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FACTORS THAT MODIFY RISKS OF RADIATION-INDUCED CANCER

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ABSTRACT

The collective influence of biologic, physical and other factors that modify risks of radiation-induced cancer introduces uncertainties and assumptions that limit precision of estimates of human cancer risk that can be calculated for populations exposed to low-dose radiation. The important biologic characteristics include the tissue sites and cell types, baseline cancer incidence, latent periods, time-to-tumor recognition, and individual host (e.g., age and sex) and competing etiologic influences. Physical factors include radiation dose, dose rate, and radiation quality. Statistical factors include time-response projection models, risk coefficients, and dose-response relationships. Sources that modify risk also include other carcinogens, and other biological factors (e.g., hormonal conditions, immune status, hereditary factors). Discussion includes examples of known influences that modify radiation-associated cancer risks, and how they have been dealt with in the risk-estimation process, including extrapolation to low doses, use of relative risk models, and other uncertainties.

INTRODUCTION

There are numerous limitations constraining precise numerical estimation of excess cancer risk of low-level radiation in exposed human populations. Three factors stand out (National Research Council, 1980; National Research Council, 1990; Upton et al, 1986; Upton, 1988). First is the limited understanding of the mechanisms of cancer induction by radiation, particularly in humans; extrapolation of observed data requires fundamental understanding that is not yet available. Second is the uncertainties of dose-response and time-response data from epidemiologic surveys, particularly at low levels of dose. Third is that experimental and theoretical considerations suggest various and different dose-response and time-response relationships may exist for different radiation-induced cancers in exposed human populations (Upton et al, 1986; UNSCEAR, 1988; National Research Council, 1990). Epidemiologic data on exposed human populations are uncertain in regard to the forms of the dose-response relationships for radiation-induced cancer (National Research Council, 1980; National Research Council, 1990; Boice and Fraumeni, 1984; Upton et al, 1986; Upton, 1988; UNSCEAR, 1988). This is especially the case for low-level, low-LET radiation, where little human data are available at doses below 0.5 Gy. Therefore, it has been necessary to estimate human cancer risk at low radiation doses primarily from observations at relatively high doses, frequently greater than 1 Gy or more (National Research Council, 1980; National Research Council 1990; UNSCEAR, 1988; Shimizu et al, 1988). However, it is not known whether the cancer incidence observed at high dose levels also applies to cancer induction at low dose levels (Pierce and Vaeth, 1989a). Furthermore, cancers induced by radiation are indistinguishable from those occurring naturally; hence, their existence can be inferred only on the basis of a statistical excess above the natural incidence. Since such radiation-associated cancers are so rarely seen after low-dose radiation because the exposures are so small,
the process of estimation of cancer risk at low dose levels may remain a controversial issue that may never be resolved--- it may be beyond the abilities of science and mathematics to decipher.

While there is no precise definition of low-level exposure, radiation scientists might define low-level radiation as that which falls within some defined dose range. In NCRP Report No. 64 (NCRP, 1980), a "low" dose of sparsely ionizing radiation is arbitrarily defined as 0-0.2 Gy; "low" dose rate is defined as less than 0.05 Gy y⁻¹. Others might define "low-dose" radiation to fall within a lower range considered allowable for occupational exposure. According to currently accepted standards, 50 mSv per year to the whole body would be an upper limit of radiation dose for the individual radiation worker (ICRP, 1977). In this context, it could be concluded that most of the estimated cancer cases which may be associated with levels of diagnostic medical radiation exposure, or with a nuclear reactor accident, or even after prolonged periods of occupational exposure among radiation workers, could be caused by exposures below these allowable limits.

DOSE-RESPONSE MODELS AT LOW DOSES

It is not yet possible to make precise low-dose risk estimates for cancer induction by low-LET radiation because the level of risk is so low that it cannot be observed directly in humans (Upton et al, 1986; Upton, 1988). In previous application of the risk estimation process, there was always great uncertainty as to the mathematical form of the dose-response function most appropriate for extrapolating to the low-dose region (National Research Council, 1980; National Institutes of Health, 1985; U.S. General Accounting Office, 1981; Upton, 1988; Pierce and Vaeth, 1989a). In studies of exposed animal and human populations, the shape of the dose-response relationships for cancer induction at low doses has been practically impossible to ascertain statistically (National Research Council, 1980; NCRP, 1980; Upton et al, 1986). Thus, it appeared that experimental evidence and theoretical considerations rather than empirical epidemiologic data was more likely to guide the choice of a dose-response function for radiogenic cancer at individual organ and tissue sites (National Research Council, 1980; U.S. General Accounting Office, 1981; National Institutes of Health, 1985; National Research Council, 1990). The BEIR III Committee (National Research Council, 1980) adopted as a working model for low-LET radiation and carcinogenesis the quadratic (with a linear term) dose-response form and with an exponential term to account for the frequently observed turn-down of the curve in the high-dose region (NCRP, 1980; National Research Council, 1980). However, in applying this multicomponent model, the Committee recognized that only certain of its derivatives, including the linear, the linear-quadratic (i.e., the quadratic with linear term), and the pure quadratic dose-response functions could prove practical for purposes of estimation of cancer risk (National Research Council, 1980; Boice and Fraumeni, 1984; National Institutes of Health, 1985; Upton et al, 1986; Upton, 1988).
In large part, the available human data from epidemiologic studies fail to illustrate any one of the
dose-response models either for whole-body radiation or radiogenic cancer at specific sites (National 
Research Council, 1980; UNSCEAR, 1988; National Research Council, 1990; National Institutes of 
Health, 1985), and do not discriminate among models suggested by the experimental and theoretical 
studies. For example, cancer of the skin is not usually observed after low radiation doses (National 
Research Council, 1980; UNSCEAR, 1988; National Research Council, 1990), whereas the thyroid cancer 
dose-response relationship for external irradiation (but not for internal irradiation by iodine-131) seems to 
the revised Japanese atomic-bomb dosimetry system DS86, the leukemia dose-response relationship 
appears to have the positive curvature of the linear-quadratic model (Shimizu et al, 1988; UNSCEAR, 1988; 
National Research Council, 1990). The incidence of breast cancer induced by radiation derived from a 
number of different studies seems to be described by a linear dose-response model but recent Canadian data 
are not in accord with these observations (National Research Council, 1980; National Research Council, 
1990; UNSCEAR, 1988). Overall it was concluded by the BEIR III Committee (National Research 
Council, 1980) that some experimental and human data, as well as theoretical considerations, suggested that 
for exposure to low-LET radiation at low doses, the linear relationship may lead to an overestimate of the 
risk of most radiation-induced cancers in humans, but that the model could be used to define the upper 
limits of risk. The lower limits could not be ascertained, but it was suggested that the pure quadratic 
relationship could be used to define the lower limits of risk from low-dose, low-LET radiation. However, 
the analysis of the epidemiologic data did not exclude zero risk at low levels of dose (National Research 
Council, 1972; National Research Council, 1980; National Research Council, 1990). The bounding range, 
however, could be spread by an order of magnitude, and particularly so when interpolating in the low-dose 
region from high-dose data. Overall, the BEIR V Committee (National Research Council, 1990) found that 
the quantitative relationship between cancer incidence and dose in the A-bomb survivors, as in other 
irradiated populations, appears to vary, depending on the type of cancer in question, the time since 
exposure, and age at exposure. The BEIR V Committee (National Research Council, 1990) concluded that 
dose-dependent excess of mortality for all cancer other than leukemia, showed no departure from linearity in 
the dose range below 4 Sv, whereas the mortality data from leukemia were compatible with a linear-
quadratic dose-response relationship.

