LBL-14198

Conf-820655--4

# Lawrence Berkeley Laboratory

UNIVERSITY OF CALIFORNIA

Presented as an Invited Speaker at the 27th Annual Meeting of the Health Physics Society, Las Vegas, NV, June 27-July 1, 1982

THE HEALTH EFFECTS IN WOMEN EXPOSED TO LOW LEVELS OF IONIZING RADIATION

Jacob I. Fabrikant

June 1982






Prepared for the U.S. Department of Energy under Contract DE-AC03-76SF00098

LBL-14198

# THE HEALTH EFFECTS IN WOMEN EXPOSED TO LOW LEVELS OF IONIZING RADIATION[1,2]



Jacob I. Fabrikant, M.D.,Ph.D.[3,4]
Lawrence Berkeley Laboratory
Donner Laboratory
University of California
Berkeley, California

and

Department of Radiology
University of California School of Medicine
San Francisco, California



[1]Presented as Invited Speaker, 27th Annual Meeting of the Health Physics Society, Las Vegas, Nevada, June 27-July 1, 1982.

[2]Research supported by the Office of Health and Environmental Research of the U.S. Department of Energy under contract No. DE-AC03-76SF00098.

[3]Professor of Radiology, University of California School of Medicine, San Francisco, California.

[4]Mailing Address: Lawrence Berkeley Laboratory, Donner Laboratory, University of California, Berkeley, CA 94720.

INTRODUCTION

The potential health effects of exposure to ionizing radiations have been the concern of the scientific community for more than five decades. The oldest of the scientific bodies that now have responsibility for radiation health and public policy are the International Commission on Radiological Protection (ICRP) formed in 1928, and the National Council on Radiation Protection and Measurements (NCRP), the American organization formed in 1929 as the Advisory Committee on x-ray and Radium Protection. The president and the driving scientific force of the NCRP for half a century, who more than any scientist has contributed more to the continued study of radiation protection problems that are of special relevance to our discussion, was Dr. Lauriston S. Taylor, Sr., the man we honor today.

During the deliberations of the recent 1977 UNSCEAR Committee [1] and the 1980 BEIR Committee [2], it was apparent that a number of important observations on radiation and health emerged over the past decade. Three are noteworthy in our concern of radiation health effects in women. First is the matter of dose-response relationships and low-dose exposure. It is not yet possible to estimate precisely the risk of cancer-induction by low-dose radiation. This is because the degree of risk is so low that it cannot be observed directly, and there is great uncertainty as to the dose-response function most appropriate for extrapolating in the low-dose region [1,2].

Second is the matter of the sex-dependency of radiation-induced cancer. The incidence of radiation-induced breast cancer and of thyroid cancer are such that the total cancer risk is greater for women than for men [2,3]. Radiation-induced breast cancer occurs almost exclusively in women, and absolute risk estimates for thyroid-cancer induction by radiation are higher for women than for men, as is the case with the natural incidence [2].

Third is the matter of low-dose radiation and the pregnant woman. This situation requires special consideration for radiological protection, both for women in the general population and in the workplace. There are implications concerning exposure of women in the childbearing age, the radiation-induction of developmental abnormalities in the newborn [2], and possibly childhood cancers [2,3].

There are other potential delayed or late health effects of radiation which may be of importance to women, such as the special sensitivity of the oocyte, or certain sex-linked genetically-related health effects. However, the three which appear to have importance at the present time in radiological protection are: (1) the probability of cancer-induction at low doses and low-dose rates; (2) the consideration of those cancers in women, notably the breast and the thyroid, attributable to radiation exposure; and (3) the probability of induction of developmental abnormalities in the newborn following low-dose exposure of pregnant women.

## DOSE-RESPONSE RELATIONSHIPS

Until the 1950s it was commonly assumed that only high-dose radiation exposure caused cancer. Unless the exposures were high enough to cause clinically detectable damage to the irradiated tissues with consequent tissue disorganization, cancer would not occur. That assumption is now considered incorrect; low-dose radiation can cause cancer, although the dose-response relationships at low-dose levels are not known with certainty. There exists a finite risk of cancer-induction at lower doses, and there is no apparent threshold dose below which exposure to radiation can be considered without risk. This has now been recognized during the past 20 years, primarily because radiation-induced cancers do not differ in any known way from those occurring naturally or those caused by other carcinogenic agents.

The 1980 BEIR Report [2] dealt with the health effects on human populations of exposure to low-dose radiation; the Report [2] also reviewed the epidemiological surveys at intermediate and high-dose levels. This was necessary to provide the epidemiological data base from which to extrapolate, if considered permissible, from higher levels to the lower intermediate and low-level dose ranges, below perhaps 0.2 Sv. Among the major conclusions on the carcinogenic risk of low-dose radiation, five stand out. (1) Cancer is the principal late somatic effect of ionizing radiation exposure in human beings. (2) There is a sex-dependency and age-dependency, as well as a dose-dependency for radiation carcinogenesis. (3) The scientific base at the present is inadequate to estimate directly from the epidemiological data the precise carcinogenic risk of low-dose, low-LET radiation, primarily because the occurrence of excess cancers induced is extremely rare at low doses. (4) A dose-rate effect may affect the risk of cancer induction, but the human data base is inadequate to allow for a dose-rate correction in epidemiological surveys. However, in the low-LET, low-dose range, say below 0.05 Sv, there is no need for a dose-rate correction. (5) Organs and tissues of the body differ in their susceptibility to carcinogenic effects of radiation.

