11.

Estimation of Cancer Risk Associated with Radiation Exposure

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INTRODUCTION

The cancer risk of low-level radiation exposure has been a subject of substantial scientific, public, and legal controversy in recent years. While this controversy has often been clouded by emotional arguments, it has roots in well-defined scientific problems associated with estimation of the risk of cancer induction. This chapter is directed toward: (1) clarification of these problems, (2) demonstration of the capabilities and shortcomings of present methodologies for risk estimation for the specific example of breast cancer, and (3) indication of the direction of future research essential to improvement of risk estimation procedures.

The central difficulty in estimating the risk of low-level radiation exposure has been, and will continue to be, determining the shape of the dose-response curve in the low-dose region. Weinberg[1] has implied that this problem, while important, may be trans-scientific, i.e., may reside in the public and scientific community's attitude toward the issue. Figure 1 shows the history of radiation worker permissible exposure levels during this century.[2] These limits have decreased from 57 rads/year in 1925 (recommended by Mutacheller and Sievert) to 5 rem/year in 1957 (adopted by the NCRP). This decrease in permissible exposure levels was prompted by our ability to use radiation with less exposure and a real increase in the body of scientific knowledge concerning potential radiation hazards.

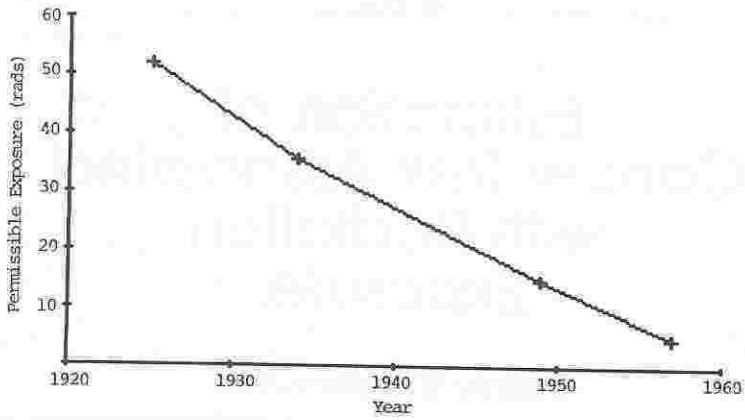


Figure 1. Recommended maximum permission occupational exposures for gamma radiation. Data from Morgan [2].

THE LOW-DOSE EXTRAPOLATION PROBLEM

The uncertainty of the shape of the radiation dose-response curve in the low-dose region is the result of ethical, economic, and experimental design constraints that force investigators to obtain data on in vivo carcinogenesis from (1) small-sample animal experiments using high-dose levels of exposure or (2) human epidemiologic studies which give relatively precise estimates of risk only at high exposure levels. Estimates of low-dose risk are generated by extrapolation outside of the dose interval where adequate data are available. Permissible exposure standards are, therefore, based on speculation as to the shape of the dose-response curve in the low-dose region.

An unavoidable consequence of this situation is that linearity versus non-linearity of radiation dose-response curves has been debated for decades.[3-9] Brown [10,11] has noted that radiation dose-response curves typically have a sigmoid shape but are approximately linear in the low-dose region. Linear extrapolation within that region is, therefore, appropriate. However, the same extrapolation procedure applied to data in the sharply rising midsection of the dose-response curve misleadingly suggests a threshold below which no response occurs.

Large-scale animal experiments have been proposed to solve the low-dose extrapolation problem. However, Schneiderman et al.[12] have noted that three million animals each in treatment and control groups would be required to assess risk at a level of 1 induced cancer per 1,000,000 population under the assumption of no spontaneous tumors occurring in the control group. Control of identification, randomization, and living conditions for millions of animals is extremely difficult. Spontaneous tumors occurring in control animals require increases in sample size of several orders of

magnitude. Errors in handling and feeding, or loss of animals could produce enough random variation in the data to preclude identification of a small carcinogenic effect.