The estimation process is, nevertheless, neither simple, nor direct. Dose-response models do not 
adequately describe phenomena as complex as cancer induction; accordingly, they no longer obtain, since 
the responses must be considered over time during and since exposure. Accordingly, what has emerged is 
an integrated process for purposes of risk estimation where the epidemiologic data are summarized for each 
tissue and organ of interest in the form of exposure-time-response models for relative risk or absolute risk, 
as was carried out by the BEIR V Committee (National Research Council, 1990). This has become
necessary to extrapolate from high dose and high dose rate data to low doses and low dose rates, to project risk in time, and to use simplifying conventions for practical applications.

**BIOLOGIC AND PHYSICAL FACTORS THAT MODIFY RISK**

The estimation of the carcinogenic risk of low-dose, low-LET radiation involves a large number of well-identified uncertainties and approximations; perhaps greatest are the shapes of the dose-response relationships, or the exposure-time-response models, particularly in the low-dose region and beyond the period of observation (National Research Council, 1980; National Institutes of Health, 1985; National Research Council, 1984). Others include the quality of the data and sampling variation, the length of the latent period for the appearance of cancer and time-to-tumor recognition, precise radiation doses and dose rates, the effect of dose rate or dose fractionation, the RBE for alpha and neutron radiation relative to gamma and x-radiation, the period during which the excess carcinogenic risk is expressed or the expression of the excess cancer deaths with time after exposure, the dose and time response models used in projecting risk beyond the period of observation, the sites and cell types of cancer, the influence of differences in the natural incidence of specific types of cancer, extrapolation to other populations, and the interaction and effects of individual or collective host factors, competing etiologic influences and other carcinogens, such as smoking and lung cancer (National Research Council, 1980; National Research Council, 1990; National Institutes of Health, 1985; Pierce and Vaeth, 1989a). Uncertainties are introduced by biologic characteristics that modify risk, e.g., the effect of age at irradiation, sex, the influence of any disease for which the radiation may have been given therapeutically, and the influence of length of observation or follow-up of the study populations. In the largest surveys of medically-exposed patients, viz., the ankylosing spondylitis and the uterine cancer patients, there is no evidence to increasing susceptibility to overall cancer induction, and the carcinogenic risk appears to be less than that predicted from the Japanese data (Boice et al, 1988). Moreover, a most important finding from the ankylosing spondylitis survey data is that for all cancers as a group the excess lifetime cancer risk has decreased with time some 30 years after exposure; this has also occurred for lung cancer in the underground miner surveys (Darby et al, 1987; National Research Council, 1988; UNSCEAR, 1988; National Research Council, 1990). In the most recent analysis of the Japanese atomic-bomb survivor data, for all cancers except leukemia as a group, and for major specific sites, the absolute excess lifetime risk has continued to increase until the current time (Pierce and Vaeth, 1989a; UNSCEAR, 1988; National Research Council, 1990; Shimizu et al, 1988). The collective influence of these modifying factors introduces uncertainties and approximations sufficient to limit precision of estimates of human cancer risk that can be calculated for low-dose, low-LET radiation (National Research Council, 1984; National Institutes of Health, 1985; National Research Council, 1990).
The task of estimating risk estimates of cancer induction in human populations exposed to low-level radiation is also limited by technical difficulties (National Research Council, 1984). The data on radiation and cancer are too sparse by themselves to support the methods and procedures of analysis, and therefore assumptions must be made in carrying out the calculations (National Institutes of Health, 1985). Among these are: what methods to use to analyze the available data on cancer in human populations exposed to radiation; which sources of information to use on baseline cancer rates and radiation-related excess cancer incidence; how to use scientific data on radiation and cancer obtained in laboratory experiments with animals and cell cultures; how to interpolate data obtained from high doses to low doses of radiation; how to determine the influence of age at exposure to radiation and time from exposure to diagnosis of the cancer; and how to treat risk factors for cancer other than radiation (National Research Council, 1984).

