38)	
Multiple myeloma	DS86	2.29 (0.67-5.31)	0.96	0.26 (0.09-0.47)	0.90
	T65DR	2.39 (0.75-5.56)		0.29 (0.11-0.53)	

T a b l e   55

Comparison of the main characteristics of the atomic bomb,
ankylosing spondylitis and cervical cancer series

	Atomic bomb survivors	Spondylitis series	Cervical cancer series
Nature of study	Prospective	Retrospective-prospective	Retrospective-prospective
Sample size	76000	14000	83000
Sex composition	F = 59%	F = 17%	F = 100%
Age at irradiation (years)	0->90	>15	<30->70
Average follow-up (years)	28.8	13.0	7.6
Type of control	Internal	National rates	National rates and internal
Type of dosimetry	Individual (DS86)	Individual for leukaemia, 1/15 random sample elsewhere	Mean dose of a sample
Type of irradiation	Instantaneous, whole-body	Fractionated, non-uniform, partial-body	Chronic, fractionated, partial-body
Dose distribution			
Mean dose (Gy)	0.24	1.9	Extremely uneven
Range of doses (Gy)	(0.01-6.0)	(0-8.06)	
Person-years at risk	2185000	184000	623800

T a b l e   56

**Summary of the estimated risk of cancer
per 1 Gy of organ absorbed dose obtained from the atomic bomb,
ankylosing spondylitis and cervical cancer series**

EXCESS RELATIVE RISK

Organ or tissue	Atomic bomb survivors (Table 54) [S49]	Spondylitis series [S31] and [D21]	Cervical cancer series [B38]
Leukaemia	5.21 (3.83-7.12) a/	3.5 b/	0.88
All cancers except leukaemia	0.41 (0.32-0.51)	0.14 c/	d/
Bladder	1.27 (0.53-2.37)	0.19	0.07 (0.02-0.17)
Breast	1.19 (0.56-2.09)	-	0.03 (0.00-1.29)
Kidney	0.58 (-0.09-1.94) e/	0.12	0.71 (0.03-2.24)
Large intestine	0.85 (0.39-1.45)	-	0.00 (0.00-0.02)
Larynx	0.51 (-0.05-1.68) e/	0.15	
Lung	0.63 (0.35-0.97)	0.13	
Multiple myeloma	2.29 (0.67-5.31)	-	
Oesophagus	0.58 (0.13-1.24)	0.29	
Ovary	1.33 (0.37-2.86)	0.00	0.01 (0.00-0.14)
Rectum	0.00 e/	0.03	0.02 (0.00-0.04)
Stomach	0.27 (0.14-0.43)	0.004	0.69 (0.01-2.25)

ABSOLUTE RISK
(excess deaths per 10^4 PYGy)

Organ or tissue	Atomic bomb survivors (Table 54) [S49]	Spondylitis series [S31] and [D21]	Cervical cancer series [B38]
Leukaemia	2.94 (2.43- 3.49)	2.02	0.61
All cancers except leukaemia	10.13 (7.96-12.44)	4.67	d/

a/ Values in parentheses are 90% confidence intervals. They are those given by the authors.
b/ This figure was derived by the Committee from [S31] using data from individuals receiving a mean marrow dose of 3 Gy or less.
c/ All cancers except leukaemia and colon cancer.
d/ An estimate of the risk of all cancers except leukaemia cannot be made for this series. An estimate of the whole-body dose does not exist, and probably cannot be estimated given the nature of the exposures.
e/ Shielded kerma.

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T a b l e   57

Summary of assumptions used in the projections

Minimum latency	For leukaemia: 2 years For all other sites: 10 years
Plateau	For leukaemia: 40 years For all other sites: Lifetime
Extrapolation models	For leukaemia: Additive and multiplicative For all other sites: Additive and multiplicative
Detriment indicators	Lifetime excess mortality for cancer of each site Loss of life expectancy in person-years
Population exposed	1,000 persons
Exposure	1 Gy to each site at a high dose rate
Baseline mortality	Cancer mortality in Japan (1982) or in the United Kingdom [W21]
Whole population Working population	Age structure of the population in 1982 Population in 1982 between 25 and 64 years of age, both sexes

T a b l e   58

Risk coefficients for adults from the atomic bomb,
ankylosing spondylitis and cervical cancer series

(These coefficients were used for the calculations in Tables 59 and 60.)