Leukemia was the first cancer associated with exposure to ionizing radiation. Cancer may be induced by radiation in most tissues, and the radiation risk of inducing solid tumors now exceeds that of leukemia. The major cancer sites affected are the breast in women, and the thyroid, lung and digestive organs in both sexes [1,2]. Solid tumors have a longer latency period, 10 to more than 30 years, than the few years before the excess risk for leukemia becomes manifest. The total cancer risk from radiation is greater in women than in men, principally because of the contribution of breast cancer, and to a lesser extent, thyroid cancer [3].

The important epidemiological surveys are the Japanese atomic-bomb survivors in Hiroshima and Nagasaki [6,7], patients exposed to medical radiation [9-11], and occupational groups, such as uranium miners [12] and radium watch dial painters [13]. Some disagreement persists in the field of radiation epidemiology and cancer, but not in laboratory animal studies, over the appropriateness of data from high-exposure human populations for estimating low-level cancer risks [4,5].

Extrapolation from High-Dose Epidemiological Data

It is still not certain which method may be used for extrapolating from the measured effects of high doses of ionizing radiation, to the most probable effects at low doses [4,5]. For example, the 1980 BEIR Committee [2] had both diverging and changing opinions on this point [4]. Members of the Committee felt that for low-LET radiation at low doses, the linear dose-response model overestimated the risk and the pure quadratic model, which estimates a lower risk, could be used as a lower bound (Figure 1). Nevertheless, some members felt that the linear model, which assumes that dose and effects are proportional at all dose levels, was the most accurate dose-response relationship. In general, most members agreed that the linear-quadratic model was most appropriate for estimating the cancer risk from low-dose, low-LET, whole-body radiation; the linear model produced the highest risk estimates, the quadratic model the lowest, and the linear-quadratic model estimated an intermediate risk [2]. Depending on which dose-response and risk projection models are used, estimates of mortality from all forms of cancer may differ by about one order of magnitude. However, they differ only by a factor of two between the linear-quadratic and the linear dose-response relationships (Table 1).

The main cause of damage to the cell from ionizing radiation is thought to be the production of double strand breaks in the DNA molecule resulting from the production of ions or free radicals which interact with these macro-molecular targets [14]. The chances of two breaks occurring simultaneously in the DNA molecule is much less for low-LET radiation than for high-LET radiation. As a consequence, many biological systems show a curvilinear response (I, incidence) for low-LET radiation as a function of the dose (D) of the form $I(D) = \alpha_0 + \alpha_1 D + \alpha_2 D^2$, where $\alpha_0$ is the spontaneous cancer rate in the population, and $\alpha_1$ and $\alpha_2$ are positive constants [15]. At low doses and low dose rates, successive traversals of the cell may interact, and the response increases with approximately the square of the dose. If an effect with a curvilinear dose-response relationship is observed in a population at high doses, and information is required on the incidence of such effects at low doses, then a linear fit is likely to overestimate the risk at lower doses. For high-LET radiation, however, the dose-response conforms to a linear nonthreshold relationship and varying little with dose rate [15].

Risk-Projection Models

An absolute-risk projection model implies that the risk of cancer-induction at a given age is the sum of the spontaneous risk at that age plus a constant dose-dependent increment that may be related to age at exposure, but not to age at the time of observation (Figure 2). The difference between the risk of exposed persons and the risk for nonexposed persons remains constant over time. A relative-risk projection model expresses the cancer risk at a given age as the product of the age-specific spontaneous risk and a factor that depends on dose and age at exposure (Figure 2) [2].

It is by no means known whether the cancer risk from radiation at low doses would have an absolute or additive effect, or a relative or multiplicative effect on the spontaneous cancer rate. This is because the mechanisms of carcinogenesis remain poorly understood. It is reasonable to estimate excess cancer risk in both absolute terms and in relative terms. The relative risk approach assumes that the excess cancer risk increases gradually and continuously, and proportional to the spontaneous cancer risk, which increases with age for nearly all cancers. The absolute risk approach assumes a constant number of additional cancers throughout life. It is not known which risk projection model is correct for radiation carcinogenesis; it could be that neither applies to the situation of low-level radiation and cancer.

Atomic-Bomb Dosimetry and Low-Dose Exposure

The entire basis for the Japanese atomic-bomb dosimetry is now under restudy [16]. There has been some concern that the TD65 dosimetry system developed at the Oak Ridge National Laboratory and used at the ABCC-RERF since 1965 may prove to be incorrect and that revisions will grossly alter the risk estimates. The early indications, which are far from any final reassessment of dose estimates, are that a reduction in the neutron radiation component of the Hiroshima bomb doses may be required, with some compensating increase in the gamma radiation component. Any changes in the Nagasaki bomb doses would be far less extensive. Until present uncertainties are resolved, and this may take a number of years, no precise conclusions can be drawn as to the effect of any necessary changes. The present indications are that low-dose, low-LET radiation risk estimates will not change uniformly for the various effects, but in some instances may be doubled under the linear or linear-quadratic models of dose-response.