Given these uncertainties, approximations and technical difficulties, the specific estimates of risk coefficients in a defined population exposed to radiation can be substantially uncertain, even when the characteristics of the cancer population and the radiation exposures are well known. Furthermore, each element of the methods or procedures for calculation has its own uncertainties that modify the risk estimates, some of which are interdependent. Complex models that can be constructed to integrate most of these modifying factors into an overall assessment or quantitative estimation of risk must necessarily influence the accuracy that can be ascribed to any value that can be calculated and necessarily introduce simplifying conventions (National Research Council, 1990; Pierce and Vaeth, 1989a; Pierce and Vaeth, 1989b). This further underscores the influence of the myriad factors that modify risk, the technical difficulties of the process of estimation, and the uncertainties of the numerical values derived (National Research Council, 1984; National Institutes of Health, 1985; National Research Council, 1990; Pierce and Vaeth, 1989a; Pierce and Vaeth, 1989b).

**BIOLOGIC FACTORS**

**TISSUE SITES AND CELL TYPES**

Carcinogenic effects of radiation on the bone marrow, breast, thyroid gland, lung, stomach, colon, ovary and other organs reported for the Japanese atomic bomb survivors (Shimizu et al, 1988) are similar to findings reported for other irradiated human populations (UNSCEAR, 1988; National Research Council, 1990). Although radiation has been shown to produce a very wide array of human cancers, for certain cell types, e.g., chronic lymphocytic leukemia, radiation seems not to be detectably carcinogenic. For many tissue sites and cell types, e.g., prostate cancer and multiple myeloma, the evidence is inconclusive. Any published lists of human cancers considered to be radiogenic (National Institutes of Health, 1985; National Research Council, 1984; UNSCEAR, 1988; National Research Council, 1990) are invariably based on
judgment as to the sufficiency of the human data available and the cogency of the medical, and particularly epidemiologic, evidence involving radiation as a cause. Nevertheless, even if the evidence is suggestive of radiation carcinogenesis in different tissues, reliable estimates of cancer risk coefficients are still necessary for each cell type observed (Pochin, 1984). At the present time, there are limited data only on the leukemias and certain of their cell types; for solid cancers, the data are lacking. Analysis of tissue specimens indicates that in several instances, the cell type distribution of solid cancers in exposed human populations follows that of the control population, with only minor exceptions; e.g., lung cancer cell types in the Japanese A-bomb survivors in Hiroshima appear to be very similar in the irradiated and control populations, and the evidence currently does not support earlier conclusions that small cell and squamous cell cancers were much more radiogenic. It is nevertheless possible that as more data become available, differential risk coefficients for certain cell types among solid tumors, as in the case of leukemias, can be established (Pochin, 1984).

BASELINE CANCER INCIDENCE

Reliable estimates of cancer incidence in any given population at a given time may be difficult to find. In Great Britain, Canada, Japan, Denmark and Sweden, for example, comprehensive cancer registries have been established providing reliable national and regional cancer mortality statistics. This has made possible extensive national surveys of cancer mortality in large numbers of radiation workers in Great Britain, e.g., employees of the U.K. Atomic Energy Authority, British Nuclear Fuels Limited, and Atomic Warfare Research Establishment, and participants in atomic-bomb tests (UNSCER, 1988; National Research Council, 1990). In the United States, on the other hand, only one national cancer registry, the SEER Report of the National Cancer Institute (Young et al, 1981), is perhaps considered most reliable for the American experience but it only records age- and sex-specific cancer incidence rates for the United States as average for a narrowly-defined period, from 1973 to 1977, and only for ten geographic regions, representing about ten percent of the United States population. The data are not homogenous; geographic and ethnic variations are very real, especially for certain anatomic sites, such as lung and breast (Young et al, 1981). Furthermore, even over the time interval recorded and to the present, there have been important time trends and changes in the incidence of cancer for certain sites, especially carcinomas of stomach and lung. Incidence and mortality for stomach cancer have been moving down steadily for some time, by a factor of two in less than two decades. Conversely, death rates from lung cancer in males increased rapidly over this same period, again by a factor of two, and somewhat more in females due primarily to the influence of cigarette smoking (Silverberg and Lubera, 1986).

In addition, throughout the United States, a considerable amount of geographic variability for some cancers sites may be noted. The incidence of lung cancer may vary by as much as a factor of three between regions with the lowest and highest rates. For example, Hawaii has a very diverse ethnic mix, and the
relatively high incidences of thyroid and stomach cancers and the low incidence of breast cancer may result from that fact, based on ethnicity-specific rates. The relatively low incidence in Utah for cancers of the lung, bronchus, esophagus, and colon may result from the differences in life style of the Mormon population of that state, for example, with a high proportion of nonsmokers and nonalcohol drinkers (National Research Council, 1984; National Research Council, 1985).

MINIMUM LATENT PERIOD

The time-to-tumor-recognition, or latent period, is usually estimated by the time interval from radiation exposure to date of diagnosis (Land and Tokunaga, 1984). This interval may be subject to uncertainty, in that the diagnosis may be delayed beyond the time when it might have been made (National Institutes of Health, 1985). Where adequate medical surveillance is available, it might be unusual if the delay were more than a year or two, except perhaps in the case of thyroid cancer. Most cancer rates do not change rapidly over such short age intervals (Young et al, 1981; Silverberg and Lubera, 1986). At the present time, assumptions must be made for minimal latent periods following brief, single exposures, and can be only estimated for leukemias and very roughly for solid tumors (National Institutes of Health, 1985; National Research Council, 1980; National Research Council, 1990; Shimizu et al, 1988). This is confounded when the radiation exposure is chronic, extending over long periods. A minimal latent period of 2-5 years is given for leukemia (National Research Council, 1980; National Research Council, 1990; National Institutes of Health, 1985; Land and Tokunaga, 1984) and appears reasonably well established from epidemiologic studies. A value of 10 years given in recent reports as the minimal latent interval for solid cancers, however, is very approximate, and it is not site-specific (National Research Council, 1980; National Research Council, 1990; National Institutes of Health, 1985; UNSCEAR, 1988; Land and Tokunaga, 1984). For lung cancer in underground miners chronically exposed to radon progeny over years, a lag period of 5 years has been used to estimate radiogenic risks (National Research Council, 1988). The evidence is that the latent interval varies greatly with organ and tissue site, and with age at exposure, being longer for younger than for older individuals. For younger individuals, the uncertainties can be appreciable (Shimizu et al, 1988; National Research Council, 1980; National Research Council, 1990; Land and Tokunaga, 1984).

