EPIDEMIOLOGICAL STUDIES ON RADIATION CARCINOGENESIS IN HUMAN POPULATIONS FOLLOWING ACUTE EXPOSURE: NUCLEAR EXPLOSIONS AND MEDICAL RADIATION[1,2]

LBL--13416

DE82 002950

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DISCLAIMER

1 Presented, as Invited Participant, in Symposium on Effects on Humans of Exposure to Low Levels of Ionizing Radiation, Yale University, School of Medicine, New Haven, CT, May 14, 1981.

2 Supported by the Office of Health and Environmental Research of the U.S. Department of Energy under Contract W-7405-ENG-48 and the Environmental Protection Agency.

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Introduction

My assignment this morning is to provide you with some understanding of our current knowledge of the carcinogenic effect of radiation in man. I think the best thing for me to do is to discuss the contributions of quantitative epidemiology to present knowledge, the reliability of dose-incidence data, and the relevant epidemiological studies of human populations which provide the most useful information for risk estimation of cancer-ind tion in man. To do this, I sha l restrict my discussion to dose-incidence da in humans, and particularly to certain of those epidemiological studies of human populations that are used most frequently for risk estimation for low-do radiation carcinogenesis in man. My emphasis here is placed solely on those surveys concerned with nuclear explosions and medical exposures, leaving others matters of occupational exposures, of high natural background areas, ar of certain special problems with internal emitters. I shall occasionally er to dose-incidence relationships from laboratory animal studies where they may obtain for problems and difficulties in extrapolation from high doses to low doses, and from animal data to the human situation. I shall not deal with specific experimental studies in laboratory animals or with studies at the cellular or molecular levels, nor shall I consider information about mechanisms responsible for cancer-induction or the pathogenesis of radiation-induced neoplasia.

What do We Know About Radiation Carcinogenesis?

The somatic effects of concern at low doses and low dose rates are those that may be induced by mutation in individual cells, singly or in small numbers. The most important of these is considered to be cancer induction. Current knowledge of the carcinogenic effect of radiation in man has been reviewed to two recent reports: the 1977 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation, the 1977 UNSCEAR Report, and the 1980 Report of the National Academy of Sciences Committee on the Biological

Effects of Ionizing Radiations, the BEIR-III Report (1,2). The epidemiological data analyzed in these reports derive mainly from the epidemiological studies of the Japanese atomic bomb survivors in Hiroshima and Nagasaki, from patients in England and Wales treated with X irradiation for ankylosing spondylitis, and from several other groups of people irradiated from external or internal sources, either for medical reasons or from occupational exposure. Both reports emphasize that cancers of the breast, thyroid, hemopoietic tissues, lung, and bone can be induced by radiation. Other cancers, including the stomach, pancreas, pharynx, lymphatic, and perhaps all tissues of the body, may also be induced by radiation. Both reports derive risk estimates in absolute and relative terms for low-dose, low-LET whole body exposure, and for leukemia, breast cancer, thyroid cancer, lung cancer, and other cancers. These estimates derive from exposure and cancer incidence data at high doses (most frequently greater than 50 rems) and at high dose rates (most frequently greater than 50 rems per minute) (1,3). There are no compelling scientific reasons to apply these values of risk per rem derived from high doses and high dose rates to the very low doses and low dose rates of concern in human radiation protection. In the absence of reliable human data for calculating risk estimates at very low doses and low dose rates, neither the UNSCEAR nor BEIR Committees felt confident to predict the reliability of such extrapolation (1-4).

Certain general principles of radiation carcinogenesis have now emerged based on the relatively large number of epidemiological surveys studied. Fristly, the younger the exposed individual, from in utero exposure through adult life, the higher is the risk per rem for induction of most tumors. Secondly, the incidence of leukemia in exposed populations rises above normal within 3 to 5 years of exposure, and returns to spontaneous levels some 15 to 20 years thereafter. The elevated induction rate for solid tumors becomes

apparent after a latent period of 10 to 15 years following exposure in adults, and then persists for an unknown period, in some cancers for over 30 to 35 years. Few irradiated populations have, as yet, been studied for more than 30 years. Thirdly, whereas initially leukemia was considered the most sensitive index of radiation carcinogenesis in man, the excess of solid tumors in irradiated populations now exceeds that of leukemia by a significant factor (1). And lastly, comparison of epidemiological data obtained from human populations exposed to very different dose rates to ascertain whether there is a reduction in risk per rem at low dose rates can not, as yet, be reliably made for different types of neoplasms. In the case of leukemia and for radiation-induced breast cancer, the evidence suggests that there may be little or no dose-rate effect. Fractionation of the total dose given over several years thus far yields excess leukemia and breast cancer risk estimates that are not significantly different from those obtained from single-dose epidemiological surveys (1,2).