EPIDEMIOLOGICAL STUDIES

For most organs and tissues, evidence of radiation-induced cancer has depended upon prolonged and accurate surveillance of large groups of people who have been exposed in the past to known amounts of radiation [2]. Since the mid-1940s there have been a number of epidemiological studies that now form an adequate basis for estimating radiation risks for the general population and for those occupationally exposed. They provide information on the effects of external radiation, and of internal radiation of certain organs and tissues. The data from these epidemiological surveys are mutually consistent; this is because of the wide confidence intervals that must be attached to the results of any epidemiological study. The magnitude of the uncertainties involved has decreased with time and with improved epidemiological data bases and statistical analyses. Ten years ago, at the time of the 1972 BEIR-I Report [17], agreement to within a factor of ten from two different epidemiological studies was considered remarkable; more recently, agreement to within a factor of two has commonly been obtained [3].

When the analyses and results of these many epidemiological studies are combined, assuming a simple linear dose-response relationship for most organs and tissues, to derive estimates of the lifetime cancer risk for both fatal and nonfatal cancers at various sites, four important observations emerge (Table 2). (1) The largest single lifetime risk of cancer induction per unit dose per million persons exposed is the breast in females. (2) The lifetime risk of nonfatal thyroid cancer induced per unit dose per million persons exposed far exceeds all other nonfatal cancers combined. (3) The total number of cancer cases induced in females exceeds that in males by

about 50% due primarily to breast and thyroid cancer. (4) These linear risk estimates overall can be applied to values for the average annual doses from various sources of exposure to calculate approximate values for the number of cancers attributable to radiation in a population.

BREAST CANCER

The female breast is now considered one of the tissues most susceptible to radiation-induced cancer [2]. The evidence is derived from epidemiological studies of women exposed to multiple fluoroscopic chest examinations during treatment for tuberculosis [9,18-20], of Japanese women atomic-bomb survivors in Hiroshima and Nagasaki [21], and women given x-ray treatment for postpartum mastitis and other benign breast diseases [22]. The dependence of breast-cancer risk on radiation dose varies with age at exposure; the age-specific data are generally too sparse for fitting any but the simplest linear dose-response functions [2]. Figure 3 shows the observed adjusted rates, standardized with respect to its own age distribution, plotted against breast tissue dose in rads [20] for the Japanese women in the Life Span Study series adjusted for city [7], the Massachusetts fluoroscopy series [9], and the New York postpartum mastitis series [22]; the crude rates from the Nova Scotia tuberculosis series [20] are plotted against the number of fluoroscopic examinations.

The generalization that at low doses and low dose rates, low-LET radiation would be less damaging because of repair processes operating in cells [14] is not supported by the epidemiological data on radiation-induced breast cancer. In the Japanese atomic-bomb survivors [21], the patients with post-partum mastitis [22], and in the tuberculosis sanitoria patients [18-20], there were very different patterns of exposure---acute single, repeated, and

highly fractionated exposures. However, the dose-response relationships were essentially linear in all studies suggesting, at least for breast cancer, relatively complete additivity of dose and little repair of radiation damage at low dose rates. The risk estimates overall based on linearity range approximately 6.0-8.5 excess breast cancers per $10^4$ women-years per Sv [2]. The fact that multiple low-dose exposures did not produce fewer breast cancers per unit dose than did a single exposure suggests that radiation damage may be cumulative and that highly fractionated radiation is approximately as effective in inducing breast cancer as unfractionated radiation [20].

Age at the time of exposure appears to be an important host factor for radiation-induced breast cancer [2]. For women first exposed between ages 10 and 39 years, the data from the Japanese atomic-bomb survivors [21], the tuberculosis-fluoroscopy survey [9], and the post-partum mastitis series [22], suggest a substantial radiation risk with evidence that breast tissue may be more susceptible to cancer-induction if irradiation occurs at times of breast proliferation, such as at menarche or during pregnancy. In addition, the latent period between radiation exposure and diagnosis of cancer caused by that exposure does not appear to depend on dose, but it does depend strongly on age at exposure. The minimal latent period may be as short as five years for women 25 years old or older at exposure; the maximal latent period may be greater than 30 years [2].

Estimates of breast cancer risk appropriate for low-dose exposures of normal breast tissue of American women may be divided into two groups: 10-19 years and 20+ years of age at exposure (Table 3). The absolute-risk projection model estimates decrease with age at exposure; this reflects the decreasing expected

number of years of life after exposure. The relative-risk projection model estimates decrease more slowly with age at exposure; this reflects the increasing average natural breast-cancer risk per year over these remaining years of life [2].

THYROID CANCER

The epidemiological surveys on radiation-induced thyroid disease have come mainly from a variety of medical procedures used between about 1925 and 1955. The radiation procedures included scalp irradiation for ringworm [11,33], chest irradiation for enlarged thymus [24], chest irradiation for whooping-cough, head and neck irradiation for enlarged tonsils and adenoids, and skin irradiation for acne and hemangiomas [26], and the use of radioiodine for thyroid disease [27,28]. The large population of Japanese atomic-bomb survivors in Hiroshima and Nagasaki [29] and a smaller group of Marshall Islanders [30] exposed to atomic explosions or nuclear fallout have been studied in detail.