Malignancy	Sex	Atomic bomb study a/		Spondylitis series b/		Cervical cancer series c/	
		Multi-plicative e/	Additive f/	Multi-plicative e/	Additive f/	Multi-plicative e/	Additive f/
Leukaemia	M	3.7	5.0	3.5	2.0	-	-
	F	3.8	2.9	-	-	0.88	0.61
	Average	3.8	3.9				
Other malignancies	M	0.24	15	0.14	4.7	-	-
	F	0.46	17	-	-	-	-
	Average	0.35	16				

a/ DS86; average values of 25-29, 30-39, and >40 weighted by the proportions
   of the Japanese population within these age groups. From [S49], appendix
   tables 5a and 5B, Part II.
b/ From [D21] and [L16].
c/ From [B36], page 1307.
e/ Excess relative risk per Gy.
f/ Excess deaths per 10^4 PYGy.

Projection of excess lifetime mortality
for an adult population of both sexes (1000 males or 1000 females)
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate

PLATEAU = 40 years

Malignancy	Sex	Atomic bomb study a/		Spondylitis series b/		Cervical cancer series b/	
		Multi-plicative	Additive	Multi-plicative	Additive	Multi-plicative	Additive
Leukaemia	M	9.0	13	14	4.4	-	-
(1) c/	F	8.1	7.0	-	-	2.8	1.4
	Average	8.6	10				
Other malignancies	M	37	29	21	7.6	-	-
(2) d/	F	46	39	-	-	-	-
	Average	42	34				
Total (1) + (2) (average)		51	44	35	12	-	-

PLATEAU = lifetime

Malignancy	Sex	Atomic bomb study a/		Spondylitis series b/		Cervical cancer series b/	
		Multi-plicative	Additive	Multi-plicative	Additive	Multi-plicative	Additive
Other malignancies	M	41	30	23	7.8	-	-
(3) d/	F	52	42	-	-	-	-
	Average	47	36				
Total (1) + (3)		56	46	37	12		

a/ Reference population: Japan, 1982.
b/ Reference population: United Kingdom, 1982.
c/ Assumed latency time: 2 years.
d/ Assumed latency time: 10 years.

Table 60

Projection of loss of life expectancy
for an adult population of both sexes (1000 males or 1000 females)
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate

PLATEAU = 40 years

Malignancy	Sex	Atomic bomb study a/		Spondylitis series b/		Cervical cancer series b/	
		Multi-plicative	Additive	Multi-plicative	Additive	Multi-plicative	Additive
Leukaemia	M	140	290	140	79	-	-
(1) c/	F	120	170	-	-	31	28
	Average	130	230				
Other malignancies	M	400	500	200	120	-	-
(2) d/	F	530	700	-	-	-	-
	Average	470	600				
Total (1) + (2) (average)		600	830	340	200	-	-

PLATEAU = lifetime

Malignancy	Sex	Atomic bomb study a/		Spondylitis series b/		Cervical cancer series b/	
		Multi-plicative	Additive	Multi-plicative	Additive	Multi-plicative	Additive
Other malignancies	M	420	510	210	120	-	-
(3) d/	F	570	710	-	-	-	-
	Average	490	610				
Total (1) + (3) (average)		620	840	350	200		

a/ Reference population: Japan, 1982.
b/ Reference population: United Kingdom, 1982.
c/ Assumed latency time: 2 years.
d/ Assumed latency time: 10 years.

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Table 61

Projection of loss of life expectancy
for a population of both sexes (500 males and 500 females)
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate
as a function of age using an age-constant risk coefficient

ADDITIVE MODEL

Organ or tissue	Age at exposure							
	0	10	20	30	40	50	60	70
Leukaemia	640	530	420	310	210	120	62	24
All cancers except leukaemia	2360	1750	1230	800	470	240	93	22

MULTIPLICATIVE MODEL

Organ or tissue	Age at exposure							
	0	10	20	30	40	50	60	70
Leukaemia	250	240	250	260	240	190	130	63
All cancers except leukaemia	920	930	920	880	790	620	370	130

Table 62

Projections of excess lifetime mortality and loss of life expectancy
for a population of both sexes (500 males and 500 females) and all ages
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate
using age-specific risk coefficients

Risk coefficients at ages 0-9 and 10-19 are given in the text;
risk coefficients for adults are given in Table 58.
All risk coefficients are based on the Japanese atomic bomb survivors.

(Based on the population of Japan in 1982.)

EXCESS LIFETIME MORTALITY

	Multiplicative risk projection model	Additive risk projection model
Leukaemia a/	10	10
Other malignancies b/	97	32
All malignancies	107	42

LOSS OF LIFE EXPECTANCY

	Multiplicative risk projection model	Additive risk projection model
Leukaemia a/	260	300
Other malignancies b/	1110	650
All malignancies	1370	950

a/ Plateau: 40 years.
b/ Plateau: lifetime.

