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The Carcinogenic Risks of Low-LET and High-LET Ionizing Radiations

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THE CARCINOGENIC RISKS OF LOW-LET AND HIGH-LET IONIZING RADIATIONS [1,2]

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Abstract

During the past decade, new and important information has become available concerning the carcinogenic effects of radiation and the implications for risk assessment and risk management. This new information comes mainly from further follow-up of the epidemiological studies of the Japanese atomic bomb survivors, patients irradiated medically for cancer and allied conditions, and workers exposed in various occupations. In the Japanese atomic bomb survivors the carcinogenic risks are estimated to be somewhat higher than previously, and this is due to the reassessment of the atomic-bomb dosimetry, further follow-up with increase in the number of excess cancer deaths, particularly in survivors irradiated early in life, and changes in the methods of analysis to compute the age-specific risks of cancer. Overall, the cancer mortality data are now more compatible with the relative risk projection model. Because of the characteristics of the atomic bomb survivor series as regards sample size, age and sex distribution, duration of follow-up, person-years at risk, and type of dosimetry, the mortality experience of the atomic bomb survivors was selected by the UNSCEAR Committee and the BEIR V Committee as the more appropriate basis for projecting risk estimates for the general population. In the atomic bomb survivors, the dose-effect relationship for overall cancer mortality other than leukemia is consistent with linearity below 3 Gy, while the dose-effect relationship for leukemia, excluding chronic lymphatic leukemia, conforms best to a linear-quadratic function. The shape of the dose-incidence curve at low doses still remains uncertain, and the data do not rule out the possible existence of a threshold for any neoplasm. The excess relative risk of mortality from all cancers combined is estimated to be 1.39 per Gy (shielded kerma), which corresponds to an absolute risk of 10.0 excess cancer deaths per 10,000 PYGy; the relative risk is 1.41 at 1 Gy (organ-absorbed dose), and an absolute risk of 13.07 excess cancer deaths per 10,000 PYGy. The BEIR V Committee developed modified multiplicative risk projection models to project lifetime risk estimates; the preferred models contained dose (and dose squared) terms as well as age at exposure, time since exposure, and interaction effects. In its report, it is estimated that if 100,000 persons received an instantaneous dose of 0.1 Gy of low-LET radiation, about 750 extra cancer deaths would be expected to occur during their remaining lifetime in addition to nearly 20,000 cancer deaths that will occur even in the absence of the radiation; a DREF of 2 or more should be applied to this estimate for cancers other than leukemia, since the linear-quadratic model applied to leukemia implies a DREF of about 2. If that population were exposed continuously to 10 mGy per year for an entire lifetime, about 5,000 extra cancer deaths would be expected to occur. The BEIR V Committee concluded that the constant additive risk model for risk estimation is no longer tenable; based on the modified multiplicative risk models for all cancers combined, the current risk estimate reported by the 1989 BEIR V Committee are appreciably higher, by a factor of about 1.5 to 2, than comparable estimates reported by the 1980 BEIR III Committee.

Opening Statement

Thank you, Mr. President. I extend to you and to your colleagues of the scientific and program committees and to the participants of this 32nd Annual Meeting of the Japan Radiation Research Society, my sincerest appreciation for the very special honor of addressing you today on the carcinogenic effects and risk estimates of low-LET and high-LET radiations. My wife, who is sharing this moment with me, and I are grateful to you for extending your very gracious invitation, and for the memorable hospitality accorded to us. The occasion of our visit, originally recorded as one for scientific interaction, has been changed---it has become an occasion for renewing old friendships, and for creating new ones.

Prologue

I plan at this time to discuss with you certain of the most recent findings of the National Academy of Sciences' 1988 BEIR IV Report (1) and the present 1989 BEIR V Report (2), i.e., the most recent report of the Committee on the Biological Effects of Ionizing Radiations which has just completed its final deliberations on the effects of low-level irradiation on human populations. I shall try to place the BEIR V Report (2) in perspective as regards the 1988 BEIR IV Report (1) and the 1988 UNSCEAR Report (3), and bring to you a new set of risk estimates of the carcinogenic effects of radiation in humans. Because of the time required for the completion of the review process of such a scholarly and detailed report, it is not surprizing that the BEIR V Report (2) underwent extensive preparation for publication and has not as yet been released in its official form by the National Academy of Sciences. This will take place in approximately two weeks. The proper reservations and boundaries of responsible scientific behavior and good taste allow for some academic license, and I have been permitted for this special occasion to give you certain of its precise numerical estimates at this time. It is not my official charge to do so and I shall refrain from any indiscretion; nevertheless, I can share with you much of the BEIR V Committee's deliberations.