What Can We Learn from Dose-Incidence Data in Animals for Extrapolation to Man?

Benign and malignant tumors of almost any type or site may be induced by irradiation in animals. Susceptibility to radiation carcinogenesis varies widely among cells, tissues, organs, and organisms, depending on the influences of species differences, genetic composition, age, sex, physiological state, and other constitutional and environmental factors. Although all ionizing radiations are qualitatively similar in carcinogenic activity, they vary considerably in carcinogenic effectiveness per rad, depending on the dose and on the distribution of the radiation in time and space (1-9).

The dose-incidence relationship for cancer induction has not been characterized sufficiently over a wide range of radiation doses, dose rates, and LET to enable risk estimation at doses, say, below 25 rems. Wide variations

occur in the shapes of the dose-response curves for cancers of different types and for cancers of the same type. The incidence of tumors to be expected under determined exposure conditions cannot be predicted reliably by extrapolation from observations in animals or in man on other neoplasms or other exposure conditions (1-7).

In spite of the uncertainties in dose-incidence relationships, the following important generalizations emerge from the extensive laboratory animal data available. The incidence of cancer is increased by irradiation; the dose-response curve rises with dose up to a certain dose level, above which it may reach a plateau and turn downward with further increase in dose. In the dose range over which the incidence increases with dose, low-LET radiations are usually more effective at high doses and high dose rates than at low doses and low dose rates. In the same dose range, high-LET radiations are usually more effective than low-LET radiations. For high-LET radiations, the effectiveness is influenced less by dose and dose rate, and in some instances, protraction may increase their effectiveness. The relative biological efficiency (RBE) of high-LET radiations tends to increase with decreasing dose and dose rate (1-10). Because of wide species differences in response in laboratory animals, the cancer dose-incidence response for any species cannot provide a reliable basis for direct quantitative risk estimates for cancer-induction in man. Furthermore, variations in the shapes of dose-incidence curves for different radiation-induced neoplasms in laboratory animals confound extrapolation from one type of neoplasm to another, from any one set of exposure conditions to another, or from any one animal species to another, and particularly to man.

What Can We Learn from High Dose Data for Extrapolation to Low Doses?

Because of the difficulty of obtaining reliable cancer incidence data in laboratory animals and in humans for low doses, for purposes of risk estimation

dose-response relationships observed at high doses must necessarily be extrapolated into the low-dose region, where human epidemiological data are not available. It is impossible to ascertain the true shape of the dose-effect curve at low dose levels, and therefore the mechanism of radiation action in the low-dose region (1). Consideration of the spatial and temporal distribution of ionizations suggests that at very low dose levels, the probability of interaction of ionizing events is negligible. Here, the molecular and cellular response to radiation at very low doses must be linear with dose, irrespective of the shape of the dose-response curve at higher doses. It is reasonable, as well, that the dose-response relationship for cancer-incidence at very low doses will be linear, irrespective of the complexity of the carcinogenic process.

The recent conclusions of the BEIR Committee (1), and of the NCRP (9,11), the ICRP (12), and the UNSCEAR (2) Committees, suggest that it is reasonable to assume for low-LET radiation a linear-quadratic dose-response relationship for cancer-induction, with linearity predominating at the very low doses, and to assume linear extrapolation at very low doses for the purpose of human risk estimation. This leads to conservatism, that is, an overestimation of risk. Such extrapolations depend on existing epidemiological data from much higher doses, which are the lowest doses that have been estimated and reliably tested. However, the required human data are not available in the very low-dose region; any low-dose data on man that are available are meager and subject to great statistical uncertainty.