AGE AT EXPOSURE

There are relatively few human data sufficient to allow estimation of carcinogenic risk below the age of 10 years, and in some cases, below the age of 20 years, except, perhaps, for thyroid cancer (National Research Council, 1990; UNSCEAR, 1988; Shimizu et al, 1988). The accuracy of a risk estimate is limited by the number of excess cancer cases among persons whose radiation doses are known
and were at least 0.1 Gy. Even when that number is large, the estimate is subject to considerable uncertainty; when the number of cases is small, the uncertainty may be so large that the risk estimate becomes spurious (National Institutes of Health, 1985; Boice and Fraumeni, 1984; National Research Council, 1980; U.S. General Accounting Office, 1981). For example, the most reliable data available for the digestive organs currently are those of the Japanese atomic-bomb survivors. Until only recently, for the 0-9 year age group at the time of exposure there has been barely sufficient data to support an estimate of risk for the digestive tract as a whole; and little adequate data were available for the pancreas and the liver (Shimizu et al, 1988; National Research Council, 1990; UNSCEAR, 1988). For ages 10-19 years at the time of exposure, there was some limited data to support risk estimates for stomach cancer, but only barely so, and not for any other digestive organs (Shimizu et al, 1988; National Research Council, 1990; UNSCEAR, 1988). It has been necessary to wait for additional data, with more than ten or more additional years of follow-up of the Japanese atomic-bomb survivors, together with the new atomic-bomb dosimetry (Jablon, 1984; National Research Council, 1985a; Roesch, 1987), compiled and analyzed at RERF (Preston and Pierce, 1987; Shimizu et al, 1987; Shimizu et al, 1988) for inclusion in the 1988 UNSCEAR (UNSCEAR, 1988) and 1990 BEIR V Reports (National Research Council, 1990); currently, certain of the cancer risk estimates for young persons, and knowledge of latent periods applicable to them, are somewhat improved.

SEX

Sex differences in the absolute risk of radiation-associated cancer are apparently small, except for breast cancer, thyroid cancer, and leukemia (UNSCEAR, 1988; National Research Council, 1990). However, when risk coefficients for these sites are used to derive relative risk factors by sex, such factors differ considerably between the sexes, most notably for lung cancer, and perhaps for certain gastrointestinal and urinary organs (National Research Council, 1990).

PHYSICAL FACTORS

RADIATION DOSE

No single factor modifies the calculation of cancer risk estimates as does the radiation dose absorbed in the cells and tissues of the body (UNSCEAR, 1977; ICRP, 1977; UNSCEAR, 1988; National Research Council, 1972; National Research Council, 1980; National Research Council, 1990; Shimizu et al, 1988; U.S. General Accounting Office, 1981; Pierce and Vaeth, 1989b). Therefore, the precision of the radiation dose is of considerable importance in the calculation of radiation-associated cancer risk estimates. For example, for low-LET radiation, the organ dose can usually be estimated within a factor of perhaps two.
in workers who wear film badges or integrating dosimeters or who work in monitored areas; however, the absorbed radiation dose estimate is considerably more uncertain for any unbadged individuals whose dose estimates depend on an environmental readings that may not be in the immediate vicinity, and are subject to environmental and body shielding, and thus vary over time (National Institutes of Health, 1985).

The exposures from internally-emitting radioisotopes absorbed within the body, such as iodine, radon daughters, radium and thorium, and are characterized by uncertainties as to level of dose, and by the lack of precise data on their temporal and morphological distribution and their relative biological effectiveness (National Research Council, 1980; National Research Council, 1988; National Research Council, 1990). When the absorbed radioisotope is long-lived and can be measured in an individual and in specific organs, dose estimation may be more reliable. On the other hand, the determination of iodine-131 dose to the thyroid gland well after the exposure, e.g., from weapons tests or nuclear reactor accidents, is difficult, and the indirectness of the exposure through the food chain and the physiologic variables affecting the uptake of the radioisotope by the gland can lead to unreliable dose estimates (National Research Council, 1985).

The absorbed dose in a specific tissue, generally an average over the organ in the case of external radiation, is the quantity used for risk estimation. These dose estimates, in turn, are based on reports on the effects of therapeutic and diagnostic irradiation that generally state dose-specific risk estimates in terms of the tissue dose (National Research Council, 1980; National Research Council, 1990; Lewis et al, 1988); on reports on the atomic-bomb survivors whose external (kerma) doses can be converted to tissue doses (Kerr, 1982; Roesch, 1987); and on reports on those occupationally exposed, such as underground miners or radium dial painters, whose exposure characteristics are poorly understood (NCRP, 1984; ICRP, 1987; National Research Council, 1988). The relevant dose to a specific organ will however, in many cases be difficult to estimate, and frequently complex dosimetric models must be developed (ICRP, 1987; National Research Council, 1984; National Research Council, 1988).