Modifying factors in radiation-associated thyroid neoplasia include biological characteristics, such as sex, age, ethnic background, and latency and incidence [1,2]. All have considerable effect on risk estimates derived from the numerous reported series in the epidemiological literature. (T) There is a greater predominance of thyroid neoplasia in females, as is the case with almost all thyroid disease [1,2]; there may be as much as a four-fold difference in the radiation induction of thyroid neoplasia between sexes. This sex-dependency noted in patients treated with thymus irradiation during infancy, in children who received scalp irradiation for tinea capitis in Israel, the Marshall Islands population exposed to fallout, and the Japanese atomic-bomb survivors. The excess among females is not fully understood.

It is probably related to the fluctuating hormonal status in females; there are considerably greater variations in the pituitary-thyroid axis relationships and in secretion of thyroid-stimulating hormone in females than in males. Other hormonal interdependencies of the thyroid gland in the endocrine system may also be involved. (2) Hereditary-familial background may be a significant moderating factor. There appears to be an increase in susceptibility to radiation-induced thyroid neoplasia in persons of Jewish descent, and here, too, a predominance appears in females [2]. The Rochester thymus-irradiation patients and the Israeli tinea capitis patients were predominantly Jewish, and these studies confirm the increased risk of thyroid cancer induction in persons of Jewish descent, and particularly in females.

The minimal latent period for radiation-induced thyroid neoplasia is about 10 years; there is frequently a peak incidence of thyroid carcinoma induction 15-25 years after irradiation [2]. Only a small fraction of thyroid neoplasms are malignant; cancer risks, therefore are usually given for incidence, because the mortality rate from thyroid cancer is extremely low. The epidemiological data suggest that thyroid cancer induction by external photon irradiation at high dose rate is a linear, nonthreshold, dose-response relationship. Ranges of external radiation dose of from 0.065 Gy to 15 Gy have been associated with the induction of thyroid carcinoma [2], and this lower dose may be in the range of some currently used diagnostic radiologic studies. The thyroid cancer risk estimates approximately 4 excess cases per $10^4$ PY per Gy for doses up to 10 Gy and perhaps down to 0.065 Gy. For benign thyroid adenomas, the absolute risk is estimated to be about 12 excess cases per $10^4$ PY per Gy [2].

DEVELOPMENTAL EFFECTS IN THE EMBRYO AND FETUS

Radiation exposure during pregnancy and the risk of induction of developmental effects in the embryo and fetus are special situations; Radiological protection standards must take into account occupational exposure of women and the increased susceptibility of the unborn child. The developmental effects of radiation on the embryo and fetus are related to the gestational stage at which exposure occurs [2,31]. While information on such effects has been derived primarily from laboratory animal studies, even the sparse human data are now sufficient to indicate quantitative correspondence for developmentally equivalent stages [2,32].

The atomic-bomb data for Hiroshima presently show that the frequency of small head size associated with mental retardation was significantly increased by an air kerma dose of 0.1 to 0.49 Gy received during the sensitive period. There are indications that an air kerma dose of 0.01 to 0.09 Gy was damaging to embryos that were in susceptible stages of development at the time of the bombing. It has been assumed that part of the effect was attributable to the neutron dose, since no significant increase in small head size was detectable below 1.5 Gy kerma in the much smaller Nagasaki sample. The present reassessment of the Hiroshima and Nagasaki atomic-bomb dosimetry will alter this assumption, since the neutron component of the Hiroshima bomb was less [16].

It appears that measurable damage in the embryo and fetus can be caused by doses well below 0.1 Gy of acute irradiation applied at gestational stages that are susceptible [2]. There may be threshold doses for most developmental abnormalities, and these levels are of a variety of magnitudes. Lowering the

dose-rate leads to a decrease in the induction of developmental effects. Because sensitive stages for many specific abnormalities are relatively short, dose protraction may result in lowering the dose to below the threshold the portion of the total dose that is received during a particular susceptible period [2].

The dose-response relationships for specific developmental abnormalities would likely be curvilinear with dose, and perhaps sometimes with a threshold. For risk estimation purposes, however, linear nonthreshold curves are more appropriate, suggesting stochastic events at the biophysical level of the cell for teratogenic effects, although gross developmental abnormalities are usually considered as nonstochastic effects, and are graded for severity rather than for frequency. The latest information from the RERF concerning severe mental retardation in children exposed in utero has considerable bearing on this problem. The data from Hiroshima and Nagasaki, now brought up to date for the age of gestation at exposure and exposure level, according to the most recent 1981 ORNL air-dose projection estimates, are based on tentative atomic-bomb dosimetric reassessments [33]. These estimates are corrected for tissue absorption, but not for structural shielding or tissue shielding.

The data suggest that the age of gestation at 10-17 weeks appears to be the period of very high sensitivity for the induction of severe mental retardation (Table 4). This is marked at Hiroshima at all dose levels, and less so at Nagasaki. An uncorrected incidence of mental retardation of 3.6% is identified in the 0.01 to 0.09 Gy group at Hiroshima; the controls, which include individuals "not in city" at the time of bombing, or who

received less than 0.01 Gy fetal dose, have an incidence of 0.0 %. These incidences are not profoundly affected when the data are combined for the two cities, and represents a factor of 2 to 4 times that of the total severe mental retardation incidence when the cities-combined are analyzed [34].

