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DISCLAIMER

FACTORS THAT MODIFY RISKS OF RADIATION-INDUCED CANCER [1,2]

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ABSTRACT

The collective influence of biologic and physical factors that modify risks of radiation-induced cancer introduces uncertainties sufficient to deny precision of estimates of human cancer risk that can be calculated for low-dose radiation in exposed populations. The important biologic characteristics include the tissue sites and cell types, baseline cancer incidence, minimum latent period, time-to-tumor recognition, and the influence of individual host (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 coeficients, and dose-response relationships. Other modifying factors include other carcinogens, and other biological sources (hormonal status, immune status, hereditary factors).

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 (10). First is the limited understanding of the fundamental mechanisms of cancer induction by radiation, particularly in humans. Second is the uncertainty of dose-response data from epidemiologic surveys, particularly at low levels of dose. Third is that experimental and theoretical considerations suggest various and different dose-response relationships may exist for different radiation-induced cancers in exposed human populations (24). Epidemiologic data on exposed human populations are highly uncertain in regard to the forms of the dose-response relationships for radiation-induced cancer (1, 10, 13, 24). This is especially the case for low-level, low-LET radiation. 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 and more (1, 10, 22). However, it is not known whether the cancer incidence observed at high dose

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 risk, some of which are interdependent. For example, among many are the sites and cell types of cancer, precise radiation doses and dose rates, minimum latent periods, radiation risk coefficients, time to tumor recognition, choice of dose-response function, choice of time-response function, and influence of individual or collective host factors and competing etiologic influences. 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. This further underscores the influence of the factors that modify risk, the technical difficulties of the process, and the uncertainties of the numerical values derived.

BIOLOGIC FACTORS

Among the most important biological characteristics that modify risk are the tissue sites and cell types, the baseline cancer incidence, minimum latent period, time to tumor recognition, and the influence of individual host and competing etiologic influences.

TISSUE SITES AND CELL TYPES

Although ionizing 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, the evidence is inadequate to establish or deny carcinogenicity, and for some, e.g., multiple myeloma, the evidence is inconclusive. Any published lists of human cancers considered to be radiogenic (10, 15, 22) are invariably based on judgment as to the sufficiency of the human data available and the cogency of the 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. 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. 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.

CANCER INCIDENCE

When dealing with a defined population, there is a tendency to restrict risk calculations to established national boundaries. Reliable estimates of cancer incidence in a given population at a given time are difficult to find. In the United States, for example, one national cancer registry, the SEER Report of the National Cancer Institute (26), is perhaps considered most reliable, but it only records age- and sex-specific cancer incidence rates for the United States as average for an nine-year period, from 1973 to 1981, and only for ten 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 (26). Furthermore, even over the nine-year interval recorded, 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 white males have increased rapidly over this same period, again by a factor of two.

In addition, throughout the United States, a considerable amount of 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.

MINIMAL LATENT PERIOD

The time-to-tumor-recognition, or latent interval, is estimated by the interval from radiation exposure to date of diagnosis. This interval may be subject to uncertainty, in that the diagnosis may be delayed beyond the time when it might have been made (8). 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 (26). 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. This is confounded when the radiation exposure is chronic, extending over long periods. A minimal latent period of 2-4 years is given for leukemia and bone cancer (10, 14, 15) and appears 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. In fact, the evidence is that the latent interval varies greatly with age at exposure, being longer for younger than for older individuals. For younger individuals, the uncertainties can be appreciable.

INFLUENCE OF 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. The accuracy of a risk estimate is limited by the number of excess cancer cases among persons whose radiation doses were at least 0.1 Gy. Even when that number is large, the estimate is subject to considerable uncertainty; when the number is small, the uncertainty may be so large that the risk estimate becomes spurious. For example, the most reliable data available for the digestive organs currently are those of the Japanese atomic-bomb survivors. However, for the 0-9 year age group at the time of exposure, there are barely sufficient data to support an estimate of risk for the digestive tract as a whole; no adequate data are available for the pancreas and the liver. For ages 10-19 years at the time of exposure, there may be some limited data to support risk estimates for stomach cancer, but only barely so, and not for any other

digestive organs. It is necessary to wait for additional data, with perhaps ten or more additional years of follow-up of the Japanese atomic-bomb survivors, together with the new atomic-bomb dosimetry, now being compiled and analyzed at RERF (20) for inclusion in the UNSCEAR and BEIR V Reports (14), at which time certain of the cancer risk estimates for young persons, and knowledge of latent periods applicable to them, promise to be much improved.