Because of uncertainties in epidemiological studies, serious limitations exist in obtaining reliable and relevant human data, particularly for cancer induction over a wide range of doses, dose rates, and LET. And, because of these limitations, experimental animal studies must provide essential

information; however, human risk estimation cannot be based directly on laboratory animal data. Nevertheless, the evidence suggests that mechanisms of cancer induction in man are similar to those in laboratory animals. It follows, therefore, that while experimental animal data are not quantitatively or directly applicable to man, dose-response relationships in animal studies may be considered for application to human populations exposed to low-level radiation (5,7,9,13).

In recent years, a general hypothesis for estimation of excess cancer risk in irradiated human populations, based on theoretical considerations, on extensive laboratory animal studies, and on limited epidemiological surveys, suggests various and complex dose-response relationships between radiation dose and observed cancer incidence (7,13-16). Among the most widely considered models for cancer-induction by radiation, based on the available information and consistent with both knowledge and theory, takes the complex quadratic form: $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2)\exp(-\beta_1 D - \beta_2 D^2)$, where I is the cancer incidence in the irradiated population at radiation dose D in rad, and α_0, α_1, α_2, β_1 and β_2 are non-negative constants (Figure 1). This multicomponent dose-response curve contains (1) initial upward-curving linear and quadratic functions of dose, which represent the process of cancer-induction by radiation; and (2) a modifying exponential function of dose, which represents the competing effect of cell-killing at high doses. α_0 is the ordinate intercept at 0 dose, and defines the natural incidence of cancer in the population. α_1 is the initial slope of the curve at 0 dose, and defines the linear component in the low-dose range. α_2 is the curvature near 0 dose, and defines the upward-curving quadratic function of dose. β_1 and β_2 are the slopes of the downward-curving function in the high-dose range, and define the cell-killing function. Analysis of a number of dose-incidence curves for cancer-induction in irradiated populations, both in humans and in animals, has demonstrated that

for different radiation-induced cancers only certain of the parameter values of these constants can be theoretically determined. Therefore, it has become necessary to simplify the model by reducing the number of parameters which would have the least effect on the form of the dose-response relationship in the dose range of low-level radiation. Such simpler models, with increasing complexity, include the linear, the pure quadratic, the quadratic (quadratic function with a linear term in the low-dose region), and finally, the multi-component quadratic form with a linear term and with an exponential modifier (1,3,7,9,13-15) (Figure 2).

What Have We Learned from the Epidemiological Studies of Human Populations?

Nuclear Explosions

The most valuable human data available for evaluation of the late effects of radiation come from the studies of the Atomic Bomb Casualty Commission, now in the Radiation Effects Research Foundation, on the Japanese A-bomb survivors in Hiroshima and Nagasaki (17). The continuing evaluation of this population provides the most comprehensive assessment of risk estimates for carcinogenic effect of radiation. The study population is the largest of any epidemiological survey (over 100,000 persons), and these persons were irradiated for other than medical reasons. The A-bomb survivors were exposed at all ages and the radiation doses ranged from a few rads to near-lethal levels.

What are the important questions concerning the mortality experience of the atomic bomb survivors? Is radiation carcinogenesis the only important late effect from the standpoint of mortality? Is the carcinogenic effect a general one, affecting all tissues and histologic types? Are there reliable city differences from which relative biological effectiveness (RBE) estimates can be made? Are Nagasaki data numerous enough to permit any close examination of the functional form of the gamma dose-response curve for specific cancers? Can

further insight be gained into the role of age in 1945 at the time of the bomb upon the carcinogenic effect of ionizing radiation?

These studies are answering the important questions with direct bearing on estimation of the cancer risk in human populations exposed to low-dose levels. The magnitude of risk of induction of all types of solid tumors in relation to dose and time since exposure requires careful evaluation. The excess risk of leukemia following irradiation disappeared by 25 years after exposure; at present, there continues to be a large increase in the radiation-induced cancer death rate during the 10-year period 1965 to 1974, up to 30 years after exposure. This increase is in solid tumor induction; there is presently no indication of a return to normal levels of the mortality rates from these cancers. Other types of cancer are occurring in excess in the surviving irradiated population, due mainly to extremely long latent periods after exposure before these solid tumors are detected. Recently, certain cancers not previously thought to be radiation-induced are appearing in excess in the irradiated population. And finally, the method of radiation action—whether to multiply or to add to spontaneous levels of the cancer death rate—is essential information for projecting the long-term carcinogenic effects in persons irradiated as children or young adults.