Even if a large population animal experiment were successfully completed, the problem of extrapolating risk from mouse to man remains. Animals used in such experiments are highly inbred and kept under carefully controlled conditions. Animal tumors are often morphologically different from human tumors at the same site. Growth patterns may be dissimilar from human tumors. Animal life spans are substantially shorter. Radford[13] concludes that "it is unwise to rely on dose-response data for cancer induction in experimental animals to support use of any particular dose-response model for human risk estimates from radiation exposure at low levels." Dethlefsen et al.[14] have strongly recommended that no further animal experiments aimed at quantifying risk per rad be funded and that research resources be directed towards experiments that elucidate the cellular and molecular events relating to carcinogenesis.

Turning to human data, Brown[15] has summarized the difficulties in using human epidemiologic data to assess risk at various dose levels. Humans are exposed to multiple carcinogenic agents. The dose levels and potential interaction between these agents are generally unknown. Measuring exposure to multiple agents over prolonged periods of time is usually impossible. The long latent period between initial exposure and the appearance of a tumor allows ample time for confounding factors naturally occurring in the human environment to distort findings. Genetic and environmental heterogeneity in human populations affects the shape of the dose-response curve.

Since available data are inadequate for direct estimation of risk of low-level radiation exposure, extrapolation from high-dose data is necessary. However, it has been shown[16,17] that even in the case of carefully controlled animal experiments, arbitrary selection of dose-response models can result in low-dose risk estimates differing by 5 to 8 orders of magnitude!

The difficulties noted above make it highly probable that no animal or human data will become available in the foreseeable future which will conclusively resolve the low-level radiation risk controversy. Experimental data derived from highly sensitive human cell culture techniques provides a promising avenue of research,[18] but such data will not provide accurate estimates of risk for free-living human populations.

THE RISK OF RADIATION-INDUCED BREAST CANCER

In order to examine the low-dose extrapolation problem in detail, it is necessary to focus on a specific cancer site. Breast cancer provides an excellent example because: (1) it is the most predominant cancer in females, (2)

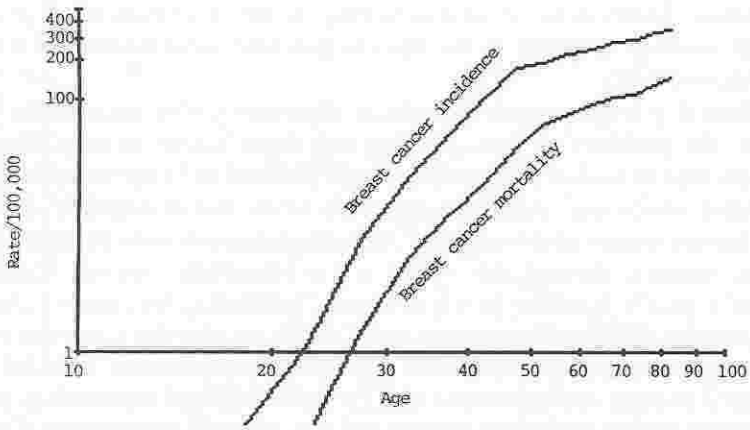


Figure 2. Log-log plot of U.S. white female breast cancer age-specific incidence and mortality. Data from Young et al. [19].

mammary tissue is highly radiosensitive, and (3) several recently published studies provide substantial new data on radiation-induced mammary tumors.

Breast Cancer Epidemiology

The best current estimate of the cumulative incidence of breast cancer in U.S. females aged 0–74 is 8.3%.[19] The cumulative rate is the sum of age-specific breast cancer rates[20] and is an indicator of the probability of disease over a lifespan. There is, therefore, an 8.3% chance that the average U.S. female will experience breast cancer before she is 75 years old. Breast cancer causes more deaths than any other cancer in U.S. females. Cumulative mortality for ages 0–74 is 2.6%. Because breast cancer incidence is much higher than breast cancer mortality (see Figure 2), the BEIR III Committee[13] recom-

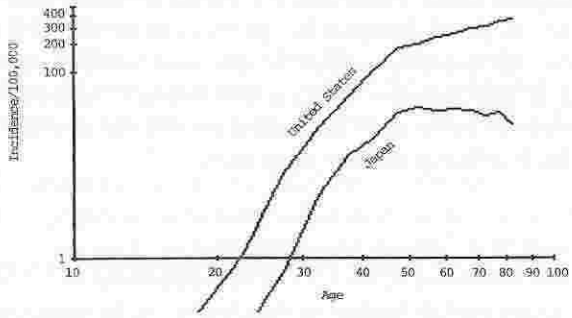


Figure 3. Log-log plot of U.S. white femal and Japanese (Osaka Prefecture) age-specific breast cancer incidence. Data from Young et al. [19] and Waterhouse et al. [21].

mended that incidence, rather than mortality, be used as an indicator of the impact of radiation on an exposed population.