SEX

Sex differences in the absolute risk of radiation-associated cancer are apparently small, except for breast cancer, thyroid cancer, and leukemia (10, 15,20, 25). However, when these coefficients 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.

PHYSICAL FACTORS

Among the most important physical factors that modify risk are radiation dose, dose rate, and radiation quality.

RADIATION DOSE

No single factor modifies the calculation of cancer risk estimates as that of the radiation dose absorbed in the cells and tissues of the body (10, 13, 15, 16,20, 25). 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.

The exposures from internally-emitting radioisotopes absorbed within the body, such as iodine-131, thorium in thorotrast, radium, and radon daughters, are characterized by uncertainties as to level of dose, and by the lack of precise data on their distribution and their relative biological effectiveness. 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.

The absorbed dose to the specific tissue, generally an average over the target 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, and on reports on the atomic-bomb survivors whose external (kerma) doses can be converted to tissue doses (7, 11, 14). The relevant dose to a specific organ will, however, in many cases be difficult to esimate. For example, attenuation by overlying tissues will in general vary with photon energy.

And furthermore, 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. 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, errors in dose estimates can result, in either direction.

The quality of the dosimetry on which risk coefficients are based is perhaps best in studies from therapeutic irradiation (1, 24, 25). 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. Average values may be fairly accurate, but individual doses are highly variable.

Because the dosimetry for the atomic-bomb survivors has now been substantially revised (12), the previously-calculated age- and sex-specific risk estimates which depended on their exposure experience are now uncertain (2, 4, 6, 10, 15, 18, 20) and are presently being recalculated (14, 20). Various attempts have been made to predict the extent to which the this revision of dose estimates will change the current cancer risk coefficients, and it appears that certain of the low-LET absolute risk coefficients may be increased, but probably by no more than a factor of 1.4 to 1.7 (14, 18, 20), depending on age, tissue site shulded karma organ absorbed dose, and many other factors. 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. 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 (3) reviewed the 1977 UNSCEAR Report (22) to estimate the overall risk of radiogenic cancer based on all sources of human data except the experience of the atomic-bomb survivors. Their estimate also differed from the current risk estimates, being higher by a factor of about two.

The dosimetry for the British ankylosing spondylitis series (4, 11), a major source of 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 (11). 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 (10, 12, 20). A difficult dose-reconstruction has been that for the thyroid gland of children with tinea capitis treated with X-rays in Israel (19).

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. However, movement on the part of the child during treatment might have led to higher doses to the thyroid than those estimated by phantom simulation.

DOSE RATE

The linear-quadratic model that may be 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 (10, 15). At low dose rates, the quadratic term becomes less important, and at very low dose rates it is assumed that the dose-response function is reduced to the linear term only (16). The exact dose rate below which the quadratic term can be ignored is not precisely determined (10, 16), but experimental studies indicate that it might be quite low. 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. However, there is 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 two to ten, depending on the experimental end-point (16). In view of this, there should be reason to take into account dose-rate effectiveness factors 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 (5, 10, 14, 15, 16, 22, 23).

RADIATION QUALITY

There are limitations to our understanding of RBE/LET relationships and their effect on 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 (10, 13). 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 (7, 13, 17, 20). 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. No epidemiologic studies are currently available for estimating neutron radiation effects; data from animal experiments have not been applied systematically to the estimatation of cancer risk in humans,but certain of the methods appear promising (13, 14).

X and gamma radiation are not equivalent in terms of RBE; energetic gamma radiation is less effective than 250 kVp X rays. 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

The statistical factors that modify risk are concerned with the assumptions, procedures and methods of risk estimation, and the most important of these appear to be the application of risk projection models, the calculation of risk coefficients, and the analysis of dose-response relationships.

TIME-RESPONSE PROJECTION MODEL

Risk coefficients are either absolute, i.e., calculated as an excess over and above baseline cancer incidence, or they are relative, 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.

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.

In the past, the absolute risk time-response model has been preferred by the ICRP (5) and UNSCEAR (22) committees. In the 1972 BEIR (9) and 1980 BEIR (10) reports, it has been used in parallel with the constant relative risk time-response model. The most recent data on the experience of the atomic-bomb survivors have provided a basis for applying the relative risk projection model in preference to the absolute risk projection model, and especially for breast cancer and lung cancer (20).