While these data are preliminary, three important points emerge which impact on radiological protection. (1) First, the changes in the atomic-bomb TD65 doses may lead to an upward reassessment of the low-LET risk estimates derived from the Japanese data. For purposes of radiological protection, it would be necessary to assess the occurrence of much lesser degrees of mental retardation for which the Japanese atomic-bomb survivor records exist. Small head size and mental retardation in humans are endpoints of gross developmental abnormality representing very severe health detriment. It is possible that more subtle changes, even in biochemical systems in the central nervous system or elsewhere, continue to go undetected. (2) Second, no other radiation-induced malformations have been quantified, or even observed in human beings. Such considerations would apply to other developmental malformations, which could be expected on the basis of extensive laboratory animal experiments. (3) Third, the weight of health detriment that must be assigned to severe mental retardation must be considered from a societal point of view, at least comparable and perhaps greater than that of a fatal cancer.

CHILDHOOD CANCER FOLLOWING EXPOSURE IN UTERO

The carcinogenic effect of small 0.01 to 0.02 Gy doses to the embryo or fetus has been a controversial issue since Stewart and her colleagues [35] first published their initial results from the Oxford Survey of Childhood Cancers. The controversy stems from the apparent absence of parallel findings in

laboratory animal experiments [32], and from two important biases in the retrospective survey: (1) the possibility of better recall of their x-ray history by mothers of children who died of cancer than by mothers of healthy control children; and (2) the possibility that one or more characteristics of the mother that led to the abdominal, obstetrical, or pelvimetric x-ray examination may be correlated with the chance that her child will die of cancer. The study by MacMahon [36] on prenatal x-ray exposure and childhood cancer eliminated the first source of bias and gave initial support for the causal role of radiation in the higher incidence of childhood cancer among those exposed in utero. Jablon and Kato [30] demonstrated that the Japanese atomic-bomb data, which are free from the two sources of bias which confounded the Oxford Survey study, on survivors exposed in utero were inconsistent with the increased risk estimates reported by Stewart [35].

There presently remains some skepticism about the matter of the conclusions of the Oxford Survey and the low-dose effects of in utero exposure for five reasons. (1) Experimental animal confirmation is lacking. (2) Other human experience, such as the Japanese atomic-bomb survivors, is lacking. (3) Selection bias remains in the Stewart [35] and initial MacMahon [36] evidence of relationship between prenatal irradiation and childhood cancer. (4) Two subgroups of the study populations, singletons and twins, manifested the same degree of carcinogenic effect but had very different frequencies of in utero x-radiation [37]. (5) The expected cancer mortality rate of 1 in 1200 by age 10 years is such that an etiological factor associated with medical indications for pelvimetry would not have to be very common to increase the mortality risk by

40% as suggested by Stewart [32]. The claim of Stewart and Kneale [38] that low-dose in utero irradiation increased the frequency by the exact same amount of each of six different classes of childhood leukemia which normally differ markedly in their epidemiologic characteristics appears implausible [39]. Indeed, MacMahon [40] has now expressed doubt as to the causality of the relationship of low-dose carcinogenic effects of in utero irradiation.

## WHAT CAN WE CONCLUDE ABOUT THE RELATIONSHIPS OF THE RADIATION RISKS OF LOW-DOSE EXPOSURE IN WOMEN?

As new information becomes available from the current epidemiological surveys on the radiation risks of low-level exposure, we will continue to refine our direct estimates of low-dose risk. However, for all epidemiological studies, the population sizes necessary to provide statistical stability must be very large, and the results of any present epidemiological surveys would give such refinements little practical value. However, such studies provide us with the human data necessary for testing the alternative dose-response models, for understanding the response to dose-rate, dose-fractionation, and continuous low-dose exposure, and the influence of sex, age, genetic variability and other biological characteristics.

While such definitive risk estimates may be forthcoming sometime in the future, determination of public policy cannot wait. Any practical approach to radiological protection in the foreseeable future compels two important conclusions: (1) We must adopt dose-response functions that provide us with the means to estimate low-level radiation risk. (2) We must base our social, economic and health decisions and radiation protection standards of

dose-limitation on those estimates of risk. We have done this effectively during the past two decades. For example, while the weight of the experimental laboratory animal data generally favor a linear-quadratic dose-response model for low-LET radiation for both somatic and genetic injury, extrapolation from mouse to man is hazardous, and interpolation from high dose data to the low-dose situation is difficult and precarious. For breast cancer and thyroid cancer, at least, the animal data are complex and do not apply readily to the human situation; and the human data provide fairly strong support for the linear dose-response model.

Furthermore, in all epidemiological surveys, the levels of uncertainty are high. Where human life and health are the central concern, and in radiological protection these are precisely the concern, a conservative position is essential. Thus, the linear dose-response model is indicated, since the scientific uncertainty about all dose-response models chiefly concerns the dose-response region below the linear regression line. For the purposes of radiological protection, the linear model provides three important advantages over other models. First, it does not require observations over a wide range of dose for organs, for tissues, and for whole-body exposures. Second, it can use all available data representing different exposure situations and populations. Third, for low-LET radiations, about which we are most concerned, it is conservative, that is, it overestimates the risk.

The observation that women are at greater risk than men to low-dose radiation is primarily derived from studies of carcinogenesis. The matter of exposure in utero is a special case, since it has implications for radiation

protection of women in the child-bearing age. Such recommendations of radiation protection based on dose-limitation address those situations that recognize the sex-dependency of radiation risk, for example, patient exposure, occupational exposure, gonadal and thyroid shielding, x-rays and pregnancy, use factors, screening mammography, and many others. Much more work needs to be done before we have a better understanding of the special susceptibility of the human oocyte, and of the potential for genetic harm to future generations. These are but a few of the very important questions that must be answered for radiological protection and public policy as we move to the end of this century and into the next, and as we resolve some of the issues of energy, health care, occupational health, national security, and waste management in our complex society.