There is a great deal we can discuss today about the recent work of these three committees and the process of risk estimation, and this is my intention. At the outset, I have made three general assumptions. First, it is assumed in radiation risk assessment that the carcinogenic health effects of ionizing radiation are stochastic phenomena, that is, lacking thresholds. Second, for protection guidance and risk management, it is assumed that these effects increase in frequency as linear nonthreshold functions of the radiation dose at low doses, and it is the magnitude of the increase per unit dose and the extent to which it may vary with different biological, physical and other variables that remain the subjects of continued scientific inquiry. And third, it is assumed that because of the new and important information on the health effects that has become available during the past decade and their broad significance for revisions of risk estimates, I should confine my remarks to the carcinogenic effects exclusively and to review the salient features of these newer approaches, concepts and data on which they are based. These represent the substance of the most recent committee reports, and have been summarized recently in the UNSCEAR (3,4) and the National Academy of Sciences' BEIR (1,2) reports.

Introduction

Important new information on humans has come mainly from further follow-up of existing epidemiological studies, notably the Japanese atomic bomb survivors and the ankylosing spondylitis patients; from new epidemiological surveys, such as the patients treated for cancer of the uterine cervix; and from combined surveys, including workers exposed in underground mines. Since the numerous and complex differences among the different study populations introduce factors that influence the risk estimates derived in ways that are not completely understood, it is not clear how to combine the different risk estimates obtained. These factors involve complex

biological and physical variables distributed over time. Because such carcinogenic effects occur too infrequently to be demonstrated at low doses, the risks of low-dose radiation can be estimated only by interpolation from observations at high doses on the basis of theoretical concepts, mathematical models and available empirical evidence, primarily the epidemiological surveys of large populations exposed to ionizing radiations.

In spite of a considerable amount of research, only recently has there been efforts to apply the extensive laboratory data in animals to define the dose-incidence relationship in the low dose region. There simply are insufficient data in the epidemiological studies of large human populations to estimate risk coefficients directly from exposure to low doses. Nevertheless, we must look to the new information on radiation carcinogenesis in exposed human populations---people exposed to nuclear radiations, the Japanese atomic bomb survivors; patients exposed to medical radiations, the ankylosing spondylitics in England and Wales, women treated for carcinoma of the cervix, and children irradiated for tinea capitis and for other benign diseases; and workers exposed occupationally, mostly involving internally-deposited alpha-emitters, such as the underground miners and the radium dial painters and chemists. From the new evidence, we may conclude that the risk estimates for the carcinogenic effects of radiation have been, in the past, somewhat low and reassessment of the numerical values is now necessary.

Epidemiological Studies

Japanese Atomic Bomb Survivors. By far, the most important survey contributing to current radiation risk assessment is that of the Japanese atomic bomb survivors. It is this study that provides the greatest amount of information, and frequently the only information, required for reassessment of previous risk estimates. This prospective study involves 76,000 survivors, with internal controls, 59% female and 41% male, with an age distribution of 0 to 90 years. The average period of follow-up to 1985 approaches 29 years, with 2,185,000 person-years at risk. The data are based on the DS86 individual dosimetry on each survivor; the radiation dose was whole-body and instantaneous, and the range of absorbed doses 10 mGy to 6 Gy, with a mean whole-body absorbed dose of 240 mGy.

The new data (5) indicate that the carcinogenic effects of atomic radiation in the Hiroshima and Nagasaki survivors---the risk per unit dose---are higher than previously estimated. There are three explanations. First, the reassessment of the atomic bomb dosimetry, i.e., the revised DS86 dosimetry, substantially reduces the high-LET neutron component. Second, there is an increase in the number of cancer deaths with continued follow-up that is particularly evident in survivors who were irradiated in early life. Third, there have been changes in the method used to calculate the cancer rate, based on age at risk and time since exposure (6).