Within the period of observation, generally up to 35 years after exposure, the uncertainties introduced by the choice between the two models is not large, but it does increase thereafter. The constant relative risk model appears superior to the constant absolute risk model; the latter simply does not fit the data. But with additional observations, beyond the 35-year interval for which data are presently available, 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 (18) in the analysis of the Japanese atom-bomb survivor data. By means of statistical regression techniques appropriate for survival-time data, the 1988 BEIR IV Report (13) developed a modified relative-risk model for estimating the lung cancer mortality rate following exposure to radon daughters. In this model, 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 models, which have assumed that the relative risk is constant over both age and time. In the 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. Moreover, the age specific excess relative risk is higher for younger persons and declines at higher ages (13). This statistical approach is presently being modified for analysis of the new epidemiologic data and low-LET radiation exposure available over the past decade, and which is currently being assembled by the BEIR V Committee for its forthcoming report (14).

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. Statistical measures of uncertainty calculated for specific data sets are meaningful when the data are reasonably numerous, as is the case for some 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 limits differ from the mean value by a factor less than two. 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 (15, 20). 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 1980 BEIR Report (10) are, except for leukemia and bone cancer, linear values. They were not obtained from cancer registries (26), 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 linear-quadratic model of the 1980 BEIR Report (10) the excess risk from an exposure to D Gy was proportional to $D + D^2/1.16$. 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 new model. However, this source of uncertainty is unimportant relative to that involved in the choice of the crossover dose of 1.16 Gy. The statistical uncertainties underlying this conversion are appreciable. The reliability of the crossover value depends more on its agreement with experimental results

obtained over a wide range of biologic systems (16) 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. It appears that there is consistency among sources, and in general the absolute risk coefficients obtained in Japan are very much like those obtained in the United States and Great Britain except that the variances in the Japanese data are smaller because the experience is larger (20).

DOSE-RESPONSE RELATIONSHIPS

In general, it has not been possible to show reliability that doses of a tens of milligray have any influence on the likelihood of cancer since the excess risk, if any, is lost in the background of the natural incidence. In this regard, the 1980 BEIR Committee (10) was unwilling to determine estimates for acute doses below 0.1 Gy or for continuous exposure to less than 10 mGy per year. The current BEIR V Committee (14) has chosen 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. 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 1980 BEIR Report (10) 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 "pure" 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. Thus, cancer risk estimates were spread by a factor of 80 depending on the mathematical model chosen to perform the interpolation.

The linear model is generally considered to overestimate the risk in the low-dose range, although it is possible to postulate a distribution of susceptible individuals in the population such that a power curve might better describe the dose-response relationship.

Animal experiments in which a wide range of doses is employed often show a turn-down in the dose-effect curve at high doses, an observation attributed to cell-inactivation (10, 24, 25). In analysis of the human epidemiologic data, it is not 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 $LD_{50/60}$ 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. But 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 incidence of second cancers in patients treated with therapeutic doses of radium and X radiation for cervical cancer

(1, 24).

OTHER MODIFYING FACTORS

Numerous modifying factors remain and many are unknown; among the most important are possibly the effects of carcinogens other than radiation, and certain host 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. 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 U.S. uranium miners suggests a multiplicative relationship, another on Swedish iron miners suggests an additive relationship, and finally, the data on the Japanese atomic-bomb suvivors suggest additivity (13, 14).

For many sites of cancer there are other carcinogenic factors that seem able to increase the risk of cancer by a factor of two or more, and for all of these it has been assumed that the multiplicative model is more appropriate. This assumption, it should be noted, 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.

OTHER SOURCES THAT MODIFY RISK

There are other sources that modify risk for which information is completely lacking: hormonal status, genetic or other differences in DNA repair capability, and other host factors, particularly immune status and genetic characteristics. 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 a cancer following exposure to ionizing radiation, should be reviewed in the context of exposures to other carcinogens that may, in fact, have been reponsible for initiating the development of neoplasia.

CONCLUSIONS

Radiation is a known carcinogenic 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 it 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. If we wish to understand the mechanisms responsible for the interaction of radiation and human cancer at low dose levels, and apparently we do, then there is no lack of research goals to pursue.

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