Present cancer risk estimates predicted to occur as a result of low-dose exposure of human populations to radiation rely on assumptions about these important questions and on assumptions on the method of extrapolation from human data obtained at high doses to low doses. At the present time, estimated excess cancer rates are derived from observations on Japanese A-bomb survivors of Hiroshima and Nagasaki averaged over the period 1960 to 1974. The excess cancer death rate of these survivors could rise, remain the same, or decrease during the coming years. For leukemia induction in the Nagasaki survivors, the

Life Span Study death certificate data appear consistent with a quadratic dose-incidence relationship (Figure 3). The shape of the Nagasaki curve is considered a strong determinant of the value for the RBE for neutrons derived from the Hiroshima (neutron-rich) and Nagasaki (neutron-deficient) exposures (17).

Another population that received irradiation as a result of a nuclear explosion was the Marshall Islanders, who were exposed to fallout from an H-bomb test explosion in 1954 (18). In this population, the main health effects came from short-lived fission iodine radioisotopes; this has contributed to our knowledge of risk estimates for thyroid cancer following irradiation. However, the data on the Marshallese are difficult to analyze, primarily because their radiation exposures were to a mixture of high dose rate external and internal gamma photons, as well as to beta radiation.

Medical Radiation Exposures

The initial reports of Stewart and her colleagues (19) described an excess of leukemia and all other cancers among children irradiated in utero when their mothers received diagnostic pelvic X-irradiation during the pregnancy. The two largest studies (19,20) indicated that diagnostic pelvic X-ray examinations during pregnancy resulted in an increase of approximately 50 percent in cancer mortality among the children during the first 10 years of life. Because the doses involved an average dose of about 1 rad to the fetus, these surveys are extremely important to radiation protection of the general population. However, failure to confirm these results in the children of the Japanese women who were exposed to atom-bomb radiation in Hiroshima and Nagasaki, and the inability to reproduce the result in laboratory animals, has led to the questioning of whether radiation alone is the etiologic agent in the human surveys (36).

Several other human populations exposed to diagnostic X-rays have been studied. Multiple diagnostic exposure to adult males appears to be associated with the increased risk of developing leukemia (21). The risk estimates for leukemia-induction from this study are similar to those obtained from data at high doses of radiation.

Studies that increase the precision of risk estimates for induction of breast cancer are those of a follow-up of pulmonary tuberculosis patients for whom the treatment of choice prior to 1950 was artificial pneumothorax, which was associated with repeated fluoroscopic exposures. The initial surveys of female patients treated in a Nova Scotia sanatorium between 1940 and 1949 (22,23) indicated that despite the uncertainty of the radiation dose estimates and the extreme fractionation of the total dose, the risk per rad for breast cancer-induction is large and very similar to single-exposure studies, in which high doses were absorbed by the breast tissue (17). These data suggest a number of surveys consistent with a linear dose-incidence relationship (16) (Figure 4).

Important information has been obtained from persons who have been irradiated either externally or by internal emitters for therapeutic reasons. Court-Brown and Doll (24) analyzed the data on leukemia and all other cancers in over 14 000 patients with ankylosing spondylitis who received external irradiation from 1935 to 1954 in the United Kingdom. The leukemia data in these patients are in reasonably good agreement with those from the Japanese A-bomb survivors. Another study of patients irradiated for ankylosing spondylitis and other diseases is that of Spiess and Mays (25,26); here, the patients received intravenous injections of the bone-seeking alpha-emitter radium-224. The evidence indicates that the younger patients are slightly more susceptible to the induction of bone sarcomas for equal protraction periods and that the data are consistent with a quadratic dose-incidence relationship.

Irradiation for medical reasons often introduces uncertainties into the interpretation of data from patients, particularly the potential influence of the disease for which the patients were treated. Furthermore, analysis of the dose-incidence relationships for carcinogenesis by internal emitters is complicated by several sources of uncertainty relating to variations in the spatial and temporal distribution of the dose, which are, in turn, dependent on the uptake, deposition, metabolism, and elimination of the radionuclide (1-8,27). In most patients, the initial dose, dose rate, and patterns of radionuclide excretion are unknown. Furthermore, the radioactivity in these individuals may be deposited nonuniformly in bone, and concentrated in hot spots, where the dose at the center is very much higher than that in surrounding bone (27).