The most important contribution of the revision of the *atomic-bomb dosimetry* concerns the contribution of neutrons to the total dose received by the survivors in both cities; currently this is considered much less significant than previously in the new DS86 system. This results in a higher gamma tissue dose in the Hiroshima survivors, and slightly less in Nagasaki, and permits pooling of the data. Given the lesser amount of neutrons, and assigning a fixed RBE of 10 or more, significantly affects on the current risk estimates. Overall the carcinogenic risk per unit dose equivalent is increased some 40 to 70% for solid tumors, and more for leukemia, depending on the tissue at risk and its depth in the body. The pooling of the Hiroshima and Nagasaki data is now possible since the previously estimated difference in risk per unit dose is no longer statistically significant. No basis remains for estimating the carcinogenic risk of neutron radiation in exposed human populations.

Two models currently used to project an estimate of the overall cancer risk for an exposed population---the additive and multiplicative *risk projection models*---were examined by the UNSCEAR (3) Committee and the BEIR V (2) Committee. Both models are flawed, but since the lifetime cancer experience for low-dose radiation is not yet available for any of the large epidemiological studies, such models suitably modified are necessary. The additive risk projection model assumes that the excess cancer risk is independent of the natural incidence, and that radiation will induce a dose-dependant excess number above the baseline level. The multiplicative model

assumes the excess cancer risk is related to the natural incidence, and that radiation will induce a dose-dependent excess percentage above the baseline incidence. The UNSCEAR Committee applied both risk projection models; the BEIR V Committee rejected the additive model, and developed modified multiplicative models. Shimizu et al. (5) have estimated that the cumulative radiation-associated excess of cancer deaths in the Japanese survivors has risen from 133 in 1975 to 236 in 1985. The excess has also increased with attained age, but the excess relative risk has remained reasonably constant. Overall, the excess cancer mortality experience appears much more closely related to the multiplicative model than the additive model, although the reliability of either model for cancer of a specific type or site, or for those persons exposed at a younger age, continues to remain uncertain.

The limited data available to examine the *dose-response relationships* at low doses of low-LET radiation has made it necessary to interpolate from high dose data. The Japanese leukemia data still conform to the linear-quadratic nonthreshold model, whereas for cancer deaths other than leukemia, the data support a linear nonthreshold model in the exposure range below 3 Gy (5). The excess mortality from cancer of various sites has been estimated to be: for leukemia, a relative risk of 6.21 at 1 Gy (organ-absorbed dose), and an absolute risk of 2.94 excess deaths per 10,000 PYGy; and for all cancers except leukemia, a relative risk of 1.41 at 1 Gy, and an absolute risk of 10.13 excess deaths per 10,000 PYGy (Table 1). The BEIR V Committee found that only for leukemia, esophagus, stomach, large intestine, lung, female breast, ovary, urinary tract, and multiple myeloma were there sufficient data to permit numerical risk estimates to be calculated. Except for the special circumstances of the carcinogenic effects of internally -deposited alpha emitters (1) and for certain selected studies of the thyroid and breast, it has been the mortality experience of the atomic bomb survivors that was selected in both the 1988 UNSCEAR Report (3) and the 1989 BEIR V Report (2) as the most appropriate basis for projecting risk estimates of carcinogenic effects for the general population.

Ankylosing Spondylitis Patients. The ankylosing spondylitis study (7) is a long-standing retrospective- prospective epidemiological survey of over 14,000 patients with average follow-up of 8.1 years, with 184,000 person-years at risk. Some 83% of the cohort are males; national life rates in the United Kingdom are used for controls. The X-irradiation was fractionated, with non-uniform, partial-body exposure at high doses, a range of 0 to 8 Gy and a mean tissue absorbed dose of about 2 Gy. Dosimetry remains incomplete; it is on an individual basis for leukemia, but a 1 in 15 random sample drawn from medical charts for all other cancers. The study is confounded, in part, by the underlying disease for which the radiation was given therapeutically and the association of certain health outcomes, such as colon cancer. This survey has provided new data on patients followed up to 48 years after a single course of X-ray therapy to the spine (7).