To do this, to see into the future, we must stand on the shoulders of giants. It is one of the tallest of these giants, Dr. Lauriston Taylor, whose 80th birthday we have the occasion and the pleasure of celebrating today.

ACKNOWLEDGEMENTS

The author thanks Mrs. Kathleen Becky and Mr. Robert Stevens for help with the manuscript and illustrations. Research supported by the Office of Health and Environmental Research of the U.S. Department of Energy under contract No. DE-AC03-76SF00098.

REFERENCES

1. UNSCEAR: Sources and Effects of Ionizing Radiation. Publ. E.77.IX.1, New York, United Nations, 1977.

2. BEIR Committee on the Biological Effects of Ionizing Radiation (BEIR III). The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Washington, D.C., National Academy of Sciences, 1980.

3. Pochin, E.E. Estimation of radiation risks in man. Radiation Protection Bull. (Suppl) 42:7-10, 1981.

4. Fabrikant, J.I. The BEIR III Controversy. Radiat. Res. 84:361-368, 1980.

5. Fabrikant, J.I. The BEIR III Report: Origin of the controversy. AJR 136:209-214, 1981.

6. Beebe, G.W., Kato, H., Land, C.E. Studies of the mortality of A-bomb survivors. 6. Mortality and radiation dose, 1950-1974. Radiat. Res. 75:138-201, 1978.

7. Beebe, G.W., Kato, H., Land, C.E. Life Span Study Report 8. Mortality Experience of Atomic Bomb Survivors 1950-1974. Radiation Effects Research Foundation Technical Report TR 1-77. Hiroshima: Radiation Effects Research Foundation, 1978.

8. Court Brown, W.M., Doll R. Mortality from cancer and other causes after Radiotherapy for ankylosing spondylitis. Br Med J 2:1327-1332, 1965.

9. Boice, J.D., Jr., Monson, R.R. Breast cancer in women after repeated fluoroscopic examinations of the chest. JNCI 59:823-832, 1977.

10. Hempelmann, L.H., Hall, W.J., Phillips, M., Ames, W.R. Neoplasms in persons treated with x-rays in infancy: Fourth survey in 20 years. JNCI 55:519-530, 1975.

11. Modan, B., Ron, E., Werner, A. Thyroid cancer following scalp irradiation. Radiology 123:741-744, 1977.

12. Archer, V.E., Gillam, J.D., Wagoner, J.K. Respiratory disease mortality among uranium miners. Ann.NY Acad.Sci.271:280-293, 1976.

13. Rowland, R.E., Stehney, A.F., Lucas, H.F., Jr. Dose-response relationships for female radium dial workers. Radiat. Res. 76:368-383, 1976.

14. NCRP: Report No. 64. Influence of Dose and its Distribution in Time on Dose-Response Relationships for low-LET Radiations. Washington, D.C. 1980.

15. Upton, A.C. Radiation Effects. (In) Origins of Human Cancer. (Hiatt, H.H., Watson, J.D., Winsten, J.A., eds.). pp. 477-500, Cold Spring Harbor Laboratory, 1977.

16. Loewe, W.E., Mendelsohn, E. Revised dose estimates at Hiroshima and Nagasaki. Health Phys. 41:663-666, 1981.

17. BEIR; Advisory Committee on the Biological Effects of Ionizing Radiation (The BEIR Report). National Academy of Sciences-National Research Council. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. Washington, D.C., 1972.

18. MacKenzie, I. Breast cancer following multiple fluoroscopies. Br. J. Cancer 19:1-8, 1975.

19. Boice, J.D., Rosenstein, M., Trout, E.D. Estimation of breast doses and breast cancer risk associated with repeated fluoroscopic chest examinations of women with tuberculosis. Radiat. Res. 73:373-390, 1978.

20. Boice, J.D., Jr., Land, C.E., Shore, R.E., et al. Risk of breast cancer following low-dose radiation exposure. Radiology 131:589-597, 1979.

21. Land, C.E., McGregor, D.H. Breast cancer incidence among atomic bomb survivors: Implications for radiobiologic risk at low doses. JNCI 62:17-21, 1979.

22. Shore, R.E., Hempelmann, L.H., Kowaluk, E. et al. Breast neoplasms in women treated with x-rays for acute postpartum mastitis. JNCI 59: 813-822, 1977.

23. Ron, E., Modan, B. Benign and malignant thyroid neoplasms after childhood irradiation for tinea capitis. JNCI 65:7-11, 1980.

24. Shore, R.E., Woodard, E.D., Pasternack, B.S., et al. Radiation and host factors in human thyroid tumors following thymus irradiation. Health Phys. 38:451-465, 1980.

25. Webber, B.M. Radiation therapy for pertussis. A possible etiologic factor in thyroid carcinoma. Ann. Intern. Med. 86:449-450, 1977.

26. Favus, M.J., Schneider, A.B., Stachura, M.E., et al. Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1056 patients. New England J. Med. 294:1019-1025, 1976.