Breast cancer incidence is dependent on geographic location. A highly relevant example for radiation studies is Japan[21] where cumulative breast cancer incidence during 1970–1971 in Osaka prefecture was 1.3% for women aged 0–74 (Figure 3). The low incidence of breast cancer in Japan is probably partially due to genetic differences in the population because descendants of Japanese who have migrated to the United States have only slightly higher breast cancer rates than women remaining in Japan.[22] The shape of the Japanese breast cancer incidence curve is different from the U.S. curve because of temporal trends in incidence, i.e., the younger Japanese are at higher risk than older persons. When curves from the United States, Japan, and other countries are adjusted for temporal trends the shape of the curves is virtually identical[23] (Figure 4), indicating that the disease is similar in all countries, but that risk varies with genetic background, diet, and other life-style factors.

Studies of breast cancer etiology must account for a wide variety of factors which have been shown to influence risk.[24] Confounding factors of age, place of residence, family history of breast cancer, and past history of

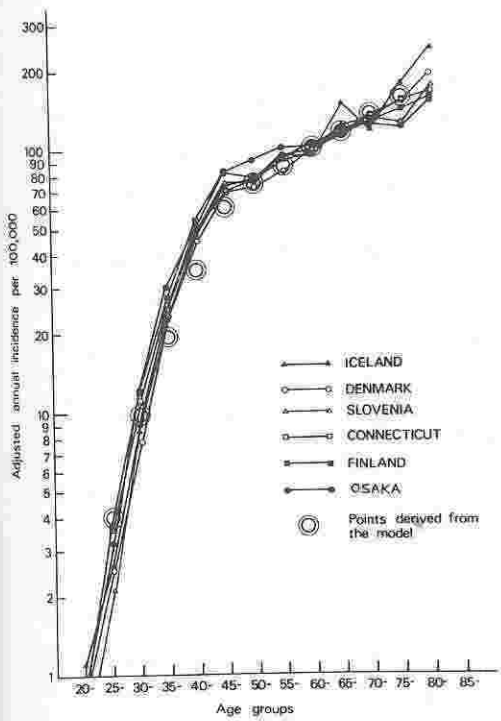


Figure 4. Shapes of breast cancer age-specific incidence curves from various countries after adjustment for temporal trends. Curves have been normalized so that the sum of the rates over all age groups is the same. Reproduced with permission from Moolgavkar et al. [23].

breast cancer have been shown to be associated with greater increases in breast cancer incidence than average levels of radiation exposure (150–250 rads) reported in most epidemiologic studies.[25] Socioeconomic status, age at menarche, menstrual history, and reproductive history can influence breast cancer risk to the same extent as these radiation levels.

Recent Concerns About Radiation-Induced Breast Cancer

Bailar[26,27] showed that the risk of radiation-induced breast cancer when using mammography for breast cancer screening of women under 50 years of age might be greater than the benefit associated with early detection of cancers. Using risk estimates developed by Upton et al.,[28] he calculated that 370 breast cancers could be induced for each round of screening of one million woman aged 35–39, assuming an average breast tissue dose of 2 rads per exam. An estimated 148 deaths would occur as a result of these incidence cases.

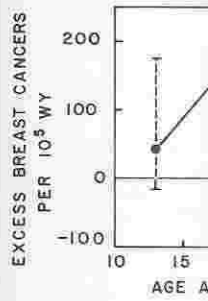
Mean dose to breast tissue at a number of breast cancer screening centers has decreased to 0.4–0.7 rads/view for xeromammographic techniques and can be reduced to 0.05–0.2 rads/view using screen-film techniques.[29] However, this reduction in risk from lower exposure has been partially offset by increases in estimates of the risk of breast cancer induced per rad of exposure due to accumulation of followup data on women in several major breast cancer studies.