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Projections of excess lifetime mortality and loss of life expectancy
for a population of both sexes (500 males and 500 females) and all ages
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate
using an age-averaged risk coefficient

The risk coefficients are based on Japanese atomic bomb survivors.
Risk coefficients given in Table 54 are averaged
over all classes of age at exposure according to the size of each class.

(90% confidence intervals in parentheses.)

EXCESS LIFETIME MORTALITY

	Multiplicative risk projection model	Additive risk projection model
Leukaemia	9.7 (7.1-13)	9.3 (7.7-11)
Other malignancies	61 (48 -75)	36 (28 -44)
All malignancies	71	45

LOSS OF LIFE EXPECTANCY

	Multiplicative risk projection model	Additive risk projection model
Leukaemia	220 (160-270)	300 (250-360)
Other malignancies	730 (570-900)	910 (710-1110)
All malignancies	950	1210

T a b l e   64

Demographic characteristics of countries used to compare risk projections
[W21]

	Japan	United Kingdom	Puerto Rico
Life expectancy (years)	76.6	73.7	73.9
Infant mortality (per 1000 births)	8	12	17
Percentage of population under 15 years	23.5	20.3	32
Percentage of population over 64 years	9.3	15.3	8
Cancer mortality rate a/ (1985) (10^{-5})	108.4	150.0	93.9
Death rates a/ (1983-1985) (10^{-3})	4.2	5.8	5.6

a/ Age-standardized.

Table 65

Comparison of projections of lifetime excess mortality
in three reference countries
for 1000 persons of the general population
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate

Excess risk coefficients derived from atomic bomb survivors (Table 56)
and the assumptions given in Table 57.

	Japan		United Kingdom		Puerto Rico	
	Multi-plicative	Additive	Multi-plicative	Additive	Multi-plicative	Additive
Leukaemia	9.7	9.3	13	8.5	9.4	9.7
Other malignancies	61	36	63	31	49	40
Total	71	45	76	40	58	50

Table 66

Comparison of projections of loss of life expectancy
in three reference countries
for 1000 persons of the general population
exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate

Excess risk coefficients derived from atomic bomb survivors (Table 56)
and the assumptions given in Table 57.

	Japan		United Kingdom		Puerto Rico	
	Multi-plicative	Additive	Multi-plicative	Additive	Multi-plicative	Additive
Leukaemia	220	300	200	260	200	360
Other malignancies	730	910	740	750	580	1090
Total	950	1210	940	1010	780	1450

Table 67

Excess relative risk per 1 Gy of organ absorbed dose in the low dose range
[S49]

	Dose range (Gy)			
Type of cancer	< 6.0	< 1.0	< 0.5	> 0.5 a/
Leukaemia	5.21 b/	3.96 b/	2.44 d/	5.53
All cancers except leukaemia	0.41 b/	0.46 b/	0.37 d/	0.41
Stomach	0.27 b/	0.41 c/	0.45 e/	0.26
Lung	0.63 b/	0.83 c/	1.06 d/	0.60
Female breast	1.19 b/	1.78 c/	0.82	1.21
Colon	0.85 b/	-0.10	-0.52	0.98

a/ Excess relative risk for doses > 0.5 Gy compared to
doses < 0.5 Gy is significantly different only for
leukaemia (p < 0.05) and for colon cancer (p < 0.1).
b/ p < 0.001.
c/ p < 0.01.
d/ p < 0.05.
e/ p < 0.10.

T a b l e 68

lung cancer risk from chronic exposure to radon daughters
indoors and outdoors
[111]

Source and location	Equilibrium equivalent concentration (Bq/m^3)	Annual exposure (10^5 Bq h/m^3)	Excess relative risk (%)	Excess frequency of lung cancers per million persons per year			
				Reference population			Non-smokers (average both sexes)
				Males	Females	Total	
Radon-222 daughters							
Indoors a/	15	0.90	9.0	54	11	32	7.2
Indoors b/	15	0.23	2.3	14	2.7	8.1	1.8
Outdoors	4	0.040	0.52	3.1	0.62	1.9	0.42
Subtotal		1.2	11.8	71	14	42	9.4
Radon-220 daughters							
Indoors a/	0.5	0.030	1.0	6.0	1.2	3.6	0.80
Indoors b/	0.5	0.0075	0.25	1.5	0.30	0.90	0.20
Outdoors	0.2	0.0020	0.66	0.40	0.079	0.24	0.053
Subtotal		0.040	1.3	7.9	1.6	4.7	1.05
Total			13	79	16	47	10.5

a/ At home.
b/ Elsewhere.

