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CARCINOGENESIS AND LOW-LEVEL IONIZING RADIATION WITH SPECIAL REFERENCE TO LUNG CANCER AND EXPOSURE TO RADON DAUGHTERS[1,2]

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INTRODUCTION

There are a number of important health effects of ionizing radiation, such as induction of cataracts in the lens of the eye or impairment of fertility, but the three important late effects - carcinogenesis, teratogenesis and mutagenesis - stand out as those of greatest concern. This is because a considerable amount of scientific information is known from epidemiological studies of exposed human populations and from laboratory animal experiments. Furthermore, we believe that any exposure to radiation, even at low levels of dose, carries some risk of such deleterious effects. And as the dose of radiation increases above very low levels, the risk of these deleterious health effects increases in exposed human populations. It is these latter observations that have been central to public concern about the potential health effects of low-level radiation, and to the task of estimating risks and of establishing standards for protection of the health of exposed populations (Fa80; Fa81a).

Cancer-induction is considered to be the most important late somatic effect of low-dose ionizing radiation (BEIR80). Solid cancers arising in the various organs and tissues of the body, such as the female breast and the thyroid gland, rather than leukemia, are the principal late effects in individuals exposed to radiation. The different tissues appear to vary greatly in their relative susceptibility to cancer-induction by radiation. The most frequently occurring radiation-induced cancers in man include, in decreasing order of susceptibility: the female breast, the thyroid gland, especially in young children and females, the blood-forming tissues, the lung, certain organs of the gastrointestinal tract, and the bones. There are a number of biological and physical factors affecting the cancer risk, such as age at the time of irradiation, and at the time of expression of the disease, sex, life-style, and radiation factors and types - LET and RBE.

At the present time, two issues compel public policy decision-making with regard to the risk of health effects in human populations exposed to low-level radiation. First, while much has been learned about the health effects of high doses of radiation exposure, scientists are still uncertain about how ionizing radiation causes detrimental health effects, and particularly cancer, and how to predict the effects of exposure to low doses. Second, with increasing use of materials and processes that produce ionizing radiations, it has become increasingly important to answer these questions. Despite the uncertainty about low-level radiation risks, federal and international regulatory and advisory bodies must set standards for radiation exposure, and individuals need information to be able to make informed judgments for themselves.

From the point of view of the policy maker, the over-riding concern for regulatory standards is the fact that small doses of radiation received by individuals in a population can cause that group of people to have more cancers than would otherwise be expected. The key point is that while concern for all radiation health effects exists, our human experience is limited almost entirely to cancer-induction in exposed human populations. Furthermore, while scientific researchers recognize the important implications about the sequence of events which leads to a particular biological effect, notably mutagenesis or carcinogenesis, public policy makers are compelled to deal with current practical issues. For example, while the total number or the incidence of ill-health a particular mutagen may cause in a population and for all subsequent generations is important, an equally important practical issue for public policy is the loss of life expectancy, that is, the additional years the average person would have lived if not exposed to carcinogens.

For these reasons, our discussion this afternoon is limited to cancer risk estimation and decision-making in relation to the health effects on populations of exposure to low levels of ionizing radiation. Here, low-level radiation exposure is a relative term that is difficult to define precisely. There is no scientific consensus on a precise definition. Whether a particular dose or dose-rate of radiation is considered low depends on circumstances and factors---the source and type of radiation, the part of the body irradiated, and even the scientific or political question. In view of our assignment, the term "low-level" radiation will refer to yearly whole-body doses up to 5 rems or 0.05 Sv, or to cumulative doses up to 50 rems or 0.5 Sv from low-LET radiation and from high-LET radiation.

WHAT IS THE FORM OF THE DOSE-RESPONSE RELATIONSHIP AT LOW-DOSE LEVELS?

At low and moderate radiation doses, the carcinogenic risk of ionizing radiation is an increasing function of the amount received. However, the precise functional form of the dose-response relationship remains controversial, and it is this issue, more than any other, that remains central to the problem of estimating the carcinogenic risk of low-level radiation (Fa80; Fa81a). Such risk estimates for practical radiation protection in the low-dose region usually are derived from extrapolation from data about populations exposed to high-dose levels. The method of extrapolation ultimately rests on the form assumed mathematically for the dose-response curve.

It is of considerable importance that the dose-response patterns in humans are based on epidemiological surveys, on laboratory animal experiments, on biophysical and mathematical theory, and on statistical methods. Because of the difficulties of obtaining and interpreting low-dose data on exposed human populations, it has become necessary to determine how the health effects at

low doses are related to those at high doses. Using these high-dose data obtained from reliable epidemiological surveys, radiation scientists attempt to estimate the extent and number of cancers caused by low-dose radiation in an exposed population. To extrapolate to low-dose effects from such high-dose data, it is now accepted that the use of appropriate mathematical equations or models may be used. However, it is recognized that such procedures are fraught with numerous uncertainties (BEIR80).

If it is assumed that at the biophysical level of the cell germ line and somatic cells share common events of radiation-induced lesions in DNA, then a general from of a dose-response relationship emerges which explains the nature, site, and magnitude of the radiation injury---cell lethality, mutation, or transformation (Figure 1).

The linear-no threshold model assumes that any radiation exposure carries some risk. It further assumes that cancer incidence is proportional to absorbed radiation dose. In other words, if the radiation dose doubles, then the number of cancers induced by radiation in the exposed population doubles. There is some support for this form in certain epidemiological studies, e.g., breast cancer (Bo79). The 1972 BEIR Committee (BEIR72) used the linear model to estimate the risk of cancer induction from low-dose, low-LET radiation. This model is also the basis of radiation protection standards (ICRP77) since it is considered conservative.

There is evidence that a quadratic dose-response relationship occurs in certain radiation-induced cancers, and this is particularly the case for higher dose levels. In this model, there is a four-fold increase in cancers as the radiation dose doubles. It follows that the quadratic dose-response model suggests that in the low-dose region, progressively lower doses of radiation are much less harmful than predicted by the linear model.

Many epidemological studies and laboratory animal experiments suggest a dose-response relationship which takes the form of the linear model at very low doses, and the quadratic form at higher doses; this is the linear-quadratic model. The 1980 BEIR Committee (BEIR80) considered this model most frequently for estimation of cancer risk for low-dose, low-LET, whole-body radiation, because this relationship appears to be consistent with epidemiological (human) and radiobiological (animal) data, in preference to more extreme dose-response models, such as the linear and the pure quadratic (BEIR80).

When comparison of the three dose-response models is made, then extrapolation from existing high-dose data to the low-dose region where data are not available can lead to inaccurate or incorrect estimation of risk. The importance of this observation in the estimation of radiation risk impacts considerably on the assessment of radiation risk. The 1980 BEIR Committee (BEIR80) noted the probability that the linear model leads to overestimates of the risk of most cancers from low-LET radiation. However, the Committee pointed out that for exposure to high-LET radiation linear risk estimates for low doses are less likely to overestimate risk, and may, in fact, underestimate risk (BEIR80).

There has been some argument that models exist which demonstrate a much higher risk per unit dose at low-dose levels than at high-dose levels. In other words, such models predict that lower doses of radiation are much more harmful than predicted by the linear model. One mathematical model of this kind has a "supralinear" dose-response relationship at the lower dose levels (NRCP80). One form is the "square root of dose model" (GA081) which predicts a 40 percent increase in radiation-induced cancer of the radiation dose doubles. The results of a few recent studies which claim a much larger risk per unit dose at low doses than at high doses also claim to support this

model. A form of this model may obtain for high-LET radiations or for genetically susceptible subpopulations, but this is not known. Those epidemiological studies that have been cited to support the form of the square root of dose model have been seriously criticized on methodological grounds (NRCP80).

HOW VALID ARE THESE DOSE-RESPONSE CURVES FOR EXTRAPOLATION INTO THE LOW-DOSE REGION?

The chief sources of epidemiological data currently considered for risk estimation of radiation-induced cancer in man are the Japanese atomic-bomb survivors exposed to whole-body irradiation at Hiroshima and Nagasaki (Be77), the English patients with ankylosing spondylitis (Co65) and other patients who were exposed to partial body irradiation therapeutically (Sh77), or to diagnostic medical radiation (Bo77), and various occupationally exposed worker populations (Ar76; Ro78), such as uranium miners and radium watch dial painters. All authors of these surveys assume that a person exposed to a radiation dose, D, will, after some minimal latency time, sustain an annual probability, P(D), for contracting and succumbing to a particular malignant neoplasm (Figure 1). Thus, one simple family of dose-response relationships which have been repeatedly observed in human studies and in laboratory animal experiments takes the form $P(D) = \alpha + \beta D^k$. α is the risk caused by background and medical radiation and nonradiation causes. When k = 1, the simple dose-response model is linear; when k = 2, quadratic; when k = 5, square root. Slightly more elaborate models include those of the form $P(D) = \alpha + \beta_1 D^{k1} + \beta_2 D^{k2}$. When $k_1 = 1$ and $k_2 = 2$, the dose-response model is linear-quadratic. Another functional form is $P(D) = (\alpha+\beta D^k)e^{-\gamma D}$. The exponential damping factor implies that at a certain dose level, additional radiation

reduces the cancer risk. There are few epidemiological studies in which this damping factor is encountered; the model has been valuable in the study of the radium dial-painters (Ro78).

Studies attempting to apply these various forms of dose-response models to the British ankylosing spondylitis patients (Co65), the U.S. uranium miners (Ar76), the U.S. radium dial painters (Ro78), and the Japanese atomic-bomb survivors (Be77) resulted in a number of important observations and conclusions on the validity of these dose-response models applied to the human data (Figure 2).