27. Pochin, E.E. Long term hazards of radioiodine treatment of thyroid carcinoma. (In) Thyroid Cancer, UICC Monograph Series, Vol. 12, (Hedinger, C. ed.) pp. 293-304. Springer-Verlag, Berlin, 1969.

28. Holm, L-E. Dahlquist, I., Israelsson, A., Lundell, G. Malignant thyroid tumors after iodine-131 therapy. A retrospective cohort study. New England J. Med. 303:188-191, 1980a.

29. Parker, L.N., Belsky, J.L., Yamamoto, T. et al. Thyroid carcinoma after exposure to atomic radiation. A continuing survey of a fixed population, Hiroshima and Nagasaki, 1958-1971. Ann. Intern. Med. 80:600-604, 1974.

30. Conrad, R.A. Summary of thyroid findings in Marshallese 22 years after exposure to radioactive fallout. (In) Radiation-Associated Thyroid Carcinoma. (DeGroot, LJ, ed.) pp. 241-257, Grune & Stratton, New York, 1977.

31. Miller, R.W., Mulvihill, J.J. Small head size after atomic radiation. Teratology 14:355-364, 1976.

32. Brent, R.L. Effects of ionizing radiation on growth and development. Contrib. Epidemiol. 1:147-183, 1979.

33. Kerr, G.D. Review of Dosimetry for the Atomic Bomb Survivors. (In) Proc. 4th Conference on Neutron Dosimetry, Neuherberg. Commission of the European Communities. EUR 7448 EN 501-513 (1981).

34. Otake, M., Schull, W.J. Mental retardation in children exposed in utero to the atomic bombs: a reassessment (in press).

35. Stewart, A., Webb, J., Hewitt, D. A survey of childhood malignancies. Br Med J 1:1495-1508, 1958.

36. MacMahon, B. Prenatal x-ray exposure and childhood cancer. JNCI 28:1173-1508, 1958.

37. Jablon, S., Kato, H. Childhood cancer in relation to prenatal exposure to atomic-bomb radiation. Lancet 2:1000-1003, 1970.

38. Stewart, A.M., Kneale, G.W. Radiation dose effects in relation to obstetric x-rays and childhood cancers. Lancet 1:1185-1188, 1970.

39. Miller, R.V. Radiation (In) Cancer Epidemiology and Prevention. (Schottenfeld, D. ed.) pp. 93-101. Charles C. Thomas, Springfield, 1975.

40. MacMahon, B. Childhood cancer and prenatal irradiation. (In) Proceedings of the 1980 International Symposium on Cancer, New York, September 14-18, 1980. Vol. 1, pp. 223-238. Grune & Stratton, New York, 1981.

TABLE 1

Estimated Excess Cancer Mortality in a Population of 1 Million Persons, Single Exposure to 0.1 Gy, low-LET Radiation [2]

| Dose-Response Model | | Absolute Risk Projection Model | Relative Risk Projection Model |
|---|---|---|---|
| | Normal Expectation of cancer deaths | 163,800 | 163,800 |
| Linear-Quadratic | Excess deaths: number | 766 | 2,255 |
| | % of normal | 0.47 | 1.4 |
| Linear | Excess deaths: number | 1,671 | 5,014 |
| | % of normal | 1.0 | 3.1 |
| Quadratic | Excess deaths: number | 95 | 276 |
| | | 0.058 | 0.17 |

TABLE 2

Estimated Lifetime Radiation Risk of Cancer-Induction per Unit Dose (mSv) for Fatal and Non-fatal Cancers at Various Sites [3]

| Cancer | Number of Cancers Induced* Fatal | Non-fatal |
|---|---|---|
| Breast (females) | 5.0 | 3.0 |
| Lung | 2.0 | 0.1 |
| Leukemia | 2.0 | 0.1 |
| Thyroid | 0.5 | 10.0 |
| Bone | 0.5 | 0.2 |
| All other | 5.0 | 2.0 |
| Total in females | 15.0 | 15.4 |
| in males | 10.0 | 12.4 |

*Assuming a linear dose-response relationship

TABLE 3

Estimated Lifetime Risk of Radiation-Induced Breast Cancer[1] [2]

Risk Estimates

| Dose-Response Model | Age[2],yr. | Absolute Risk[3] | Relative Risk[4] |
|---|---|---|---|
| Linear risk[5] | 10-19 | 10.4±3.8 | 1.03±0.64 |
| | 20+ | 6.6±1.9 | 0.42±0.15 |
| Linear risk[6] | 10-19 | 22.8±5.3 | 2.70±1.30 |
| | 20+ | 8.7±3.6 | 0.57±0.29 |

[1]American women; adapted from Boice et al. [20]
[2]Age (years) at exposure
[3]Absolute risk per Gy (excess breast cancers per $10^6$ WY/0.01 Gy)
[4]Increase in relative risk/0.01 Gy
[5]Linear risk = $\alpha_0 + \alpha_1 D$
[6]Linear with cell killing risk = $(\alpha_0 + \alpha_1 D)e^{-\beta_2 D^2}$

TABLE 4

Mental Retardation in Children[1] Exposed in Utero in Hiroshima[2] [34]

| Dose Group (Gy) | Fetal Dose (Gy) | Subjects | Retarded | Percent |
|---|---|---|---|---|
| Control | 0.0 | 208 | 0 | 0.0 |
| 0.01-0.09 | 0.05 | 55 | 2 | 3.6 |
| 0.10-0.49 | 0.23 | 56 | 6 | 10.7 |
| 0.50-0.99 | 0.76 | 5 | 3 | 60.0 |
| 1.00-1.99 | 1.26 | 3 | 3 | 75.0 |
| 2.00+ | 4.72 | 1 | 0 | |
| Total | | 328 | 14 | 4.3 |