Occupational Exposures

Valuable epidemiological surveys exist on populations of workers exposed as a result of their occupations; these include, for example, uranium and fluorspar miners, radiologists, radium-dial painters, and workers in the processing of plutonium (1-4). Some of these groups have been followed for many years. Important data are available in spite of the complexities of long-term epidemiological studies, such as mobility of populations, nonuniformity of occupational histories, and inadequacy of dosimetry. These studies will be discussed at length by my colleagues in this symposium.

High Natural Background Areas

There are populations exposed to lifetime doses of very high natural background radiation; two are those living in the monazite sands regions of Brazil and India, where they have resided for many generations. Attempts to obtain reliable epidemiological data from these populations have failed due primarily

to the complications of collecting human epidemiological data and further confounded by local cultural, religious, and political practices.

Natural background radiation may vary from one geographic region to the next (1). Attempts to correlate background dose with human epidemiological data are confounded by errors and lack of uniformity in the dosimetric estimates of radiation levels, and by varying quality of vital statistics information among the various communities, states, regions, and countries (1-4). The sources of bias introduced by these factors have thus far been greater than differences that are likely to be of any value.

What Are the Sources of Epidemiological Data for the Estimation of Excess Cancer Risk in Exposed Human Populations?

The tissues and organs about which we have the most reliable epidemiological data on radiation-induced cancer in man, obtained from a variety of sources from which corroborative risk coefficients have been estimated, include the bone marrow, the thyroid, the breast, and the lung (1-2). The data on bone and the digestive organs are, at best, preliminary, and do not approach the precision of the others. For several of these tissues and organs, risk estimates are obtained from very different epidemiological surveys, some followed for over 30 years, and with adequate control groups. There is good agreement when one considers the lack of precision inherent in the statistical analyses of the case-finding and cohort study populations, variability in ascertainment and clinical periods of observation, age, sex and racial structure, and different radiation dose levels, and constraints on data from control groups.

The most reliable data have been those of the risk of leukemia, which come from the Japanese atomic bomb survivors (17), the ankylosing spondylitis patients treated with X-ray therapy in England and Wales (24), the metropathia patients treated with radiotherapy for benign uterine bleeding (28), the tinea

capitis patients treated with radiation for ringworm of the scalp (29), and the early radiologists (30,31). There is evidence of an age-dependence and a dose-dependence, a relatively short latent period of a matter of a few years, and a relatively short period of expression, some 10 years. This cancer is uniformly fatal.

The data on thyroid cancer are more complex. These surveys include the large series of children treated with radiation to the neck and mediastinum for enlarged thymus (32), children treated to the scalp for tinea capitis (29), and the Japanese atomic bomb survivors (17) and Marshall Islanders (18) exposed to nuclear explosions. Here, there is an age-dependence and sex-dependence—children and females appear more sensitive. Although the induction rate is high, the latent period is relatively short, and it is probable that no increased risk will be found in future follow-up of these study populations. In addition, most tumors are either thyroid nodules, or benign or treatable tumors, and only a few are fatal.

Much information has become available on radiation-induced breast cancer in women (33,37). The surveys include primarily women with tuberculosis who received frequent fluoroscopic examinations for artificial pneumothorax (23), postpartum mastitis patients treated with radiotherapy (34), and the Japanese atomic bomb survivors in Hiroshima and Nagasaki (17). Here, there is an age-dependence and dose-dependence, as well as a sex-dependence, the latent period is long, some 20 to 30 years. Perhaps about half of these neoplasms are fatal.

Another relatively sensitive tissue, and a complex one as regards radiation dose involving parameters of the special physical and biological characteristics of the radiation quality, is the epithelial tissue of the bronchus and lung. These surveys include the Japanese atomic bomb survivors (17), the uranium miners in the United States and Canada (35), and the ankylosing

spondylitis patients in England and Wales (24). There is some evidence of age-dependence from the Japanese experience, and a relatively long latent period. This cancer is uniformly fatal.

The risk of radiation-induced bone sarcoma, based primarily on surveys of the radium and thorium patients who had received the radioactive substances for medical treatment, or ingested them in the course of their occupations (26), is low. For all other tumors arising in various organs and tissues of the body, values are extremely crude and estimates are, at best, preliminary.

What Can We Conclude?