In the case of partial-body exposure, or whole-body exposure to highly directional radiation fields, calculation of a mean organ dose may be very uncertain. For partial-body irradiation, the dose to an organ may be markedly nonuniform and this is especially true for the active bone marrow which is widely distributed within the body (Lewis et al, 1988; Darby, 1987; Smith and Doll, 1982). If the dose-response function were truly linear, it would be appropriate to estimate the average dose over the entire organ and, for small doses--of the order of 0.1 Gy or less--linearity can be assumed. If, however, the maximum and minimum doses to the various parts of the organ are very different, as in the case of complex distributions of ingested or inhaled radioisotopes, errors in dose estimates can result, in either direction (National Institutes of Health, 1985; National Research Council, 1988).
The quality of the dosimetry on which risk coefficients are based is perhaps best in studies from therapeutic irradiation (Boice and Fraumeni, 1984; Upton et al, 1986; Upton, 1987; Darby et al, 1987; Lewis et al, 1988; Ron and Modan, 1980). Treatment plans are usually carefully made and recorded to permit the calculation of doses to tissues and organs within and outside the primary radiation field. The dose estimates for diagnostic irradiation are more uncertain and can be difficult to reconstruct with precision, e.g., in the case of fluoroscopy for monitoring artificial pneumothorax therapy for tuberculosis, or prenatal irradiation in obstetrical pelvimetry (National Research Council, 1980; National Research Council, 1990; UNSCEAR, 1988). In the latter situation, radiation quality could be an important factor; in the United Kingdom, for example, pelvimetry was probably carried out using about 100 kVp X rays, and this could be associated with an increased risk of leukemia in the fetus, conditions unlike those existing in the Japanese atomic bomb survivors. Average dose values may be fairly accurate, but individual doses are often highly variable (Lewis et al, 1985; National Institutes of Health, 1985; National Research Council, 1990; Roesch, 1987).

Because the dosimetry for the atomic-bomb survivors has now been substantially revised (Roesch, 1987), the previously-calculated age- and sex-specific risk estimates which depended on their exposure experience were considered uncertain (National Research Council, 1980) and have been recalculated (Shimizu et al, 1987; Shimizu et al, 1988; National Research Council, 1990). Various reports have predicted the extent to which the this revision of dose estimates would change the current cancer risk coefficients, and it appears that certain of the low-LET absolute risk coefficients are increased, probably overall by no more than a factor of 1.5 to 2.0, depending on age, tissue site, shielded kerma and organ-absorbed dose, and a number of other well identified factors (Preston and Pierce, 1987; Shimizu et al, 1987; Shimizu et al, 1988; UNSCEAR, 1988; National Research Council, 1990). The cancers for which the coefficients depend mainly on the Japanese atomic-bomb data are primarily leukemia, esophagus, stomach, colon, lung, breast, bladder, and kidney (Shimizu et al, 1988; UNSCEAR, 1988; National Research Council, 1990). Sites for which the risk coefficients are relatively independent of the atomic-bomb data are bone, salivary gland, liver, pancreas, brain, thyroid and skin. Charles et al (Charles et al, 1983) reviewed the 1977 UNSCEAR Report (UNSCEAR, 1977) to estimate the overall risk of radiogenic cancer based on all sources of human data except the experience of the atomic-bomb survivors. Their cancer estimates also differed from the UNSCEAR (UNSCEAR, 1977) risk estimates, perhaps higher by a factor of about two; the DS86 dose revision and the extended period of follow-up has now brought the Japanese data into substantially better agreement.

The dosimetry for the British ankylosing spondylitis series (Darby et al, 1987; Lewis et al, 1988), a major source of epidemiologic data for the calculation of cancer risk coefficients, is now being reconstructed, and organ and tissue doses are being estimated from the radiotherapy records of a selected
patient subpopulation (Lewis et al, 1988). The modified Monte Carlo method provides estimates that are
average doses over the entire organ derived from the selected records, rather than individual doses in
specific individuals; here again, average values might be accurate, but individual doses, the estimates of
importance, can be highly variable. A difficult dose-reconstruction has been that for the thyroid gland of
children with tinea capitis treated with X-rays in Israel (Ron and Modan, 1980; UNSCEAR, 1988;
National Research Council, 1990). The excess thyroid cancer observed after an average tissue dose of
about 90 mGy has important implications for the shape of the dose-response curve.

DOSE RATE

The linear-quadratic model that has been used for the cancer risk estimates with low-LET radiation
for all cancers other than breast and perhaps thyroid cancer is based on acute (i.e., fairly high dose rate)
exposures to radiation (National Research Council, 1980; UNSCEAR, 1986; NCRP, 1980). At low doses
and low dose rates, the quadratic term becomes less important, and at very low doses and dose rates it is
assumed that the dose-response function is reduced to the linear term only (National Research Council,
1980; NCRP, 1980; UNSCEAR, 1986). The exact dose rate below which the quadratic term can be
ignored is not precisely determined (National Research Council, 1980; NCRP, 1980; UNSCEAR, 1986),
but experimental studies indicate that it might be quite low (NCRP, 1980). The human data are sparse; for
thyroid and female breast cancer, the available data suggest a linear dose-response model which implies that
there should be no influence of dose rate. The recent Canadian data on breast cancer may not be in
agreement with this. However, there are considerable experimental data to suggest that decreasing the dose
rate, or protraction of dose, of low-LET radiation decreases the carcinogenic and genetic risk per unit dose
possibly by a factor of 2 to 10, depending on the experimental end-point (NCRP, 1980). In view of this,
there should be reason to take into account dose-rate effectiveness factors (DREF) in estimating the risk of
low doses delivered at low dose rates. Although the human data are lacking, no sound approach has
emerged to apply the experimental data derived from dose rate studies in laboratory animals to the estimation
of human cancer risk coefficients.