Projection of excess lifetime mortality for specific cancers for 1000 persons exposed to 1 Gy of organ absorbed dose of low-LET radiation at high dose rate

(Based on the population of Japan.
90% confidence intervals in parentheses.)

Malignancy	Multiplicative risk projection model	Additive risk projection model
Red bone marrow	9.7 (7.1-13)	9.3 (7.7-11)
All cancers		
except leukaemia	61 (48 -75)	36 (28 -44)
Bladder	3.9 (1.6- 7.3)	2.3 (1.1- 4.0)
Breast a/	6.0 (2.8-10.5)	4.3 (2.2- 6.9)
Colon	7.9 (3.6-13.4)	2.9 (1.4- 4.6)
Lung	15.1 (8.4-23.0)	5.9 (3.4- 8.8)
Multiple myeloma	2.2 (0.6- 5.1)	0.9 (0.3- 1.7)
Ovary a/	3.1 (0.9- 6.8)	2.6 (0.8- 4.8)
Oesophagus	3.4 (0.8- 7.2)	1.6 (0.3- 3.1)
Stomach	12.6 (6.6-19.9)	8.6 (4.5-13.1)
Remainder	11.4 b/	10.3 b/
	11.8 c/	6.6 c/
Total	70.7 d/	45.3 d/
	71.2 e/	41.6 e/

a/ These values have to be divided by 2 to calculate the total and other organ risks.

b/ This value is derived by subtracting the sum of the risks at the sites specified from the risks for all cancers except leukaemia.

c/ This value is derived by fitting a linear relative risk model to the basic cancer data after the exclusion of those cases of cancer at the specific sites listed. (Coefficient 0.19 excess relative risk per Gy and 1.87 per 10^4 PYGy).

d/ Red bone marrow plus all other cancers.

e/ Red bone marrow plus other individual sites including remainder.

Table 70

Projection of loss of life expectancy for specific cancers
per person exposed to 1 Gy of organ absorbed dose
of low-LET radiation at high dose rate

(Based on the population of Japan.
90% confidence intervals in parentheses.)

Malignancy		Multiplicative risk projection model	Additive risk projection model
Red bone marrow		0.22 (0.16-0.27)	0.30 (0.25-0.36)
All cancers			
except leukaemia		0.73 (0.57-0.90)	0.91 (0.71-1.10)
Bladder		0.03 (0.01-0.06)	0.04 (0.02-0.07)
Breast	a/	0.11 (0.05-1.90)	0.11 (0.05-0.17)
Colon		0.09 (0.04-0.15)	0.07 (0.04-0.12)
Lung		0.17 (0.09-0.25)	0.15 (0.09-0.22)
Multiple myeloma		0.03 (0.0 -0.06)	0.02 (0.01-0.04)
Ovary	a/	0.06 (0.02-0.12)	0.07 (0.02-0.12)
Oesophagus		0.04 (0.01-0.08)	0.04 (0.01-0.08)
Stomach		0.15 (0.07-0.23)	0.22 (0.11-0.33)
Remainder		0.14 b/	0.28 b/
		0.14 c/	0.17 c/
Total		0.95 d/	1.2 d/
		0.94 e/	1.1 e/

a/ These values have to be divided by 2 to calculate the total
and other organ risks.
b/ This value is derived by subtracting the sum of the risks
at the sites specified from the risks for all cancers
except leukaemia.
c/ This value is derived by fitting a linear relative risk
model to the basic cancer data after the exclusion of those
cases of cancer at the specific sites listed. (Coefficient
0.19 excess relative risk per Gy and 1.87 per 10^4 PYGy).
d/ Red bone marrow plus all other cancers.
e/ Red bone marrow plus other individual sites including
remainder.

Table 71

Summary of projections of lifetime risks
for 1000 persons (500 males and 500 females)
exposed to 1 Gy of organ absorbed dose
of low-LET radiation at high dose rate

(Based on the population of Japan.)

		Risk projection model	Excess fatal cancers	Years of life lost
Total population	a/	Additive	40 c/ - 50 d/	950 c/ - 1200 d/
		Multiplicative	70 d/ -110 c/	950 d/ - 1400 c/
Working population		Additive	40 d/ - 60 c/	880 d/ - 1330 c/
(aged 25-64 years)		Multiplicative	70 c/ - 80 d/	820 c/ - 970 d/
Adult population	b/	Additive	50 d/	840 d/
(over 25 years)		Multiplicative	60 d/	620 d/

a/ Derived from Tables 62 and 63.
b/ Derived from Tables 59 and 60.
c/ Age-specific risk coefficient.
d/ Constant (age-averaged) risk coefficient.

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