Of various somatic effects that might be produced by ionizing radiation at low levels of dose and dose rate, cancer-induction is presently considered to be the most important potential hazard to health in exposed human populations. Studies of irradiated human populations indicate a dose-dependent increase in the incidence of most types of cancer. The dose-response relationships for these cancers are consistent with a range of linear, linear-quadratic and quadratic relationships between cancer incidence and dose. The data on the influence of dose rate in man are limited and at present fail to indicate a reduction of risk per rad with decreasing dose rate. The available dose-incidence data suggest an age-dependency and a sex-dependency; the overall susceptibility appears higher in children than in adults.

All tissues of the body are susceptible to cancer-induction by radiation. The epidemiological data are inadequate to define the dose-response relationships at doses below 25 to 50 rems. Data for high-LET radiation are only fragmentary; these suggest a high RBE with little change in effectiveness per rad with decreasing dose and dose rate. Data for low-LET radiation, on the other hand, generally show decrease in the effectiveness per rad with decreasing dose and dose rate.

Numerical estimation of the risk of radiation-induced cancer in man must necessarily be based primarily on human dose-incidence data. However, risk estimation at very low doses and low dose rates at present must also necessarily depend on extrapolation from observations at higher doses and higher dose rates, based on assumptions about the dose-incidence relationships and the mechanisms of carcinogenesis. Improvements in our knowledge of the carcinogenic effectiveness of ionizing radiation will depend on the elucidation of mechanisms of carcinogenesis, especially at the very earliest stages of malignant transformation, and on the provision of empirical dose-incidence data for low doses both in human populations and in laboratory animal experiments, insofar as this is possible.

And finally, we must conclude that the estimation of the carcinogenic risk of low-dose, low-LET radiation is subject to numerous uncertainties. The greatest of these concerns the shape of the dose-response curve. Others include the length of the latent period, the RBE for fast neutrons and alpha radiation relative to gamma and X-radiation, the period during which the radiation risk is expressed, the model used in projecting risk beyond the period of observation, the effect of dose rate or dose fractionation, and the influence of differences in the natural incidence of specific types of cancer. In addition, uncertainties are introduced by the biological risk characteristics of humans, for example, the effect of age at irradiation, the influence of any disease for which the radiation was given therapeutically, and the influence of length of observation or follow-up of the study populations. The collective influence of these uncertainties is such as to deny great credibility to any estimates of human cancer risk that can be made for low-dose, low-LET radiation. Nevertheless, despite all the uncertainties I have chosen to

discuss, there is greater knowledge of the risks of radiation than of any other potentially hazardous physical or chemical agent in the environment.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the generous assistance of his many colleagues in epidemiology, statistics, and the radiation sciences, and from whose labors and works he has drawn on for this presentation. He thanks Mrs. Diana Morris for her generous help in the preparation of this manuscript. This work was supported by the Director, Office of Energy Research, Office of Health and Environmental Research of the U.S. Department of Energy under contract No. W-7405-ENG-48.

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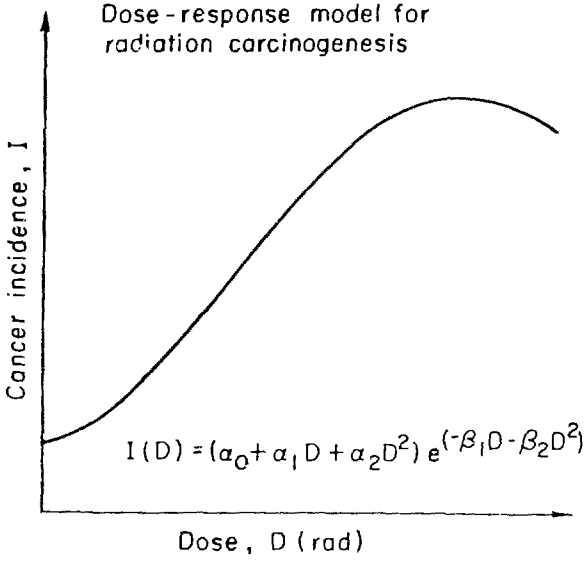