Cancer mortality of several of the heavily irradiated tissues has increased significantly between the 5th and 25th year following irradiation, after which time the excess decreased for certain sites, such as the lung and stomach. Whatever the pattern of temporal distribution of excess cancers, it appears that susceptibility to a specific radiation-associated cancer demonstrates no consistent relationship to the spontaneous incidence of the cancer in the general population. This suggests unexplained and complex organ-, tissue-, and cell- dependant differences in susceptibility to radiation carcinogenesis. Overall, the cancer excess per unit dose is less than in the atomic bomb survivors. Dose-response relationships are complicated by incomplete dosimetry; there are wide variations among different organs and tissues and within any given organ, and are limited by the absence of dose data for individual patients.

Medical Radiation Surveys:. It is primarily from the wide array of epidemiological evidence from medical radiation exposure that support the use of the linear and linear-quadratic extrapolation models of dose-incidence relationships at low doses (2). The evidence includes an excess of childhood leukemia at doses of 10 to 50 mGy after *in utero* exposure; an excess of thyroid tumors at doses of 60 to 80 mGy after childhood exposure for tinea capitis; an excess of breast cancer in women exposed to multiple fluoroscopic chest examinations or to treatment for benign breast conditions. Since the publication of the 1980 BEIR III Report (8), additional cohort studies have provided data that are consistent with the findings of the atomic-bomb survivors. Individually, no one study provides sufficient information to define the dose-incidence relationships at low doses,

but collectively the data from these studies are consistent with a linear nonthreshold function at low doses for each of the carcinogenic effects.

The largest of these studies is the multi-institutional survey of women treated for carcinoma of the cervix, in whom leukemia and cancers of the urinary bladder, breast, kidney, stomach and rectum have occurred in excess (9). This retrospective-prospective study is especially noteworthy; it involves 83,000 women, ages less than 30 to greater than 70 years, an average follow-up of 7.6 years, with 623,800 person-years at risk. The control groups involve national rates and internal controls. The radiation was chronic, fractionated and partial-body exposure to low-LET gamma and X-rays, and the doses were high and extremely uneven throughout the abdomen and pelvis, approaching 60 Gy to the affected tissues. Currently, the dosimetry is sparse, and represented by the mean dose of a sample population.

Other cohort studies of importance involve children treated for leukemia in whom an excess of brain and other tumors has been observed (10,11); patients treated for Hodgkin's disease in whom cancers of bone and soft tissues, skin, oropharynx, nervous system, respiratory system and digestive tract has been observed in excess (10); patients treated for ovarian cancer in whom uterine, colon, bladder, and hematologic cancers have been observed in excess (12); patients treated with radium-224 for tuberculosis and ankylosing spondylitis in whom an excess of bone cancers has been observed (13); and patients treated for tinea capitis in whom thyroid tumors and intracrainial cancers have been observed in excess (14). Although the number of cancers in these study populations are relatively small and the relevant radiation doses too uncertain, and thus not adequate to define the shape of the dose-incidence relationship in the low-dose region, the data from each of these studies are consistent with existing quantitative dose-incidence information derived from the Japanese experience. The last two studies are noteworthy in that the radium-224 patients were exposed to high-LET alpha-emitting bone-seeking radionuclides, and the excess thyroid cancer appeared in the tinea capitis cohorts who were exposed to quite small average estimated doses to the thyroid gland. Recent studies extend the observations of childhood cancers observed following *in utero* irradiation; in Connecticut, a study of twins irradiated *in utero* (estimated median dose of 10 mGy) demonstrated relative risk of 1.6 for leukemia and 3.2 for all childhood cancers, consistent with the study in Great Britain, and the expanded multi-institutional New England survey (2,3).

Occupational Exposure. The studies of underground miners in the United States, Canada, Sweden, and Czechoslovakia, who developed lung cancer after exposure to high levels of alpha radiation from radon progeny in the mines (1,15,16) are of considerable importance. The risk estimates derived imply that the dose from inhalation of naturally occurring radon in domestic environments may account for up to 10% of all lung cancers. This risk is especially elevated in heavy cigarette smokers, in whom the lung cancer risk is as much as ten times greater than in nonsmokers (1,15).

Factors that Influence Risk

New information from experiments in laboratory animals as well as improved statistical analysis of large epidemological studies has extended our understanding of many of the factors that influence the cancer risk estimation process. Among the most important of these are dose-response relationships, dose rate, age and sex affecting susceptibility to cancer induction, and the temporal distribution of risk.