There is little direct information in the epidemiologic data about low-dose risks, and the best
approach currently appears to be to describe the data in a way which permits combining evidence from them
with information from other sources. Even when a linear dose-response fits the data very well, there will
invariably be dose-response relationships with proportionally much smaller risk at low doses which also fit
the data well (Pierce and Vaeth, 1989a; Pierce and Vaeth, 1989b). Useful inferences about low-dose risks
can be drawn from the epidemiologic data; linear-quadratic models are frequently used for this purpose,
particularly because of the radiobiological evidence for substantially concave dose-response curves (NCRP,
1980). Extrapolation to low doses usually relies on linear risk estimates and factors by which these linear
estimates might be divided in low-dose extrapolation from high dose data. A linear extrapolation overestimation factor (LEOF) has been used applied to the Japanese data, for example, in an attempt to distinguish between acute low doses and dose rates, and provides some guidance for the extent to which linear extrapolation may overestimate low-dose risks (Pierce and Vaeth, 1989a; National Research Council, 1980). In this regard, the LEOF is closely related to the dose-rate effectiveness factor (DREF) (NCRP, 1980). The BEIR III Report (National Research Council, 1980) recommended implicitly an LEOF of about 2.2, derived from comparison of lifetime leukemia risk estimates for linear models and those under the Committee's recommended linear-quadratic model. The NCRP Report No. 64 (NCRP, 1980) considered DREF factors in the range of 2 to 10, based on the extensive experimental data. The 1986 UNSCEAR Report (UNSCEAR, 1986) recommended DREF factors in the range of 1.5 to 3.0. The 1985 Nuclear Regulatory Commission's Report (Evans et al, 1985) used a DREF value of 3.3, derived from the NCRP range (NCRP, 1980). Pierce and Vaeth (Pierce and Vaeth, 1989a; Pierce and Vaeth, 1989b) demonstrated that for the Japanese atomic-bomb survivors, for leukemia and for all cancers, LEOF values greater than about 1.5 are inconsistent with the data. The matter of the dose rate effectiveness factor, or the linear extrapolation overestimation factor taken in the context of linear quadratic models, is far from resolved. The 1988 UNSCEAR Report (UNSCEAR, 1988) remained unclear, suggesting application of DREF factors of 2 to 10; the BEIR V Report (National Research Council, 1990) recommended a factor of 2 or more; and the United Kingdom's NRPB Report (National Radiological Protection Board, 1988) recommended a factor of 3 for all cancers, except for breast, where a factor of 2 is given.

RADIATION QUALITY

There are limitations to our understanding of RBE/LET relationships and their effect on the process of cancer-induction. Epidemiologic studies on human populations are currently inadequate for many alpha-radiation effects; for example, risk estimates for bone cancer induction apply perhaps only to alpha radiation from radium-224 (National Research Council, 1988). Risk estimates are now available for lung cancer following exposure to alpha particles from inhaled radon daughters, but these are based primarily on limited epidemiologic studies of underground miners or dosimetric models in which a number of variables are unknown or can not be verified (NCRP, 1984; ICRP, 1987; National Research Council, 1988). The experience with radium-224 may be used currently as a basis for risk estimation, but it is not yet known how this information may be applied reliably to the long-lived isotopes of radium, the transuranic radionuclides, or uranium (National Research Council, 1988). With the reassessment of the Japanese atomic-bomb dosimetry and the reduction in estimation of neutron dose in Hiroshima, it now appears that no epidemiologic studies are currently available for estimating neutron radiation effects. Data from animal experiments have not been applied systematically to the estimation of cancer risk in humans, but certain of the methods appear promising (National Research Council, 1988; National Research Council, 1990).
X and gamma radiation are not equivalent in terms of RBE; energetic gamma radiation is less effective than 250 kVp or 100 kVp X rays (Fabrikant, 1972). While this difference is relatively small at higher doses and dose rates, it may be important at low doses and dose rates, where exposures to energetic gamma radiation is less damaging than exposure to orthovoltage X rays. This implies that risk estimates derived from radiotherapy studies may differ and insofar as some of the site-specific risk estimates derive in part from the Hiroshima-Nagasaki atomic-bomb experience, these latter risk values may be somewhat less than they would for 250 kVp X rays.

STATISTICAL FACTORS

TIME-RESPONSE PROJECTION MODELS

It has been necessary to provide some useful summary of excess cancer risks, and this is usually done by calculating projections in time of the excess lifetime risks. Risk coefficients are either absolute or additive, i.e., calculated as an excess over and above baseline cancer incidence, or they are relative or multiplicative, i.e., expressed in multiples of the natural incidence. Absolute risks are frequently expressed as excess cancer cases per ten thousand persons per year per gray (excess per $10^4$ PYGy), whereas a relative risk estimate may be some (generally constant) fraction of the baseline incidence corresponding to the effect of a fixed dose, e.g., per gray. When a constant absolute risk is used as a time-response model it suggests that the risk of radiogenic cancer is viewed as independent of the underlying baseline risk. A constant relative risk model for time-response suggests mechanisms by which radiation interacts with other causes to multiply the baseline risk by some constant. The BEIR V Committee (National Research Council, 1990) found neither form of risk projection models to fit the data satisfactorily, and developed a number of modified multiplicative risk model for deriving risk estimates for projection in time of excess lifetime risks of radiogenic cancer.

These models, and the measures they generate, have very different implications for the estimation of excess cancers that occur following exposure to radiation. Under the constant absolute risk model for distributing radiogenic cancers over time, once expression of the cancer excess has been established, the excess per unit of population, dose, and time, is constant. Under the constant relative risk time-response model, the number of excess cases during the period of expression is a fixed multiple of baseline incidence and, therefore, for most solid cancers, increases with age. For the interval of observation from which the risk estimates are generated, both measures yield the same total excess, but the excess will be distributed differently over time. For the period beyond the interval of observation, the predicted excess will frequently be very different for the two measures and greater with the relative risk model, since baseline
rates of cancer generally increase markedly with age (National Research Council, 1980; National Research Council, 1990). The terminology of "constant additive" or "multiplicative" models should probably be avoided, in favor of more specific descriptions (Pierce and Vaeth, 1989a). These terms are often overinterpreted from the perspective of what is supported by the data, as meaning that the radiogenic increase acts multiplicatively with most other risk factors.

In the past, the absolute risk time-response model has been preferred by the ICRP (ICRP, 1977) and UNSCEAR (UNSCEAR, 1977) committees for projecting excess lifetime cancer risks. The 1972 BEIR (National Research Council, 1972) and 1980 BEIR III (National Research Council, 1980) Reports, and the 1988 UNSCEAR Report (UNSCEAR, 1988) used the constant absolute in parallel with the constant relative risk time-response model. The most recent data on the experience of the Japanese atomic-bomb survivors and the underground miners have provided a basis for applying modified relative risk projection models in preference to the absolute risk projection model, and especially for breast cancer and lung cancer (National Research Council, 1988; National Research Council, 1990; Pierce and Vaeth, 1989a). These modified multiplicative models depend strongly on age at exposure and time since exposure (National Research Council, 1988; National Research Council, 1990).