First, the precise functional form of the dose-response curve for cancer-induction by radiation is in dispute, and remains so. This appears to be the case, because the data available are unable to select a particular dose-response curve from among the various forms that can be tested reliably. In all individual data sets, more than one dose-response curve give an acceptale fit. Dose-response curves derived from various forms of the $P(D) = \alpha + \beta_1 D^k$ model, whether linear, linear-quadratic, quadratic, or square root, at low levels of dose all gave acceptable fits for at least one data set. If a dose-response curve gives an acceptable fit to the data, it does not necessarily mean that the curve is the correct one. In general, statistical tests on radiation epidemiological data can show that some dose-response curves are wrong, but they cannot show which one is correct. By and large the epidemiological data of a particular population can fit a number of functional forms of dose-response relationships, and do not necessarily discriminate in favor of any one form (BEIR80).

One must conclude that it is very unlikely that the best or most appropriate functional form of dose-response curves for cancer induction in humans exposed to low-level radiation will be resolved using statistical

methods only. Studies of human populations exposed to low-dose radiation cannot be expected to determine the relationship between low-level ionizing radiation exposure and cancer-induction in man. It would appear that what is needed is a better understanding of the fundamental mechanisms by which cancers are induced by radiation (Up77).

WHAT IS THE SIGNIFICANCE OF THE LATENCY PERIOD IN ESTIMATING CANCER RISK OF LOW-LEVEL RADIATION

From the time of induction of the radiation lesion in DNA to the time of appearance of a neoplasm in a human being, something caused cancer. Because a complex chain of events occurred, or did not occur, a particular cancer may have many causes, and interfering with any one of them may or may not have prevented the cancer from occurring.

Cancer-induction is considered to be a complex multistage process. Thus far, a coherent picture of the nature and mechanisms of cancer induction by radiation has failed to emerge. A major factor involves the complexity of the phenomena---there are many kinds of cancer; there is an uncertain relationship between the human response to radiation and the responses seen in a variety of animal and cell experiments; carcinogenic effects occur only after a latency period of variable length; and, there are effects of biological repair mechanisms, immunological systems, and viruses that can affect the observed phenomena in unknown ways. Perhaps most important, the nature of the experimental effort has precluded an understanding of mechanisms of ionizing radiations and carcinogenesis---we place great effort into analysis of experimental data, but we have placed less effort into the synthesis of the accumulated data, and thus there have been few attempts to develop theoretical models of radiation response (GA081).

One model of carcinogenesis involves damage to DNA by ionizing radiation---single-strand breaks, double-strand breaks, and base damage, and there can be different types of damage around the site of a strand break. After cells have been exposed to ionizing radiation, repair to DNA occurs. However, it is not known exactly what is repaired or how it is repaired, and whether repair mechanisms are error-free or error-prone. DNA damage caused by radiation can lead to the appearance of mutation, and cancer might be a type of mutation. If cancer can be caused by DNA mutation, then error-free DNA repair processes might lessen the carcinogenic potential of radiation by correctly repairing DNA damage. However, error-prone repair mechanisms might increase the probability of a cancer arising (FREIR81).

But the events at the biophysical level of the cell represent the initial mechanisms of something causing cancer; the critical events in cancer-induction happen at different times. The time between the cause of the cancer and its appearance in a clinically-defined form which can be diagnosed medically is the latency period. However, since there is no single cause of cancer-induction, there is no defined time for the cause to occur. Furthermore, there is no way to distinguish between a cancer which has had radiation and one which has not. But given these constraints, we can draw some valid conclusions about the relationship in time between the causation of cancer and cancer incidence expressed in human populations (Figure 3). First, cancers occur spontaneously, but also cancers occur which would not have occurred if the population had not been exposed to the carcinogen. Second, these latter cancers do not usually occur immediately after exposure, but rather after a minimal latent period, implying that no cancer of which radiation is a cause has occurred during this time. Third, there seems to be an average delay of several years. There may be, in some instances, a maximum latency period, or a time after which there

ceases to be an annual excess of cancer. Fourth, latency period is measurable only in a statistical sense, as a characteristic of a large number of cancer cases in a population. And last, latency period may depend on the type of cancer; the characteristics of the people exposed, including age, sex, and life-styles; the characteristics of the radiation, such as type, dose and dose-rate; and a host of other factors.

RISK PROJECTION MODELS: ARE THEY VALID FOR PREDICTING CANCER PATTERNS

The concept of a latency period is important to scientific understanding of the sequence of events which leads to cancer. But it also is of importance for public policy makers who must depend on valid projections on cancer incidence in the population in the future---that is, in the estimation of risk, or loss of life expectancy, to persons exposed to the carcinogen. There are a number of risk projection models which may be used---two reasonable ones are the relative- and the absolute-risk models for cancer-induced by radiation (Figure 3).

The 1972 and the 1980 BEIR Committees (BEIR72; BEIR80) used both models. Both models use the concepts of probability, radiation dose, latency period and age. Under the relative-risk model, the age at which radiation-induced cancer appears is fairly insensitive to the age at which it is induced. The key feature of the absolute-risk model is its assumption that, after a defined minimum latency period, a cancer caused by radiation is equally likely to show up at all ages.

It is not surprising that, in estimating the long-term effects of a given exposure to radiation, the 1980 BEIR Committee (BEIR80) got very different numbers from their absolute- and relative-risk models. These differences arise from the models' differing assumptions about when a radiation-induced cancer

will appear. Absolute-risk predictions of radiation-induced cancers are stated in terms of the number added to the natural cancer incidence. Relative-risk predictions are stated in terms of a multiple of the natural incidence. Thus, under the relative-risk model, a higher number of radiation-induced cancers are predicted at high natural cancer risk (GA081). When testing the absolute- and relative-risk projection models using the largest body of epidemiological data available---that is, the Japanese atomic-bomb survivor data---it became apparent that both models are inadequate to explain cancer patterns that have emerged over the past 35 years after the bombings (GA081). The data are inadequate to determine which of the two risk models is correct. This suggests that for some cancers, both might be wrong.

CAN WE RELIABLY ESTIMATE RISK OF RADIATION-INDUCED CANCER IN HUMAN POPULATIONS EXPOSED TO LOW-LEVEL RADIATION

Despite the uncertainty about low-level radiation risks, federal and international regulatory and advisory bodies on radiation must set standards for radiation exposure to the general population and in the workplace. A major approach to assessing the risks of exposure to low-dose ionizing radiation has been through epidemiology---statistical analyses of the cancer incidence among large groups of people who have had some special exposure to radiation. We now know that small doses of radiation received by a group of people can cause that group to have more cancers than would otherwise be expected. However, it is not possible to tell which cancers resulted from radiation exposure and which resulted from other causes. Thus, the excess cancer incidence in the exposed population cannot be measured directly; it is measurable only in a statistical sense, i.e., as a characteristic of a large number of cases.

Epidemiological and statistical analyses have demonstrated increased cancer incidence among groups exposed to occupational and medical radiation and to radiation from atomic bombs (BEIR80; Fa81b). Generally, the exposures studied have involved high doses of radiation received at high dose rates. Epidemiologists have used estimates of the numbers of cancers induced by these high-level exposures to predict the numbers of cancers that may be induced by lower exposures. These predictions can vary widely depending on which of the risk projection models are used and on which of the several mathematical equations for dose-response relationships is used. The choice of the equation is a subject of considerable scientific controversy (Fa80; Fa81a). One conclusion may be drawn---there is as yet no way to determine precisely the cancer risks of low-level ionizing radiation exposure, and it is unlikely that this question will be resolved in the near future.

WHAT ARE THE RISK ESTIMATES OF CANCER INDUCED IN EXPOSED HUMAN POPULATIONS?

The most important epidemiological surveys of exposed populations for risk estimation of cancer-induction are the Japanese atomic-bomb survivors (Be77), the British ankylosing spondylitis patients (Co65), other patients who were treated with radiation (Sh77) or exposed to diagnostic medical radiation (Bo77), and a number of occupationally-exposed populations (Ar76; Ro78). Most epidemiological surveys do not systematically cover the range of low to moderate radiation doses which are available in the Japanese atomic-bomb survivor data. Analyses in terms of dose-response, therefore, necessarily rely greatly on the Japanese data (Be77). The neutron component of dose in Hiroshima, and its correlation with gamma dose, limit the value of the more numerous Hiroshima data for the estimation of cancer risk from low-LET

radiation. The Nagasaki data, for which the neutron component of dose is extremely small, are less reliable for doses below 1.0 Gy. (Lo81).

The 1980 BEIR Committee (BEIR80) chose three exposure situations for illustrative computations of the lifetime cancer risk of low-dose, low-LET whole-body radiation: (1) a single exposure of representative (life-table) population to 0.1 Gy; (2) a continuous, lifetime exposure of a representative (life-table) population to 0.01 Gy per year; and (3) an exposure to 0.01 Gy per year over several age intervals approximating conditions of occupational exposure. These three exposure situations were not chosen to reflect any circumstances that would normally occur, but to embrace the areas of concern---general population and occupational exposure, and single and continuous exposure. The selected annual level of chronic exposure of 0.01 Gy per year, although only one-fifth the maximum permissible dose for occupational exposure, is nevertheless consistent with the occupational exposure experience in the nuclear industry. The 1969-1971 U.S. life-table was used as the basis for the calculations. The expression time was taken as 25 years for leukemia and the remaining years of life for other cancers.