Dose-Response Relationships. The analysis by the BEIR V Committee and the recent follow-up of the Japanese atomic bomb survivors (5) demonstrate that the dose-effect relationship for cancer mortality other than leukemia shows no significant departure from linearity over the range of doses below 3 Gy. Different neoplasms vary widely in their dose-response relationships, and not all neoplasms are induced by irradiation. The dose-response relationship for leukemia, excluding chronic lymphocytic leukemia, is best described by a linear-quadratic relationship. For certain solid cancers, such as breast and thyroid, the data conform to linearity, while for other organs, e.g., colon, the data are more consistent with a linear-quadratic or quadratic functions.

basis remains for estimating the carcinogenic risk of neutron radiation in exposed human populations.

Two *risk projection models* currently used to project an estimate of the overall cancer risk for an exposed population---the *additive* and *multiplicative* models---were examined by the UNSCEAR Committee (3) and the BEIR V Committee (2). Both models are flawed, but since the lifetime cancer experience for low-dose radiation is not yet available for any of the large epidemiological studies, such models suitably modified are necessary. The additive risk projection model assumes that the excess cancer risk is independent of the natural incidence, and that radiation will induce a dose-dependant excess number above the baseline level. The multiplicative model assumes the excess cancer risk is related to the natural incidence, and that radiation will induce a dose-dependent excess percentage above the baseline incidence. The UNSCEAR Committee applied both risk projection models; the BEIR V Committee rejected the additive model, and developed modified multiplicative models. Shimizu et al. (5) have estimated that the cumulative radiation-associated excess of cancer deaths in the Japanese survivors has risen from about 135 in 1975 to about 260 in 1985 for the DS86 cohort. The excess has also increased with attained age, but the excess relative risk has remained reasonably constant. Overall, the excess cancer mortality experience appears much more closely related to the multiplicative model than the additive model, although the reliability of either model for cancer of a specific type or site, or for those persons exposed at a younger age, continues to remain uncertain.

The limited data available to examine the *dose-response relationships* at low doses of low-LET radiation has made it necessary to interpolate from high dose data. The Japanese leukemia data still conform to the nonthreshold linear-quadratic model, whereas for cancer deaths other than leukemia, the data support a nonthreshold linear model in the exposure range below 3 Gy (5). The excess mortality from cancer of various sites has been estimated to be: for leukemia, a relative risk of 6.21 at 1 Gy (organ-absorbed dose), and an absolute risk of 2.94 excess leukemia deaths per 10,000 PYGy; and for all cancers except leukemia, a relative risk of 1.41 at 1 Gy, and an absolute risk of 10.13 excess cancer deaths per 10,000 PYGy (Table 1). Only for leukemia, esophagus,

stomach, large intestine, lung, female breast, ovary, urinary tract, and multiple myeloma were there sufficient data to permit numerical risk estimates to be calculated. Except for the special circumstances of the carcinogenic effects of internally-deposited alpha emitters (1) and for certain selected studies of the thyroid and breast, it has been the mortality experience of the Japanese atomic bomb survivors that was selected in both the 1988 UNSCEAR Report (3) and the 1990 BEIR V Report (2) as the most appropriate basis for projecting risk estimates of carcinogenic effects for the general population.

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Cancer mortality of several of the heavily irradiated tissues has increased significantly between the 5th and 25th year following irradiation, after which time the excess decreased for certain sites, such as the lung and stomach (Table 2). Whatever the pattern of temporal distribution of excess cancers, it appears that susceptibility to a specific radiation-associated cancer demonstrates no consistent relationship to the spontaneous incidence of the cancer in the general population. This suggests unexplained and complex organ-, tissue-, and cell- dependant differences in susceptibility to radiation carcinogenesis. Overall, the cancer excess per unit dose is less than in the atomic bomb survivors. Dose-response relationships are complicated by the incomplete dosimetry; there are wide variations among different organs and tissues and within any given organ, and are limited by the absence of dose data for individual patients.

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The largest of these studies is the multi-institutional survey of women treated for carcinoma of the cervix, in whom leukemia and cancers of the urinary bladder, breast, kidney, stomach and rectum have occurred in excess (9). This retrospective-prospective study is especially noteworthy; it involves 83,000 women, less than 30 to greater than 70 years of age, an average follow-up of 7.6 years, with 623,800 person-years at risk. The control groups involve national rates and internal controls. The radiation was chronic, fractionated and partial-body exposure to low-LET gamma and X-rays, and the doses were high and with extremely uneven distribution throughout the abdomen and pelvis, approaching 60 Gy to the affected tissues. Currently, the dosimetry is sparse, and represented by the mean dose of a sample population.