[1] age 10-17 weeks gestation

[2] ORNL revised dosimetry

FIGURE-LEGENDS

Figure 1. Alternative dose-response models. The functional forms fitted to the dose-response data are special cases of the general form: $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) \exp(-\beta_1 D - \beta_2 D^2)$ where $D$ is the radiation dose in Gy, I(D) is the incidence of effects (e.g., cancer) at dose D, and the parameters $\alpha_0$, $\alpha_1$, $\alpha_2$, $\beta_1$, and $\beta_2$ have positive values, and $\alpha_0$ is the control or spontaneous rate of the effect under study.

Figure 2. Relationship of absolute and relative risk-projection models in relation to the radiation-induced cancer effect and spontaneous cancer incidence by age. a, age at exposure x; b, age at minimal latent period, LP; c, age at observation.

Figure 3. Incidence of breast cancer in relation to radiation dose. Data from Boice et al. [20].

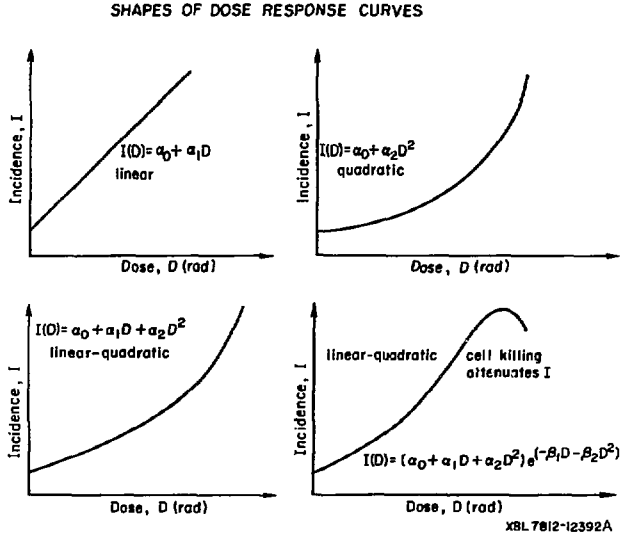
SHAPES OF DOSE RESPONSE CURVES
Incidence, I
I(D)= α0+ α1D
linear
Dose, D (rad)
Incidence, I
I(D)=α0+α2D2
quadratic
Dose, D (rad)
I(D)= α0 + α1D + α2D2
linear-quadratic
Incidence, I
Dose, D (rad)
linear-quadratic
cell killing
attenuates I
I(D)= (α0+ α1D + α2D2) e(-β1D - β2D2)
Incidence, I
Dose, D (rad)
X8L 7812-12392A

Figure 1

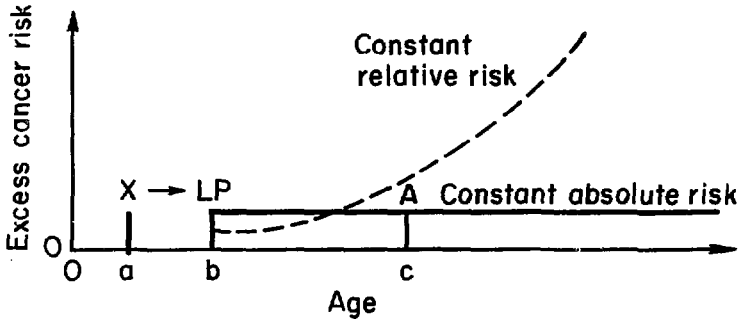
Excess cancer risk
Constant
relative risk
X → LP
A Constant absolute risk
O
O
a
b
c
Age
XBL801-3028

Figure 2

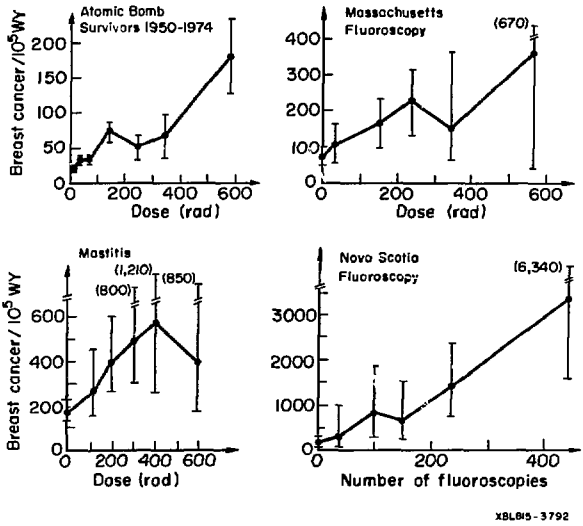
Atomic Bomb
Survivors 1950-1974
Breast cancer /10^5 WY
Dose (rad)
Massachusetts
Fluoroscopy
(670)
Dose (rad)
Mastitis
(1,210)
(800)
(850)
Breast cancer / 10^5 WY
Dose (rad)
Novo Scotia
Fluoroscopy
(6,340)
Number of fluoroscopies
XBL815-3792

Figure 3