In the absence of any increased radiation exposure, among one million persons of life-table age and sex composition in the United States, about 164,000 persons would be expected to die from cancer according to present cancer mortality rates. For a situation in which these one million persons are exposed to a single dose increment of 0.1 Gy of low-LET radiation, the linear-quadratic dose-response model predicts increases of about 0.5 percent and 1.4 percent over the normal expectation of cancer mortality, according to the projection model used. For continuous lifetime exposure to 0.01 Gy per year, the increase in cancer mortality, according to the linear-quadratic model, ranges from 3 percent to 8 percent over the normal expectation, depending on the risk projection model (Table 1).

Table 2 compares the cancer risk following exposure to 0.1 Gy, calculated according to three different dose-response models, viz., the linear-quadratic, the linear, and the quadratic, and to two risk projection models, viz., the absolute- and relative-risk models. The upper and lower limits of these cancer mortality risk estimates suggest a very wide range or envelope of values which may differ by as much as an order of magnitude. The uncertainty derives mainly from the dose-response models used, from the alternative absolute- and relative-risk projection models, and from the sampling variation in the source data. The lowest risk estimates---the lower bound of the envelope---are obtained from the pure quadratic model; the highest---the upper bound of the envelope---from the linear model; and the linear-quadratic model provides estimates between these two extremes (BEIR80).

Table 3 compares the 1980 BEIR-III Report (BEIR80) cancer mortality risk estimates with those of the 1972 BEIR-I Report (BEIR72) and the 1977 UNSCEAR Report (Fa81b). To do this, it was most convenient to express the values as cancer deaths per 10,000 persons per Gy of continuous life-time exposure. For continuous lifetime exposure to 0.01 Gy per year, the linear-quadratic dose-response model for low-LET radiation yields risk estimates considerably below the comparable linear-model estimates in the 1972 BEIR Report (BEIR72); the differences mainly reflect changes in the assumptions made by the two BEIR Committees (BEIR80; BEIR72) almost a decade apart. The 1980 BEIR Committee (BEIR80) preferred a linear-quadratic rather than linear dose-response model for low-LET radiation, and did not assume a fixed relationship between the effects of high-LET and low-LET radiation (which was based on the Japanese atomic-bomb survivor studies). Furthermore, in the 1980 BEIR Report (BEIR80) cancer risk estimates do not, as in the 1972 BEIR Report (BEIR72), carry through to the end of life the very high relative-risk coefficients obtained with respect to childhood cancers induced in utero by radiation.

HOW DO THESE OBSERVATIONS APPLY TO HIGH-LET RADIATIONS, PARTICULARLY EXPOSURE TO RADON DAUGHTERS?

We are now aware that the radioactive gas, radon, is a major source of human exposure. Radon emits alpha particles known to have a high biological effectiveness for the induction of cancer. Some radon daughters also emit alpha particles. Because all radon daughter products are electrically charged when formed, they tend to attach themselves to the dust particles in the air, thus becoming the most important natural source of radiation exposure through inhalation. Radon and its daughter products are present in underground mines. Natural gas and coal contain radon. Much of the radon trapped in buildings and homes is emitted from ordinary building materials---concrete or granite---or from the ground. And sealing up buildings to save energy could substantially increase the amount of radon which remains in the air in the houses (Ne81).

The scientific basis for our concern with high-LET radiations emerges from physical, biological and epidemiological studies (FREIR81). The linear energy transfer of radiation depends upon the type of radiation, its energy, its charge, and the process by which it interacts with matter. Passive repair processes---both protection and repair mechanisms---within the DNA molecule are more effective against low-LET radiation than high-LET radiation. In cell studies, high-LET radiation is, in general, more lethal than an equal amount of low-LET radiation. A low dose-rate is not as lethal as a high dose-rate for low-LET radiation; there is sometimes only a small variation with high-LET radiation. Cellular repair of radiation damage can ameliorate the lethal effects of radiation; damage from low-LET radiation appear to be more easily repaired than damage from high-LET radiation. The inactivation response of cells to radiation appears to be fundamentally different for high-LET and

low-LET radiations. The effectiveness of high-LET radiations for mutation-induction can be twice as high as that for cell killing, and this has important implications for risk estimates. The transformation of cultured cells is believed to correspond to the induction of cancer in vivo; high-LET radiation is more effective in producing in vitro transformations than low-LET radiation. The damage produced in DNA by high-LET radiation generally is more difficult to repair than the damage produced by low-LET radiation. High-LET radiation, in general, appears to have a greater biological effectiveness in producing cancer in animals and in human populations than does low-LET radiation (BEIR80;FREIR81; Fa81b).

The 1980 BEIR Report (BEIR80) attempted to address the question of the various ranges of dose and dose rates for which different numerical risk estimates were appropriate for both low-LET and high-LET radiations. In general, notwithstanding the limitations of risk estimation following exposure to low-level radiation, the 1980 BEIR Committee (BEIR80) recognized the need to estimate the effects in human populations exposed to radiation at very low doses. In most cases, the linear hypothesis, as the 1972 BEIR Report (BEIR72) also indicated, probably overestimates, rather than underestimates, the risk from low-LET radiation. For high-LET radiation, such as from internally deposited alpha-emitting radionuclides, the application of the linear hypothesis is less likely to lead to overestimates of risk and may, in fact, lead to underestimates of risk (BEIR80). It is this latter situation that deserves our urgent consideration, not only because of our concerns with the attendant health risks associated with mining, nuclear power and potential increases in ambient radon levels in our homes, but also with the paucity of laboratory animal data, the unreliability of the human data, and the special situation of the health effects of incorporated radionuclides in the human

body. The problems serve to confound our attempts to provide a scientific basis for risk estimation for guidance for radiation protection of human populations exposed to high-LET radiations in general, and radon and its daughters in particular.

Three important questions concerning human exposure to radon deserve our attention. First, what are the factors which determine the distribution of this internal radiation emitter in human tissue, and how are they related to the biological effectiveness? Second, how well are these factors understood in laboratory animals for extrapolation to the human situation? Third, to what extent has the study of physiological and metabolic processes that determine the dose-distribution from internal radiation sources provided some understanding of mechanisms to aid in evaluating risk? In order to provide a basis for responding to these questions, it would be worthwhile to review the available information on radon and lung cancer in laboratory animal studies, and in humans exposed under certain occupational situations, primarily mining of radioactive ores. It is from these epidemiological studies, almost exclusively, that we have limited information on the health risks in human populations of exposure to low levels of radon in our environment (BEIR80; FREIR81).

ARE THE LABORATORY ANIMAL STUDIES RELEVANT TO THE HUMAN SITUATION

Perhaps the most important animal studies relevant to radon toxicity health effects are those which concern the experimental production of cancer of the respiratory tract. The animal data stress evidence that a relationship can be defined that is pertinent to the human experience (BEIR80). However, studies of lung cancer in rodents and dogs suggest that laboratory animal experiments provide models for extrapolating to the human situation rather than an understanding of underlying mechanisms.

There has been some concern about the applicability of the laboratory animal data to the human situation; these relate to the pathogenesis of lung cancer under certain circumstances (BEIR80). In experimental studies of lung-cancer, the origin of tumors in rodents and dogs that have inhaled alpha-emitting elements commonly is found to be broncho-alveolar; they arise in regions of lung tissue adjacent to the respiratory bronchioles. In contrast, human lung cancers, or more appropriately, bronchial cancers, induced by cigarette smoking or exposure to environmental agents, nearly always arise in the proximal regions of the bronchial tree (down to the first few generations of branching). This difference in the site of origin has raised important questions concerning the direct relevance of animal studies. Nevertheless, a considerable amount of information about radiation dosimetry related to lung cancer associated with inhalation of radionuclides has become available in the last decade, both in animals and in humans. There are also new experimental and epidemiologic data concerning cigarette smoking in relation to radiation exposure and lung-cancer induction, albeit somewhat equivocal, but at least, insofar as possible, indicating important trends.

In general, the results of animal---both rodent and dog---experiments lead to five general conclusions (BEIR80). (1) Respiratory tract tumors develop in animals exposed to radiation at sites where the local radiation exposure is greatest. (2) Bronchial and nasal sinus tumors are produced in animals by exposure to radon and its daughters. (3) The effect of cigarette smoking on the development of bronchial cancers in radon-inhalation experiments in rodents and dogs remains equivocal (Mo77). (4) The sensitivity of the respiratory tract in animals to cancer-induction by radiation may be increased by irritant or other proliferative stimuli given after the radiation exposure (Li75). (5) The bronchial tissue in the lungs acts as a separate anatomical and

functional compartment whose uptake and release of inhaled materials may play an important role in cancer-induction in the bronchial epithelium (Pa77).

WHICH EPIDEMIOLOGICAL SURVEYS PROVIDE RELIABLE DATA FOR LUNG-CANCER RISK ESTIMATION?

Several important epidemiological studies contribute to our understanding of the potential risk of radon exposure---all are associated with workers exposed to radon daughters while working in underground mines (BEIR80). These groups of miners who were occupationally exposed to alpha radiation from short-lived radon daughters include Czechoslovakian (Se76), Canadian (Ha76), and U.S. uranium miners (BEIR80; Ar74), Newfoundland fluorspar miners (BEIR80), and Swedish metal miners (BEIR80; Ax78).