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intracranial cancers have been observed in excess (14). Although the number of cancers in these study populations are relatively small and the relevant radiation doses too uncertain, and thus not adequate to define the shape of the dose-incidence relationship in the low-dose region, the data from each of these studies are consistent with existing quantitative dose-incidence information derived from the Japanese experience. The last two studies are noteworthy in that the radium-224 patients were exposed to high-LET alpha-emitting bone-seeking radionuclides, and the excess thyroid cancer appeared in the *tinea capitis* cohorts who were exposed to quite small average estimated doses to the thyroid gland. Recent studies extend the observations of childhood cancers observed following *in utero* irradiation; in Connecticut, U.S.A., a study (15) of twins irradiated *in utero* (estimated median dose of 10 mGy) demonstrated a relative risk of 1.6 for leukemia and 3.2 for all childhood cancers, consistent with the study in Great Britain (16), and the expanded multi-institutional New England survey (17).

Occupational Exposure. The studies of underground miners in the United States, Canada, Sweden, and Czechoslovakia, who developed lung cancer after exposure to high levels of alpha radiation from radon progeny in the mines (1,2,18,19) are of considerable importance. The risk estimates derived imply that the dose from inhalation of naturally occurring radon in domestic environments may account for up to 10% of all lung cancers. This risk is especially elevated in heavy cigarette smokers, in whom the lung cancer risk is as much as ten times greater than in nonsmokers (1,2,18).

Factors that Influence Risk

New information from experiments in laboratory animals as well as improved statistical analysis of large epidemological studies has extended our understanding of many of the factors that influence the cancer risk estimation process. Among the most important of these are dose-response relationships, dose rate, age and sex affecting susceptibility to cancer induction, and the temporal distribution of risk.

Some Final Comments

Let us turn now to three important questions that faced the BEIR V Committee in its deliberations. First, what dose response models should be used, and what are the characteristics of the parameters? Second, how do the application of these models take into consideration dose rate effectiveness factors for low dose-rate exposures? Third, what changes occur in the cancer risk estimates compared with a decade previously, and do these changes, if any, warrant a revision of the risk estimates of the carcinogenic effects of low-dose ionizing radiations?

The BEIR V Committee chose a number of preferred risk models, appropriate for each site, with dose-response relationships derived for leukemia and all other cancers from seven different cohort data sets used for fitting for different cancer sites. For all cancers, including leukemia, the Japanese atomic-bomb survivor data contributed most to the estimation process, whereas the remaining epidemiological studies provided additional information primarily for leukemia, breast and thyroid. The preferred model for leukemia is a relative risk model with both dose and dose squared terms as well as age at exposure and time since exposure and interaction effects. The preferred model for the Life Span Study data is a relative risk model with a decreasing effect of time since exposure and a declining effect of attained age. A minimum latency of 5 years is assumed. For cancers other than leukemia, the preferred models are relative risk models with a linear dose-response, and age at exposure and time since exposure and interaction effects. In fitting these data, a 10 year latency is assumed. As for leukemia, the effects of time since exposure and of attained age both significantly improved the fit; the relative risk models were more parsimonious or required weaker modifiers.

Since the risk models were derived primarily from data on acute or single high dose-rate exposures, the application of these models to continuous low dose-rate exposures requires consideration of a dose rate effectiveness factor (DREF). The BEIR V Committee (2) believed that some account should be taken of dose rate effects and suggests a range of DREFs that may be applicable. Such reductions are applied only to the nonleukemia risks, as the leukemia risks already contain an implicit DREF of about 2 owing to the use of the linear-quadratic model. For this reason, the tables of risk estimates in the BEIR V Report (2) record excess risks for leukemia and for all other cancers separately. The 1980 BEIR III Committee (8) chose a DREF of 2.25 from the leukemia data and applied it to the nonleukemia data as a fixed constant. The BEIR V Committee (2) concluded that is could not justify assuming the same dose-response model for all cancer sites, and used separate dose-response models, with no DREF. However, both the 1988 UNSCEAR Committee and the 1989 BEIR V Committee have suggested that the use of a DREF at the lower end if a 2 to 10 range, a DREF if 2 or more, applied to human radiation carcinogenesis, would be reasonable.