Figure 1

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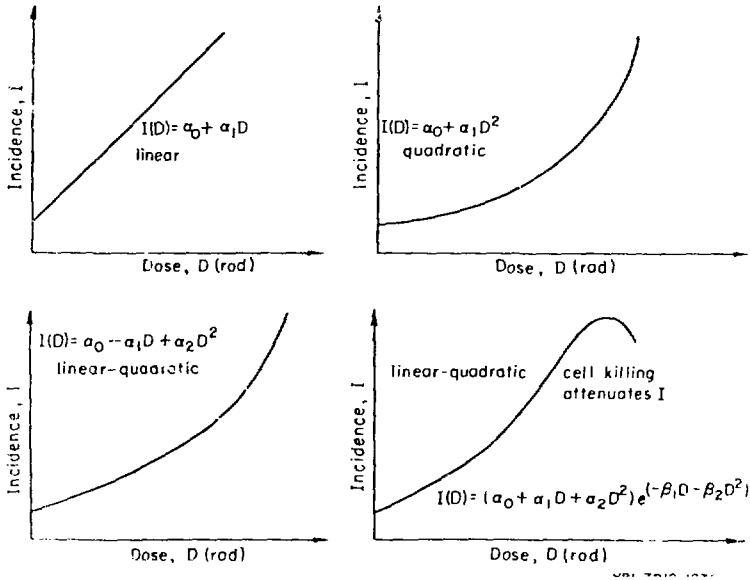
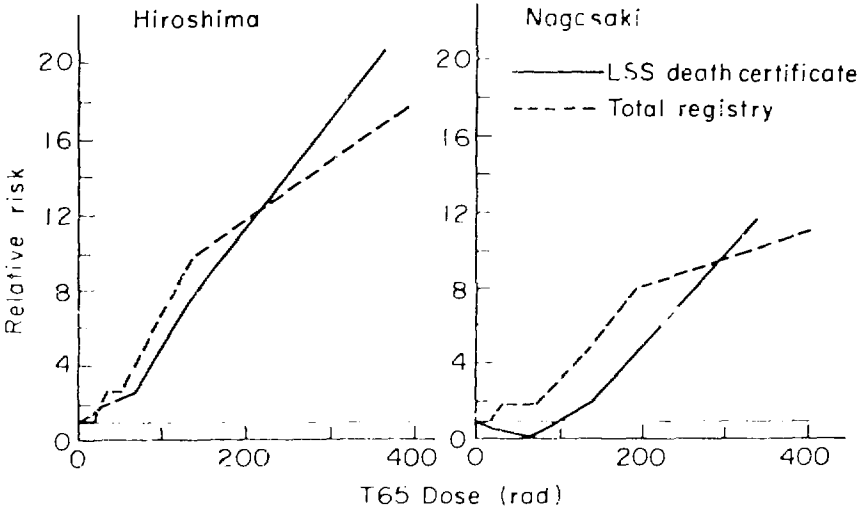
SHAPES OF DOSE RESPONSE CURVES




Hiroshima
Nagasaki
LSS death certificate
Total registry
Relative risk
0
4
8
12
16
20
0
200
400
T65 Dose (rad)

XBL 815-3791

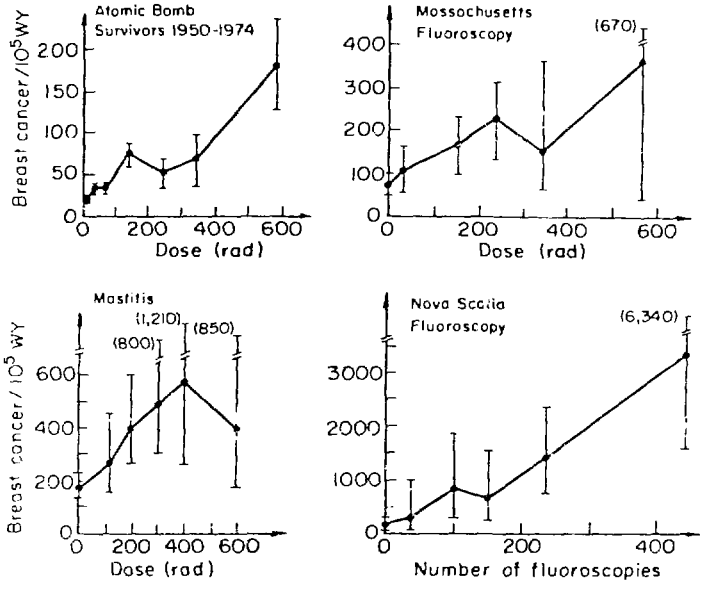


Figure 4

XBL815 3792