There are three important confounding problems in all these surveys which require consideration. First, these are data confined almost exclusively to high-levels of occupational exposure in males, limiting our understanding of risk of low-level exposure in the general population. Second, the studies do not have precision of dosimetric estimation of lung tissue exposure levels, and involve high-LET radiations, making analysis of dose-response relationships, even at high-dose levels,difficult to ascertain. Third, the populations studied generally are not analyzed according to life-style risk factors, particularly to cigarette-smoking experience. Prevalence of smoking among males and among miners has been commonly estimated by comparison with Swedish, American and Czechoslovakian habits, and therefore make the effects of such complex life-style factors difficult to interpret.

DOSIMETRY

The principal biological effects of radon daughters in man are considered to be from the polonium-214 daughter, because its alpha particle has a high

energy, enabling it to reach the basal cell layer of the bronchi more readily than the polonium-218 alpha particle (Figure 4). The dosage to the bronchial tree and to the lung tissue is measured in working levels (WL). This is defined as any combination of radon daughters in one liter or air that will result in the ultimate emission of 1.3×10^5 MeV of potential alpha energy (BEIR80). In terms of population exposure, however, the working-level month (WLM) is used. This is defined as that exposure resulting from inhalation of air with a concentration of one working level of radon daughters for 170 working hours (BEIR80; Ne81).

Conversion of the working-level month to a lung dose to the basal-cell layer of the bronchial segments from radon daughters is a complex matter. The RBE for alpha irradiation for induction of lung cancer, based on comparisons with the Japanese atomic-bomb survivors and the British ankylosing spondylitis patients,suggests a value of about 10 to 15, with very large uncertainties. The conversion factors applied for working-level month to Sv are complicated by such physical or biological factors as the fraction of free ions compared with the fraction of inhaled and bound to dust particles, breathing patterns, e.g., mouth-breathing or nose-breathing, and thickness of upper and lower respiratory epithelium. Nevertheless, a gross figure can be arrived at, at the present time---a value of about 0.06 Sv per working-level month is not inappropriate, and given the uncertainties involved, should not be off by more than a factor of two or three (BEIR80; Ha72; Ja72).

An important factor in dosimetry in these epidemiological studies which affect risk estimation is that the degree of equilibrium of lead-214 (RaB) and bismuth-214 (RaC) with polonium-218 may vary considerably; thus, the proportion of polonium-214 alpha decays to total alpha decays will vary as well. In mines, the extent of this equilibrium will depend on relative

ventilation; in practice, the ratio of polonium-214 to total alpha activity does not vary greatly. In other atmospheres, such as in homes and in buildings, the degree of disequilibrium can be substantial (Ne81).

EPIDEMIOLOGICAL SURVEYS

The Czechoslovakian uranium miners survey (Se76) suggests that exposure levels in the mines were not high. If the underground worker experience was 20 years or more and the average cumulative exposure was about 300 WLM, then the concentrations of radon daughters would be estimated to be about one WLM. If the years at risk are 13, then the total excess risk is found to be 19 excess lung cancer cases per million person-years per WLM (BEIR80). This results in an approximate relative risk of 1.8 percent excess lung-cancer risks per WLM. These risk estimates are subject to large statistical uncertainties.

The United States uranium miners survey (BEIR80; Ar74), comprises over 4,000 miners in the Colorado Plateau region. These miners had exposures to high concentrations of radon daughters, ranging from 10 to 100 WLM or more. The average cumulative exposures was 1,180 WLM, or four times that of the Czechoslovakian miners, and well above that of most other mining populations surveyed. The range of cumulative exposure is from 0 to perhaps 10,000 WLM. In Figure 5, the absolute risk values range from about 2.7 to 8.0 excess lung cancer cases per million person-years per WLM. The relative risk values range from 0.3 percent to 1.2 percent increased risk per WLM. The estimates of risk are heavily weighted by experience associated with high cumulative doses at relatively high dose rates. The data, when segmented according to cumulative WLM suggest that except for the lowest dose group, in whom lung-cancer excess has thus far been observed, the lower exposure groups above a mean of 180 WLM

have risk estimates some 2 to 3 times greater than those for the higher dose groups (Figure 5).

The Canadian uranium miners survey (Ha76) includes some 15,000 workers, but many worked underground for only a short period of time. Despite limitations in the population data base, reasonably good exposure estimates in the mines are available. These demonstrate trends of low-dose effects; there is a suggested relative risk of 1.6 percent increase per WLM in the 1 to 30 WLM group. However, for a number of reasons, risk estimates cannot be derived with any confidence. Nevertheless, the Royal commission study (Ha76) recognized that the lung-cancer data in this miner population may have unusual potential for defining low-dose risks, since the population is larger than that of other mining groups under study, and the radiation exposures have generally been low. There has been reasonably good dosimetry monitoring of the Ontario mines since they were opened, and evaluation of the effects of cigarette-smoking should be possible (BEIR80).

The Newfoundland fluorspar miners survey (BEIR80) involves some 2,500 men, approximately 17,000 person-years of follow-up and estimates of radon-daughter concentrations varying from 0.5 to 8 WLM. In this group, the risk of lung cancer had a significant correlation with cumulative dose and with age at the start of undergound mining. The average cumulative exposure weighted for person-years at risk was about 200 WLM; the absolute risk was 17.7 excess lung cancer deaths per million person-years per WLM. The relative risk was 8.0 percent increase per WLM, but this value is strongly biased upward since these miners were nearly all smokers. This life-style factor affects the relative risk substantially, but would have little effect on the absolute risk. Furthermore, the heavy smoking factor in these miners resulted in the

observation that there was no effect of age on the latent period (Figure 6) which is in sharp contrast with observations on the Japanese atomic-bomb survivors (Is75) (Figure 7).

The Swedish metal miners survey (BEIR80; Ax78) has a relatively small data base, and all reports thus far are preliminary and with incompete follow-up. Approximately 2,000 person years at risk are involved, a mean cumulative exposure of 270 WLM, and an absolute risk estimate of about 30.4 excess lung cancer deaths per million person-years for WLM.

LUNG CANCER RISK ESTIMATES

From these limited series, five conclusions can be drawn. (1) The absolute risk estimates for lung cancer from exposure to radon daughters range from about 5 to 50 excess cases per million person-years per WLM (BEIR80). (2) A wide range of risk coefficients is associated with an effect of age at the beginning of exposure in the mines or at the onset of lung cancer. (3) The absolute risk estimates vary considerably; the Swedish metal miners have high estimates, and the U.S. uranium miners have low estimates, well below those of the other groups. (4) A number of confounding problems arise in these studies---host factors such as age, life-style risk factors such as cigarette smoking, and physical factors such as radon daughter dosimetry measurements in the mines---can lead to very large uncertainties in numerical estimation of risk. (5) The most likely lung-cancer risk estimates, at exposure to 1 WLM and with characteristic smoking experience, are about 10 excess lung cancer cases per million person-years per WLM for the 35-49 year age group; about 20 excess cases for the 50-65 year age group; and about 50 excess per million person-years per WLM for miners over age 65 (Figure 8) (BEIR80). These values appear consistent with age at the time of lung-cancer diagnosis and years of follow-up.

WHICH FACTORS INTRODUCE THE MOST IMPORTANT CONFOUNDING BIASES IN THE AVAILABLE EPIDEMIOLOGICAL SURVEYS?

Confounding is a mixing of effects. In contrast to selection and information biases which seriously limit the precision of these limited epidemiological studies, confounding is potentially present in all these data. Three factors of interest are the effects of age, the effects of cigarette-smoking, and the effects of dose-estimation. Perhaps among the most important biases in the evaluation of an association between radon daughter radiation exposure and lung cancer is the confounding resulting from the existing cigarette-smoking. Cigarette-smoking is a cause of lung cancer and also, many uranium miners smoke cigarettes. Archer and his colleagues (Ar73) examined the relationship between uranium mining and lung cancer and found that the rate of lung cancer was higher in miners than in non-miners, and that this relationship between mining and lung cancer was confounded by cigarette-smoking. When underground miners were classified according to cigarette-smoking, the association between mining and development of lung cancer was present in both groups, and the incidence of lung cancer increased with increasing radiation exposure to radon daughters among miners with similar smoking habits. Smokers, however, appeared to have a shorter induction-latent period for lung cancer than nonsmoking miners.

With longer periods of follow-up, however, the excess cancer cases among nonsmoking miners may rise proportionately more rapidly because the latent period for nonsmokers is longer. However, the effect of cigarette-smoking on these lung-cancer risk estimates cannot be evaluated with the present information available. Nevertheless, trends are evident. If smoking risks and radiation risks for lung-cancer induction are additive, then the lung-cancer risk estimates in miners apply to both smokers and nonsmokers. The Japanese

atomic-bomb survivor data suggest the lung cancer risks could develop among nonsmokers at higher ages than presently estimated (Is75). Further information is required to determine whether exposure of underground miners to radon daughters adds to the effect of cigarette smoking, or whether the effects are greater than additive when both are present. The evidence now indicates that a purely multiplicative effect on lung-cancer related to radiation exposure and cigarette-smoking is highly unlikely (BEIR80).

AGE

Age at initial exposure in the mines influences the reported lung-cancer risk among underground miners (BEIR80). Among the Czechoslovakian miners there was a marked effect of age at initial exposure on lung-cancer excess from radon daughters (Se76). Among the Canadian fluorspar miners (BEIR80), there was an increasing risk of radiation-induced lung cancer with increasing age at entry into the mines. While the effects of smoking and high-LET versus low-LET radiations are not clearly understood, both the data on the Japanese atomic-bomb survivors (BEIR80; Is75) and on the underground miners (BEIR80) suggest that lung-cancer induction by radiation depends markedly on age of exposure, with no evidence as yet of excess cancer risk before the age of 35 (Figure 9 and Figure 10).