Within the period of observation, generally up to about 35 to 40 years after exposure, the uncertainties introduced by the choice between the two models is not large, but it does increase thereafter (National Research Council, 1980). The constant relative risk model appears superior to the constant absolute risk model; generally the latter simply does not fit the data. But with additional observations, beyond the 35-40-year interval for which data are presently available, e.g. in the Japanese atomic-bomb survivors, the constant relative risk model may fit less well than it does for the earlier period. This has led to modifications of the relative risk model (Preston and Pierce, 1987; Shimizu et al, 1988; National Research Council, 1990) in the analysis of the Japanese atomic-bomb survivor data. By means of statistical regression techniques appropriate for survival-time data, the BEIR IV Report (National Research Council, 1988) and the BEIR V Report (National Research Council, 1990) developed modified multiplicative risk projection models for estimating the excess lifetime lung cancer risks following exposure to radon daughters, and for all tissues exposed to low-LET radiations, respectively. In these models, the excess relative risk varies with time since exposure, rather than remaining constant, and depends on age at risk; the expression, therefore, is a departure from most previous risk projection models, which have assumed that the relative risk is constant over both age and time. In the BEIR IV Committee's modified relative risk model, radon progeny exposures more distant in time have a lesser impact on the age-specific excess relative risk than more recent exposures (National Research Council, 1988). Moreover, the age specific excess relative risk is higher for younger persons and declines at higher ages (National Research Council, 1988). This statistical approaches have been further modified into exposure-time-response models for
relative risk for analysis of the new epidemiologic data and low-LET radiation exposure available over the past decade, and which has been assembled in the BEIR V Report (National Research Council, 1990).

RISK COEFFICIENTS

Although the risk coefficients for cancer mortality may be the most complex element in the estimation of risk, it does not appear that these measures are subject to errors as large as those of most dose estimates for persons exposed to fallout or nuclear weapons tests, for example (National Institutes of Health, 1985). Statistical measures of uncertainty calculated for specific data sets are meaningful when the data are reasonably numerous, as is the case for some organ or tissue sites in the Japanese atomic-bomb survivors. However, such instances are uncommon and sampling variation is only one part of the uncertainty surrounding risk coefficients. In these data, it is only for leukemia, lung cancer, and breast cancer that the 90 percent confidence limits differ from the mean value by a factor less than 2 (National Research Council, 1990). It is only for leukemia, and cancers of the breast, bone, salivary glands, and thyroid, that there appears to be sufficient experience upon which to base risk coefficients for those exposed under age 10 years (National Institutes of Health, 1985; National Research Council, 1990; Shimizu et al, 1988). Most recorded survivors are associated with exposure during adult life, and even the atomic-bomb survivors exposed before age 10 provide limited information on the risk of radiation-induced cancers of the gastrointestinal, urinary, and respiratory organs.

Site-specific risk coefficients for cancer incidence in the BEIR III Report (National Research Council, 1980) are, except for leukemia and bone cancer, linear values. They were not obtained from cancer registries, but were derived as an adjunct to the mortality estimates, and represent the radiation exposures reported in the literature before 1979. In some instances incidence risk estimates were obtained by transforming mortality risk estimates; the technique involved the lifetime expectation of developing and dying of cancer of a specific site.

In the BEIR III Report (National Research Council, 1980) the conversion of the linear-model risk coefficients to coefficients for the linear-quadratic model was accomplished by dividing the linear coefficients by 2.5. The results obtained by this procedure are not identical to those that would have been obtained by reanalyses of the original data using the linear-quadratic model. However, this source of uncertainty is unimportant relative to that involved in the choice of the crossover dose for the linear-quadratic relationship. The statistical uncertainties underlying this conversion were appreciable. The reliability of the crossover value would depend more on its agreement with experimental results obtained over a wide range of biologic systems (NCRP, 1980) than on its statistical stability.
Finally, there is considerable dependence of risk coefficients upon the experience of the Japanese atomic-bomb survivors and their applicability to other populations, for example, that of the United States. In attempting application of methods for extrapolation to other populations, it appears that there is consistency among sources, and in general the absolute risk coefficients obtained from the Japanese experience are very similar to those obtained in the United States and Great Britain except that the variances in the Japanese data are smaller because the experience is larger (Shimizu et al, 1987; Shimizu et al, 1988).

DOSE-RESPONSE RELATIONSHIPS

In general, it has not been possible to show reliably that doses of in the range of 50 milligray or less have any influence on the likelihood of cancer since the excess risk, if any, is lost in the background of the natural cancer incidence. In this regard, the BEIR III Committee (National Research Council, 1980) was unwilling to determine estimates for acute doses below 0.1 Gy or for continuous exposure to less than 10 mGy per year. The BEIR V Committee (National Research Council, 1990) chose to be somewhat less conservative by extending risk projections to the 10 mGy realm.

In the very low dose region useful estimates cannot be made without interpolation between the risk at 0 Gy and the demonstrable and measurable risk at relatively high doses, for example, greater than 0.5 Gy and frequently greater than 1 Gy (National Research Council, 1990; UNSCEAR, 1988). There is no satisfactory theory of radiation carcinogenesis to guide the choice of mathematical function to perform this interpolation; therefore, considerable uncertainty attaches to risk coefficients derived from interpolation in the low-dose range. In the BEIR III Report (National Research Council, 1980) for example, the calculated linear coefficients (i.e., the limiting slopes of the dose-response curves at very low doses) for the risk of leukemia from low-LET radiation were approximately 1 to 2 excess cases per $10^4$ PYGy under the linear-quadratic model, and about 2 under the linear model. In the quadratic model, the linear term vanished entirely. At 20 mGy, the risk of leukemia under these three models was about 2 excess cases per million persons per year for the linear-quadratic, about 4 for the linear, and about 0.05 for the quadratic dose-response. Thus, the excess lifetime leukemia risks projected in time with interpretation no more strongly dependent on the available length of follow-up were spread by a factor of 80 depending on the mathematical model chosen to perform the interpolation.