The BEIR V Committee (2) estimated lifetime risks for leukemia and for all other cancers resulting from two continuous exposure situations, lifetime and ages 18 to 65 years, and a population-weighted instantaneous exposure to all persons of all ages (Table 10). The results obtained using the committee's preferred modified multiplicative risk models for each site and a life table analysis accounts for all competing risks including those due to radiation-induced cancer. In general, in the BEIR V Committee (2) estimated that if 100,000 persons received an instantaneous exposure of 0.1 Gy of low-LET radiation, about 750 extra cancer deaths would be expected to occur during their remaining lifetimes in addition to nearly 20,000 cancer deaths that will occur even in the absence of the radiation. Accumulation of the same dose over weeks, months or years, however, is expected to reduce the risk appreciably, possibly by a factor of 2 or more. If that population were exposed continuously to 10 mGy per year for an entire lifetime, about 5,000 extra cancer deaths would be expected to occur (Table 10).

In the analysis of the follow-up of the atomic bomb survivors, two projection models were examined by the BEIR V Committee. The present data are limited to only 40 years, and those survivors who were irradiated in childhood are yet to attain the age when cancer become prevalent in the general population. It is still not known how the cancer mortality this younger age group will experience in the future will compare with that observed in the populations irradiated at older ages.

The most recent data suggest that for all cancers other than leukemia, the excess relative risk varies with age for a given age at exposure than does the absolute risk, indicating the data are more consistent with a multiplicative risk projection model. Because of incomplete follow-up, the projected lifetime risk estimates obtained---either excess absolute or excess relative risks---necessarily differ with time, and the risk projected from the multiplicative model are considerably larger than from the corresponding absolute model. This difference continues to disappear with time as the follow-up of the study populations near completion. Even though the new information has now resulted in higher lifetime risk estimates projected for the general populations, than previously, nevertheless, the risk estimates based on the additive model have increased considerably more than those based on the multiplicative model, and this difference between two projected estimates has decrease in large measure over the past 20 years .

The Committee recognized that the new information and data available since the 1977 ICRP Report (19) resulted in risk estimates that were appreciably higher than previously recorded. Comparison of the risk projections in the 1989 BEIR V Report (2) and the 1980 BEIR III Report (8) indicated, overall, the risk estimates were now consistently larger, by factors of 2 or more, depending on the exposure conditions and the projective risk model---additive or multiplicative---applied (Table 11). There are several reasons for the differences between the two sets of estimates, including the new DS86 atomic-bomb dosimetry applied to the Life Span Study data, the additional years of follow-up, and the changes in the structure of the fitted models. The major differences between the two sets of estimates are for the 1980 BEIR III additive risk models. The 1989 BEIR V Committee concluded that the assumption of a constant additive excess risk is no longer tenable in the light of the data now available, and that the risk estimates from the model provided in the 1980 BEIR III Report were much too low. An evaluation of these risk estimates over the past two decades made by the BEIR and other committees, corrected to be comparable for the excess cumulative lifetime mortality from all cancers attributable to 1 Gy of instantaneous whole-body, low-LET irradiation in 10,000 persons in the general population presents a compelling illustration of these changing events (Table 12) (2). Based on the modified relative risk models for all cancers combined, the current risk estimates are appreciably higher since the BEIR III Report, by factors of about 1.5 to 2.0. Accordingly, the Committee can conclude that the new data, and the methods for their analysis, require a reassessment of the previous risk estimates for the carcinogenic effects of low-dose radiation.

Epilogue

In concluding my remarks today, I wish to emphasize that my review does not speak for either the BEIR IV or BEIR V Committees or the UNSCEAR Committee or any of its individual members. I speak only for myself. I have spoken freely about the labors of others, and have quoted extensively from the remarks and conclusions of my scientific colleagues in the committee room; it is their work we recognize. Mr. President, it has been a great personal honor to be invited to address this assembly of scientists of the 32nd Annual Meeting of the Japan Radiation Research Society, and to describe the experiences of some 5 years of work. I am grateful for this very special privilege, and my wife, Irene, and I thank you, and the scientific and program committees with our deep gratitude, for the opportunity of sharing this remarkable odyssey in science with all of you today.

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