CAN THE UNDERGROUND MINERS EXPERIENCE APPLY TO RISK ESTIMATION FOR THE GENERAL PUBLIC FROM INDOOR RADON DAUGHTER EXPOSURES?

What have we learned from the underground miners experience First, the incidence of lung cancer among uranium and certain other underground miners is considerably higher than that among the general population. Second, this difference has been attributed to large exposures to high-LET alpha-emitting

radon daughters accumulated by the miners from working for prolonged periods in high radon daughter concentrations. Third, the elevated incidence of lung cancer among these underground miners provides the basis for determining a numerical dose-response relationship between radon daughter exposure and the induction of lung cancer. Fourth, based on the estimates in the 1980 BEIR Report [3], each WLM of radon daughter exposure in miners induces an additional chance of lung cancer of about 200 to 400 in a million, based on an absolute risk estimate of about 10 to 20 excess lung cancer cases per million person years per WLM. Thus, a miner who received about 10 WLM per year for 30 years---a total of 300 WLM---stands about a 10 percent chance of developing lung cancer from cumulative radon daughter exposures (Ne81). This, of course, is a most conservative estimate, but does not take into account the numerous confounding variables involved in estimation of risk.

Nevertheless, even with highly uncertain constraints on such estimates, an appropriate range of lung-cancer risk in the general population can be calculated. It difficult to assess the reliability of radon-daughter risk estimates because of the uncertainty associated with the assumption that the cancer risk is proportional to exposure, even for low exposures. However, it is possible to predict that for indoor randon-daughter exposures in the typical range of 0.04 to 0.8 WLM per year in our buildings (Ne81), such levels of radon-daughter exposures may cause many thousands of radiation-induced lung cancers per year in the United States population. Assuming, for example, average annual exposures of 0.2 WLM per year, and averaging these rates for men and women, correcting for age-distribution differences between miners and the general population, and assuming linearity with no threshold and simple additivity for cigarette smoking, it would not be unreasonable to estimate a

risk as high as 10 to 20 radiation-induced lung cancers per million persons per year, or approximately 2,000 to 4,000 excess cases annually among the U.S. population (Nel9).

WHAT CAN WE CONCLUDE ABOUT LOW-DOSE, HIGH-LET RADIATION EXPOSURE?

The quantitative estimation of the carcinogenic risk of low-dose, high-LET radiation in the case of exposure to radon daughters and lung-cancer is subject to numerous uncertainties. The greatest of these concerns the parametric values of the dose-response curve. We lack knowledge and an understanding of the dosimetry and the distribution of aggregates of radioactivity that remain localized as "hot spots" in specific regions of the lungs and the influence on greater or lesser risk of lung cancer per average lung dose than uniformly deposited radiation (NRC76). We have only a limited understanding of the response to exposure to high-LET radiations, such as alpha particles, for which linear risk estimates for low doses are less likely to overestimate the risk, and may, in fact, underestimate the risk (BEIR80).

Other uncertainties include the length of the latency period, the RBE for alpha radiation relative to gamma radiation, the period during which the radiation risk is expressed, the risk projection model used---whether absolute or relative---for projecting risk beyond the period of observation, the effect of dose rate and protraction of dose, and the influence of differences in the natural incidence of lung cancer in different populations. In addition, uncertainties are introduced by the biological and life-style risk characteristics of humans, for example, the effect of sex, the effect of age at the time of irradiation and at the time of appearance of the cancer, the influence of length of observation or follow-up of the study populations, and the influence of perhaps the most important confounding bias, cigarette-smoking. The

collective influence of these uncertainties is such as to deny great credibility to any estimate of human lung cancer risk and other cancer risk that can be made for low-dose, high--LET radon daughter radiation exposure.

It is understandable that these many reasons, and more, compel the conclusion that emphasis should be placed on our assumptions, procedures, and uncertainties involved in the risk estimation process and not on specific numerical estimates derived thereby. Nevertheless, there is little doubt that even the most crude estimate of the projected lung-cancer incidence due to radon daughters would appear sufficiently high to require careful examination of any measures that could decrease existing human exposures, and of measures that could increase existing exposures significantly. The scientific question is now restated: Knowing or suspecting that radiation from exposure to radon daughters causes ill-health at some level of exposure, what are its effects on health at the lowest levels to which humans are being or may be exposed What is required is a credible estimate of risk at actual dose levels likely to be experienced by exposed human individuals---in the general population and in the workplace---so as to inform the inescapable political judgement.

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Table 1.
Estimated excess mortality per million persons from all forms of cancer, linear-quadratic dose-response model for Low-LET radiation (BEIR80).

	Absolute-Risk Projection Model	Absolute-Risk Projection Model
Single exposure to 0.1 Gy		
Normal expectation	163,800	163,800
Excess cases: number	766	2.255
% of normal	0.47	1.4
Continuous exposure to 0.01 Gy/yr, lifetime:		
Normal expectation	167,300	167,300
Excess cases: number	4,751	12,920
% of normal	2.8	7.7

Table 2.
Estimated excess mortality per million persons from all froms of cancer, single exposure to 0.1 Gy of Low-LET radiation, by dose-response model (BEIR80).

Dose-Response Model			Absolute-Risk Projection Model	Absolute-Risk Projection Model
Leukemia And Bone	Other Cancer			
		Normal expectation or cancer deaths	163,800	163,800
LQ-L	LQ-L	Excess deaths: number	766	2,255
		% of normal	0.47	1.4
L-L	L-L	Excess deaths: number	1,671	5,014
		% of normal	1.0	3.1
Q-L	Q-L	Excess deaths: number	95	276
		% of normal	0.058	0.17

Table 3.
Comparative estimates of the lifetime risk of cancer mortality induced by Low-LET radiation---excess deaths per million, average value per 0.01 Gy by projection model, dose-response model, and type of exposure (BEIR80).

Source of Estimate	Dose-Response	Projection Model: Single Exposure 0.1 Gy		Projection Model: Continuous Lifetime Exposure to 0.01 Gy/yr	
Estimates	Models	Absolute	Relative	Absolute	Relative
BEIR, 1980[a]	LQ-L, $\overline{\text{LQ-L}}$	77	226	67	182
1972 BEIR report factors	Linear	117	621	115	568
UNSCEAR 1977	Linear		75-175		

a For BEIR 1980, the first model is used for leukemia, the second for other forms of cancer. The corresponding estimates when the other models are used (thereby providing an envelope of risk estimates) are:

L-L, $\overline{\text{L-L}}$	167	501	158	430
Q-L, $\overline{\text{Q-L}}$	10	28		

b The values are average values per 0.01 Gy and are not to be taken as estimates at only 0.01 Gy of dose.

FIGURE LEGENDS

Figure 1. Alternative dose-response models, including the linear, pure quadratic, linear-quadratic, and general linear-quadratic with a dose-modifier in the high-dose range (BEIR80).

Figure 2. Dose-incidence data for the British ankylosing spondylitis patients (leukemia), the U.S. uranium miners (lung cancer), the Japanese atomic bomb survivors (Nagasaki, leukemia), and the U.S. radium dial painters (bone cancer).

Figure 3. Schematic of the absolute- (solid line) and relative- (dash line) risk projection models relating excess cancer risk estimates to age (A) at the time of and following radiation (X); a, age at exposure; b, age after minimal latent period (LP); c, age at estimated risk coefficient (BEIR80).

Figure 4. Decay chain of radium-226 to lead-210. The half-lives and the alpha and beta decay energies (MeV) are indicated. Because the polonium-214 alpha particle has high energy (7.69 MeV), it reaches the basal cell layers of the bronchi more readily than the polonium-218 alpha particles (6.00 MeV). Therefore, the principle biological effects of radon daughters exposure in man are from the polonium-214 daughter (Ne81).

Figure 5. U.S. uranium miners radiation-induced lung-cancer risk. The cumulative WLM man exposure is plotted against absolute (left ordinate, circles) and relative (right ordinate, crosses) risks, respectively. Except for the lowest exposure group (range 0-119 cumulative WLM, mean 760 WLM), in whom no lung-cancer excess has been observed, the lower exposure groups have risk estimates some 2-3 times those for the higher dose groups (BEIR80).

Figure 6. Lung-cancer risk in Newfoundland fluorspar miners (BEIR80). Latency period is plotted as a function of age at the start of mining. In these workers, there appears to be little or not effect of age on the latent period up to the present. The influence of cigarette smoking may affect this observation. See text.

Figure 7. Cumulative incidence of cancer of the respiratory tract (trachea, bronchus, and lung) in Japanese atomic-bomb survivors (1950-1974) (BEIR80; Ha76).

Figure 8. Lung-cancer risk estimates in underground miners from exposure to radon daughters; influence of cigarette smoking. The excess number of lung cancers, estimated per million person-years per WLM, rises rapidly with age after 35 years (BEIR80).

Figure 9. Age-specific lung cancer risk estimates in underground miners from exposure to radon daughters. The excess risk (cases), estimated per 10,000 person-year per Sv, rises rapidly with age after 35 years (BEIR80).

Figure 10. Respiratory-cancer risk in Japanese atomic-bomb survivors. Age-specific mortality risks for cancer of the trachea, bronchus and lung for the period 1950-1974 for the Hiroshima and Nagasaki survivors combined (BEIR80; Is75).