Animal experiments in which a wide range of doses were employed often show a turn-down in the dose-effect curve at high doses, an observation attributed to cell-inactivation (NCRP, 1980; National Research Council, 1990; Upton et al, 1986; Upton, 1987; Upton, 1988). In analysis of the human epidemiologic data, it has not been possible to employ a model with a term that brings the curve down at
high doses since the concern is with low dose estimation and, since the LD50/60 for acute whole-body doses to humans is in the range of 3.5-4.5 Gy, the turn-down is not as definite in the data on the Japanese atomic-bomb survivors. For partial-body irradiation as in cancer radiotherapy, this aspect of dose-response may have considerable importance when organ doses are very high, as is suggested by the low but definite incidence of second cancers in patients treated with therapeutic doses of radium and X radiation for cervical cancer (Boice and Fraumeni, 1984; Upton et al, 1986; UNSCEAR, 1988; National Research Council, 1990). The problem is much more complex; most human cell lines irradiated in vitro exhibit a $D_0$ of about 1.5 Gy; thus, cell interaction is included in dose-response models in the dose range of 1 to 5 Gy, even when the response appears linear.

OTHER MODIFYING FACTORS

OTHER CARCINOGENS

The prevalence of numerous carcinogenic influences in our environment and life-style suggests that any individual with cancer following exposure to ionizing radiation will also have been exposed to other carcinogens. The only competing risk factor for which there are adequate quantitative data for analysis is cigarette smoking in association with lung cancer (National Research Council, 1990; UNSCEAR, 1988; National Research Council, 1988). Smoking is the strongest known risk factor for lung cancer. The relative risk of lung cancer for heavy smokers versus non-smokers, about 24, is exceeded for very few other risk factors. The literature is unclear as to the nature of the interaction between smoking and ionizing radiation in this case; a recent analysis of the experience of the United States uranium miners suggests a multiplicative relationship, another on Swedish iron miners suggests an additive relationship, and finally, the data on the Japanese atomic-bomb survivors suggest both additive and submultiplicative interactions (UNSCEAR, 1988; National Research Council, 1988; National Research Council, 1990).

For many sites of cancer there are other carcinogenic factors that seem able to increase the risk of cancer by a factor of perhaps two or more, and for all of these it has been assumed that the multiplicative interaction is more appropriate. This assumption, however, is not based, as is the choice of model for smoking, on empirical studies of radiation and other specific carcinogens, but on the fact that, in the few series with relevant observations, the distribution of the radiation-induced excess over time appears to be proportional to baseline incidence (Boice and Fraumeni, 1984; National Research Council, 1988; National Research Council, 1990).

OTHER SOURCES
There are other sources that modify risk of radiogenic cancer for which information is completely lacking or incompletely known: e.g. hormonal status, genetic or other differences in DNA repair capability, and other host factors, particularly immune status and genetic characteristics (National Institutes of Health, 1985; UNSCEAR, 1988; National Research Council, 1990). It is difficult to establish the etiology of an individual cancer, but epidemiologic and toxicologic studies have identified a number of specific carcinogens for humans and any instance of the appearance of a cancer following exposure to ionizing radiation should be reviewed in the context of exposures to other carcinogens that may, in fact, have been responsible for initiating the development of neoplasia.

CONCLUSIONS

Radiation is a known carcinogen that causes cancer in a largely random manner. When a large number of people have received a moderate-to-large amount of radiation, the numbers of cancers of specific tissue and organ sites (e.g., leukemia, breast cancer, and lung cancer) produced by that radiation can be estimated. However, it cannot be predicted which individuals will develop cancer, and after the cancer has developed, whether was caused by radiation; it is usually not possible to differentiate cancers induced by radiation from those which occur spontaneously in the population.

Cancers are associated with a large number of environmental and genetic factors. In any individual case, it is usually not possible to be sure of the cause of the cancer, or the mechanisms of its development. The events that may cause or predispose to cancer interact, but only a few of these interactions are known and none are fully understood. Different individuals are exposed differently to the various carcinogenic factors as the result of cigarette smoking, alcohol consumption, viral infection, life-style, dietary habits, occupation, heredity, and many others. If knowledge were available about the effects of all these exposures and their interactions, it might be possible to classify individuals into a large number of groups among which the causation of a particular cancer by a given agent could be characterized. But, for any carcinogen, including radiation, the number of such groups is limited at present. From available data it is possible to define populations at risk as to categories based only on a few factors, such as age at diagnosis, sex, smoking history and age at exposure to radiation.

Any generalizations regarding radiogenic cancer risks and the elements of the risk estimation process involve a large number of well-identified uncertainties, assumptions, and approximations. Extrapolation of high dose data to low doses and projections in time of excess lifetime cancer risks, the common measure to express ultimate conclusions, has considerable limitations; since everyone must eventually die, excess cancer mortality can occur only by decreasing mortality due to other causes. Nevertheless, consideration of lifetime risks remains an important measure. In addition, simplifying
conventions that are frequently used when making public statements about radiation-associated lifetime cancer risks, e.g., reports of national and international councils and committees, should take into account the important decisions which may be based upon them. This has been especially relevant to statements that are currently being made concerning how the estimated risk estimates have been evolving over time. Inferences might be drawn from incomplete data and their analyses, derived from interpretations beyond the period of observation. Thus such statements may have a greater effect on risk management and decisions regarding safe levels of exposure, that the actual levels of estimated cancer risk; and example of this involves summaries which can be misleading when comparing risk estimates (National Research Council, 1988; National Research Council, 1990; UNSCEAR, 1988). If we wish to understand the mechanisms responsible for the interaction of radiation and human cancer at low dose levels, and develop sound methods of risk estimation and risk management for public policy decision, and apparently we do, then there is no lack of research goals to pursue.

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