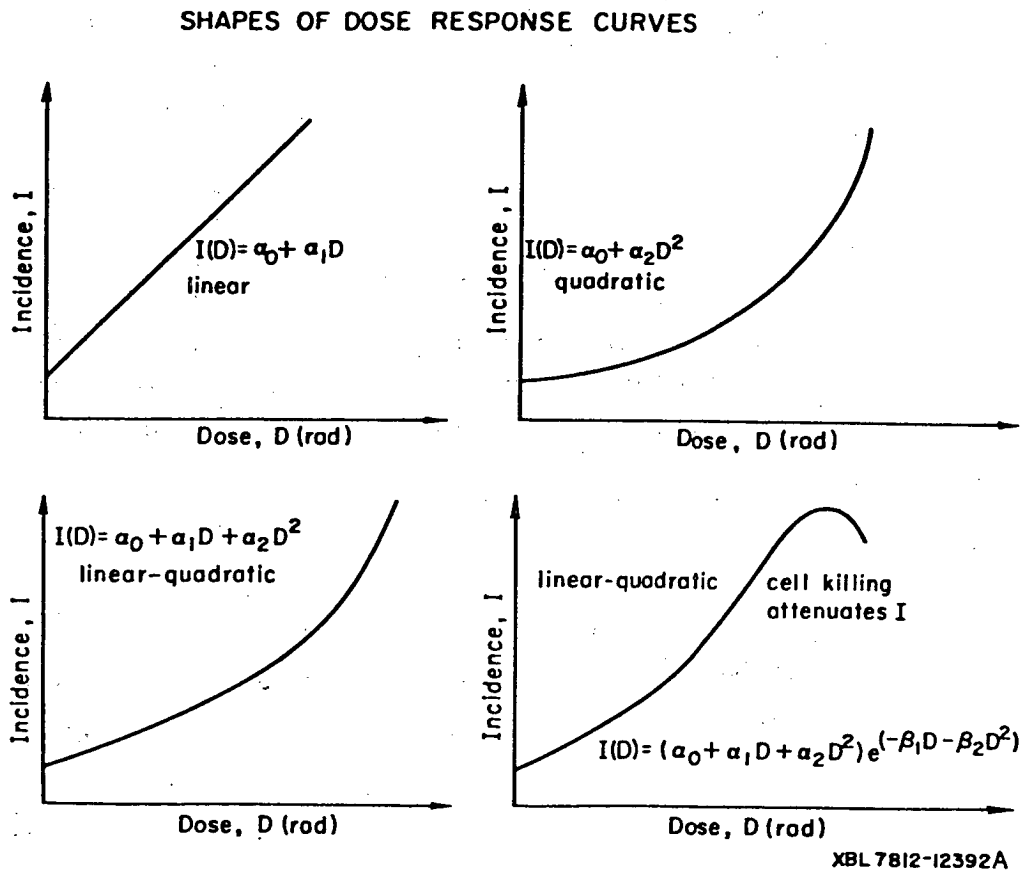

SHAPES OF DOSE RESPONSE CURVES
Incidence, I
I(D)= $\alpha_0 + \alpha_1 D$
linear
Dose, D (rad)
Incidence, I
I(D)= $\alpha_0 + \alpha_2 D^2$
quadratic
Dose, D (rad)
Incidence, I
I(D)= $\alpha_0 + \alpha_1 D + \alpha_2 D^2$
linear-quadratic
Dose, D (rad)
Incidence, I
linear-quadratic
cell killing
attenuates I
I(D)= $(\alpha_0 + \alpha_1 D + \alpha_2 D^2) e^{(-\beta_1 D - \beta_2 D^2)}$
Dose, D (rad)
XBL 7812-12392A

Figure 1

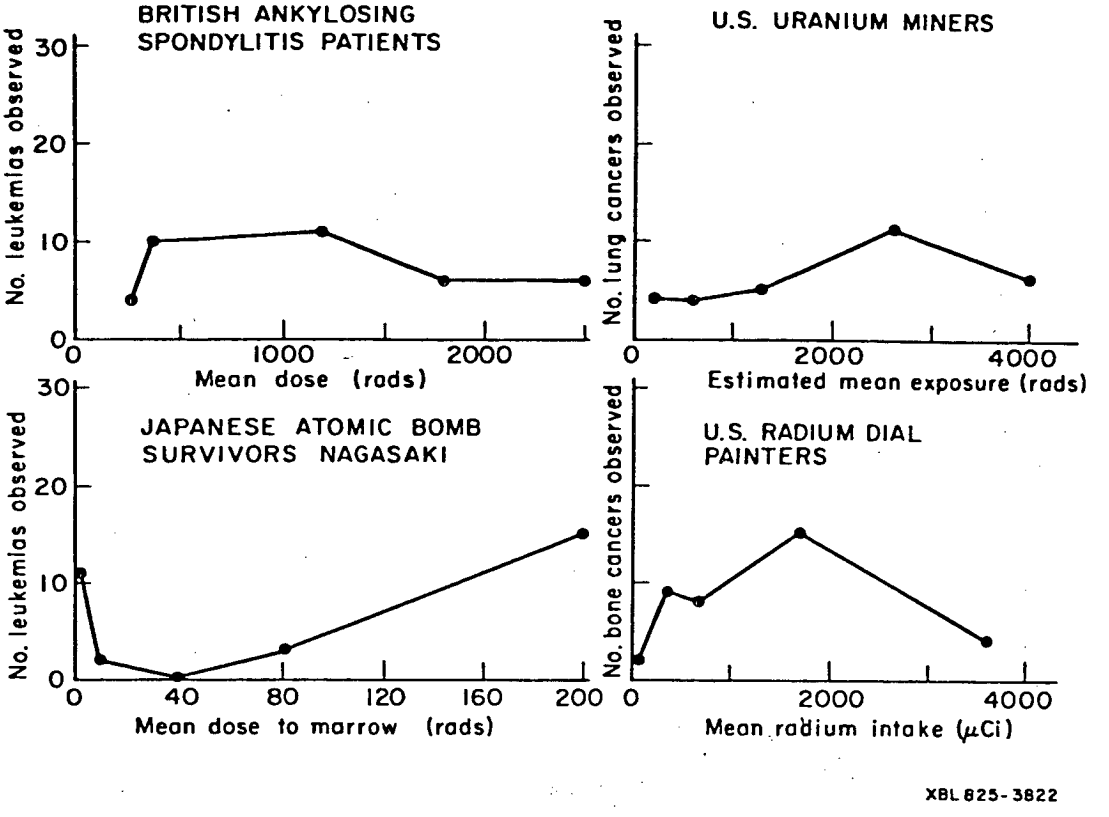
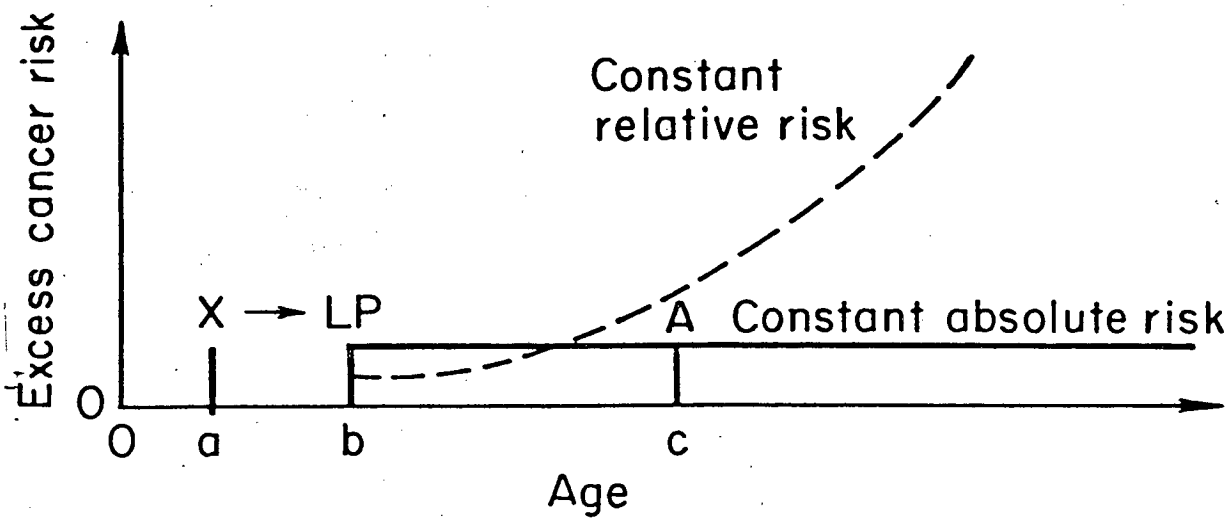

BRITISH ANKYLOSING SPONDYLITIS PATIENTS
No. leukemias observed
30
20
10
0
0
1000
2000
Mean dose (rads)
U.S. URANIUM MINERS
No. lung cancers observed
0
2000
4000
Estimated mean exposure (rads)
JAPANESE ATOMIC BOMB SURVIVORS NAGASAKI
No. leukemias observed
30
20
10
0
0
40
80
120
160
200
Mean dose to marrow (rads)
U.S. RADIUM DIAL PAINTERS
No. bone cancers observed
0
2000
4000
Mean radium intake (μCi)
XBL 825-3822

Figure 2



XBL801-3028

Figure 3

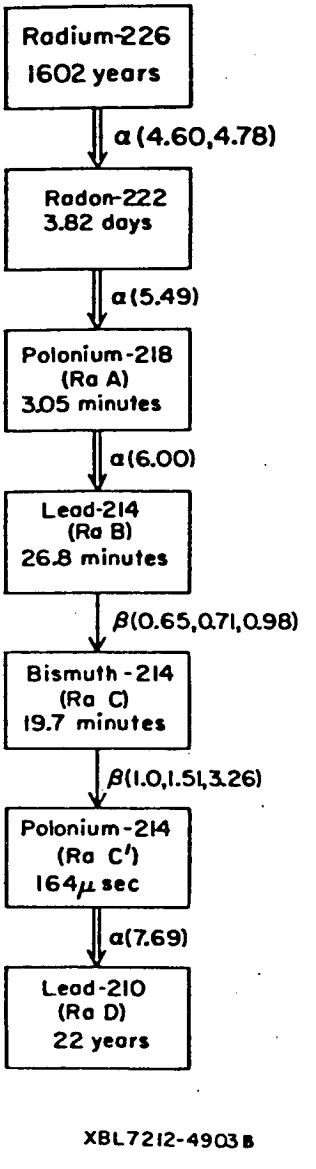

Radium-226
1602 years
α (4.60,4.78)
Radon-222
3.82 days
α (5.49)
Polonium-218
(Ra A)
3.05 minutes
α (6.00)
Lead-214
(Ra B)
26.8 minutes
β (0.65,0.71,0.98)
Bismuth-214
(Ra C)
19.7 minutes
β (1.0,1.51,3.26)
Polonium-214
(Ra C')
164μ sec
α (7.69)
Lead-210
(Ra D)
22 years
XBL7212-4903B

Figure 4

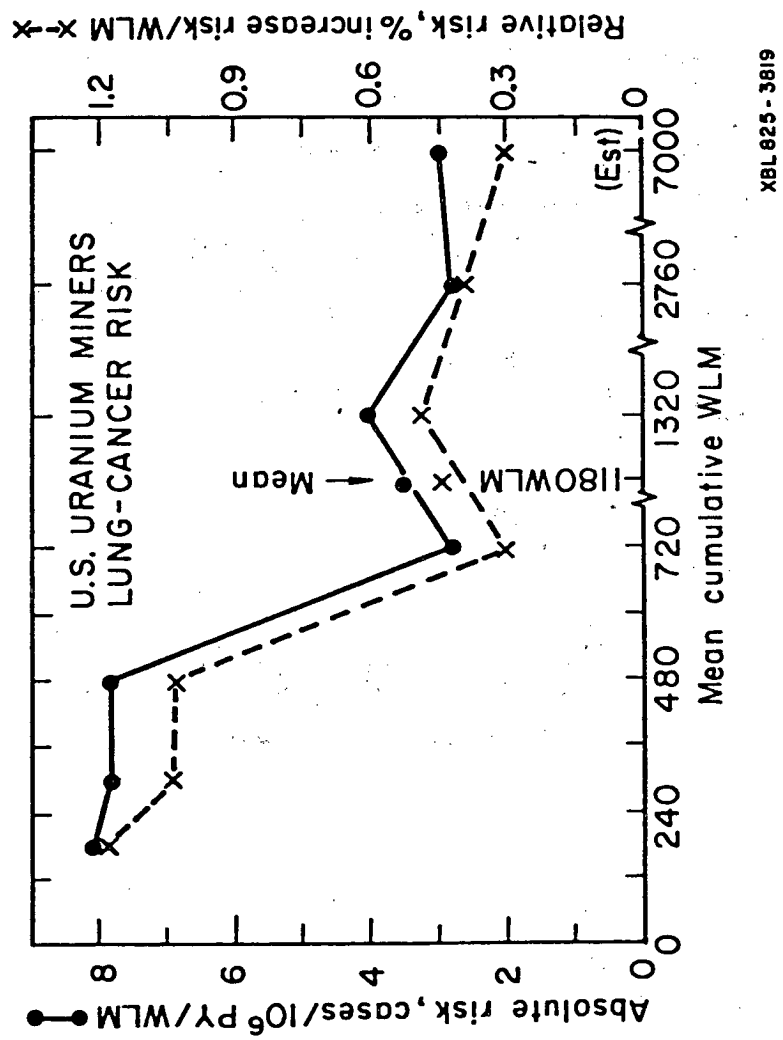

U.S. URANIUM MINERS
LUNG-CANCER RISK
Absolute risk, cases/10^6 PY/WLM
Relative risk, % increase risk/WLM
Mean
1180WLM
(Est)
Mean cumulative WLM
0
240
480
720
1320
2760
7000
2
4
6
8
0.3
0.6
0.9
1.2
XBL 825-3819

Figure 5

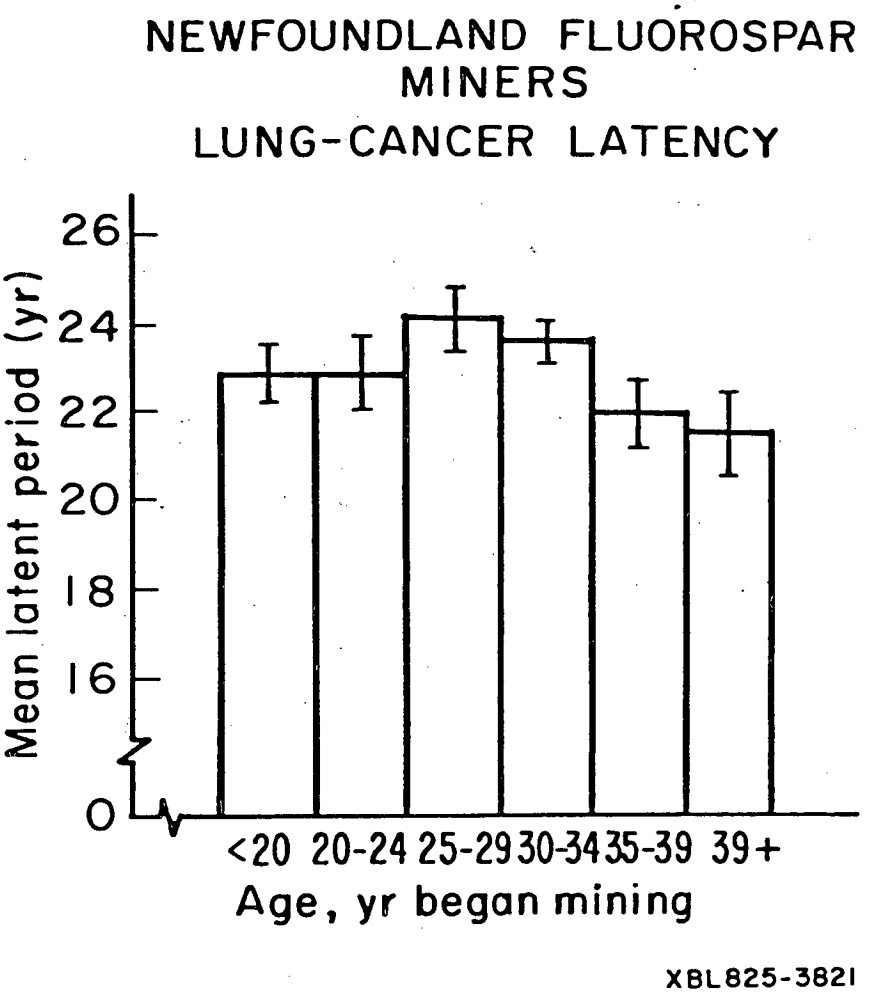

NEWFOUNDLAND FLUOROSPAR
MINERS
LUNG-CANCER LATENCY
Mean latent period (yr)
26
24
22
20
18
16
0
<20
20-24
25-29
30-34
35-39
39+
Age, yr began mining
XBL825-3821

Figure 6

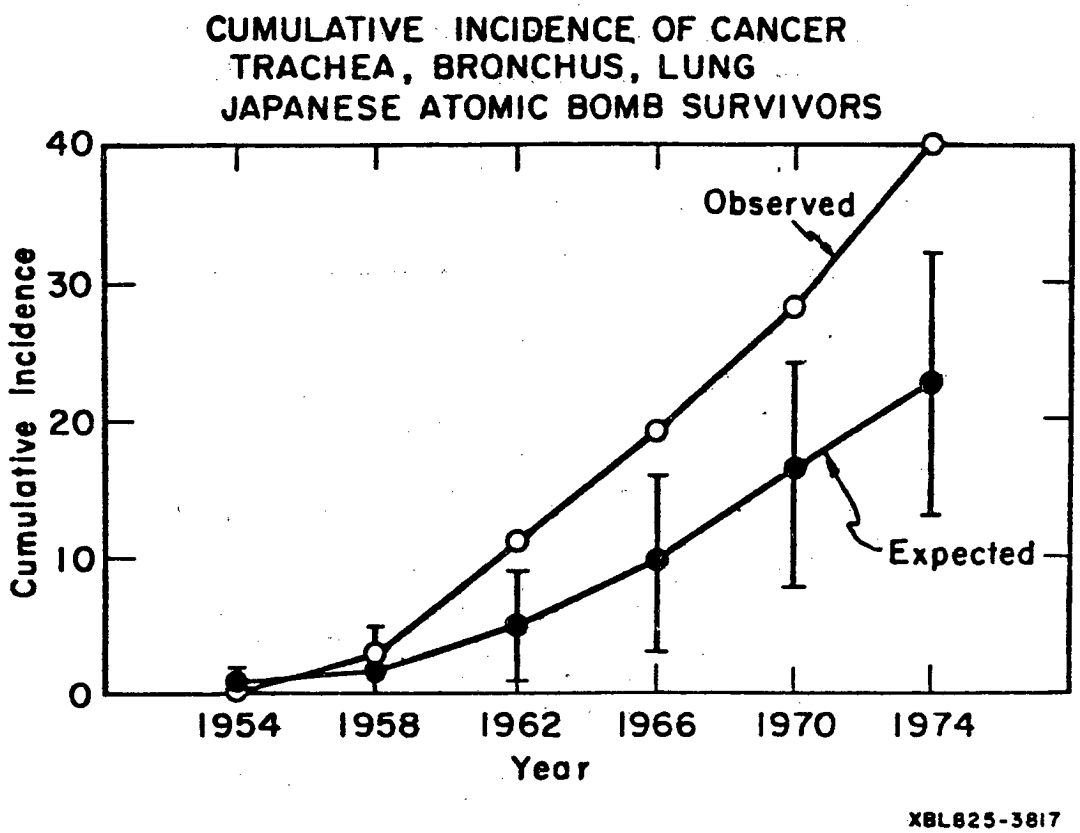

CUMULATIVE INCIDENCE OF CANCER
TRACHEA, BRONCHUS, LUNG
JAPANESE ATOMIC BOMB SURVIVORS
Cumulative Incidence
40
30
20
10
0
Observed
Expected
1954
1958
1962
1966
1970
1974
Year
XBL825-3817

Figure 7

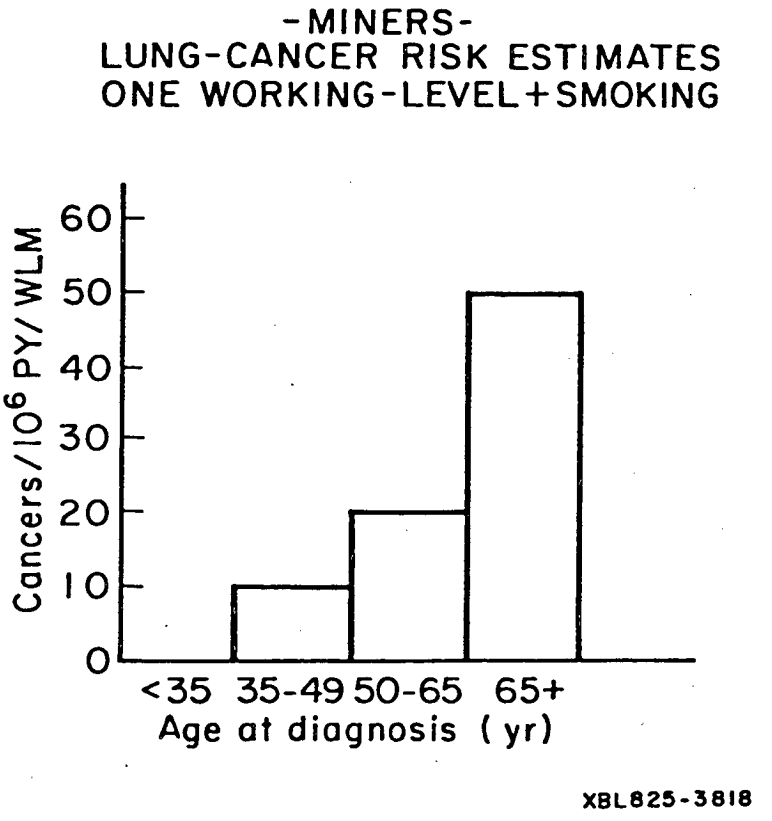

-MINERS-
LUNG-CANCER RISK ESTIMATES
ONE WORKING-LEVEL+SMOKING
Cancers/10^6 PY/WLM
60
50
40
30
20
10
0
<35
35-49
50-65
65+
Age at diagnosis (yr)
XBL825-3818

Figure 8

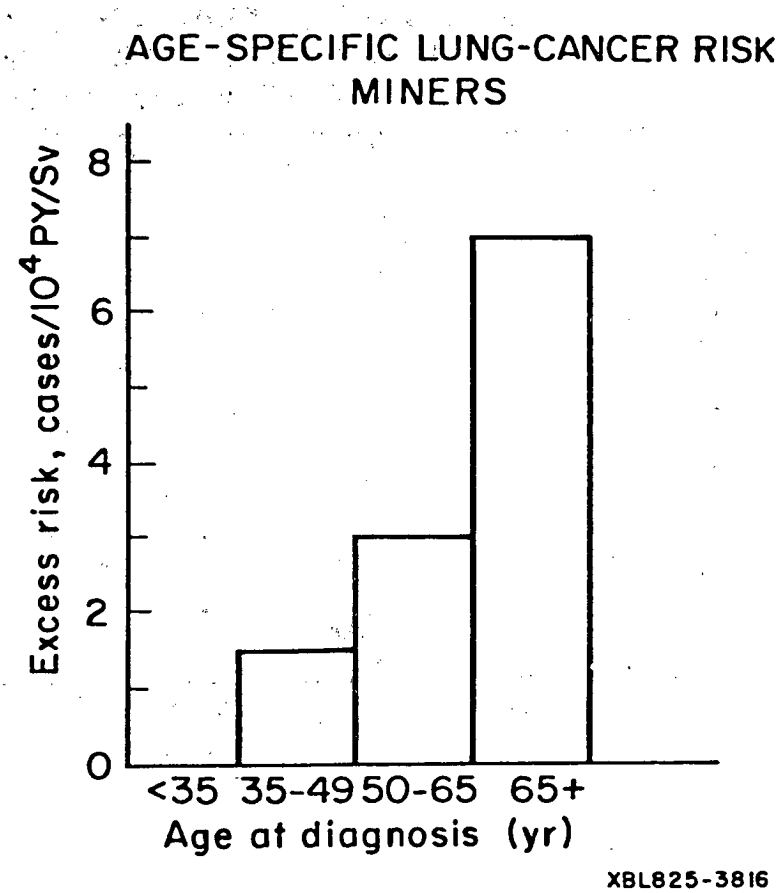

AGE-SPECIFIC LUNG-CANCER RISK
MINERS
Excess risk, cases/10^4 PY/Sv
0
2
4
6
8
<35
35-49
50-65
65+
Age at diagnosis (yr)
XBL825-3816

Figure 9

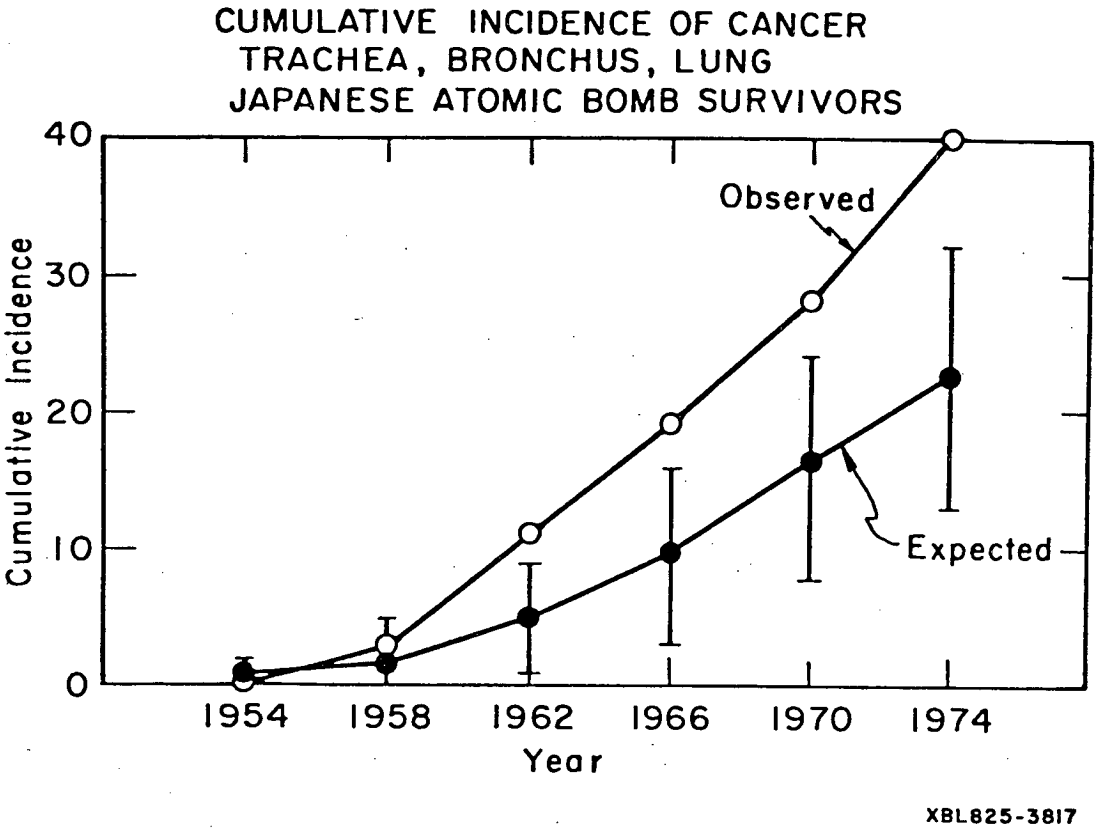

CUMULATIVE INCIDENCE OF CANCER
TRACHEA, BRONCHUS, LUNG
JAPANESE ATOMIC BOMB SURVIVORS
Cumulative Incidence
40
30
20
10
0
Observed
Expected
1954
1958
1962
1966
1970
1974
Year
XBL825-3817

Figure 10

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