Current Estimates of Risk of Radiation-Induced Breast Cancer

Recent followup data on radiation-induced breast cancer is available from three primary sources: (1) tuberculosis patients treated with multiple fluoroscopic exams, (2) Japanese atomic bomb survivors, and (3) patients with postpartum mastitis treated with radiation therapy. A recent study of Swedish women given radiotherapy for various nonneoplastic breast conditions is also of interest.

Breast Cancer in Patients Subjected to Repeated Fluoroscopies. In 1961, MacKenzie noticed radiation dermatitis in a Nova Scotia woman diagnosed with breast cancer. The woman's medical history indicated repeated flouroscopic examinations during the course of pneumothorax therapy for tuberculosis. After investigation of a group of women who received the same treatment in a sanitarium in Nova Scotia, MacKenzie[30] reported an incidence of 13 breast cancers in 271 irradiated women versus 1 case in 510 unirradiated women. Myrden and Hiltz[31] extended this study to include 783 female tuberculosis patients. Of those given pneumothorax treatment, 22 out of 300 developed breast cancer within 15–25 years of exposure compared to 4 cases out of 483 women who were not given pneumothorax treatment.

Reliable dose estimates were not available for these studies. The BEIR I Committee[13] reported an estimated average dose of 1215 rads and calculated a 0.78% increase in relative risk of breast cancer per rad and an absolute risk



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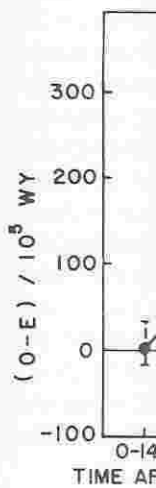


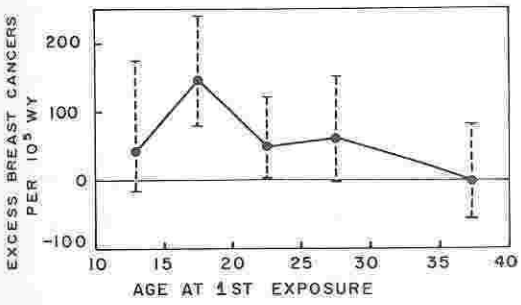


Figure 5. Excess breast cancer cases by age-group observed in fluoroscopy series with 80% confidence intervals. Reproduced with permission from Boice and Monson [32].

of 8.4 excess cases per million women years at risk per rad (henceforth, women-year-rad or WY-rad).

More recently, Boice and coworkers[32] reported on a series of 1047 irradiated patients in two Massachusetts tuberculosis sanitaria who developed 41 breast cancers in 10–44 years of followup versus 23.3 cancers expected. A control group composed of 717 women with tuberculosis who were not irradiated developed 15 cancers versus 14.1 expected. Expected numbers were calculated from age and calendar year using age-specific incidence rates from the Connecticut Tumor Registry. Assuming 1.5 rads per fluoroscopic exam, the average dose to irradiated women was 150 rads. The increase in relative risk per rad was 1.11% and the absolute risk was 6.2 excess cases per million WY-rad.

The fluoroscopy studies indicated that younger women may be particularly sensitive to radiation exposure (Figure 5), that excess risk did not appear until 15 years after the first fluoroscopy (therapy lasted an average of 3.3 years) and was still present at 40 years after exposure (Figure 6), and that

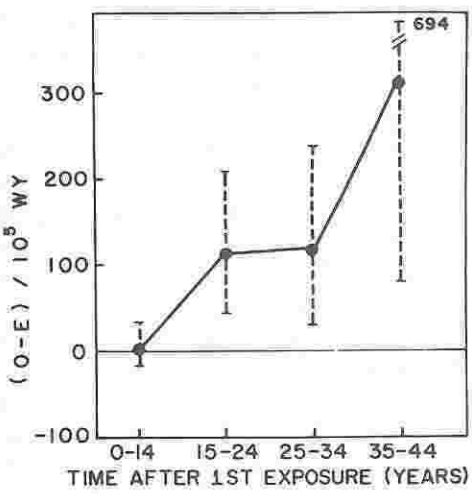


Figure 6. Excess breast cancer cases by time after time first exposure in flouroscopy series with 80% confidence intervals. Reproduced with permission from Boice and Monson [32].

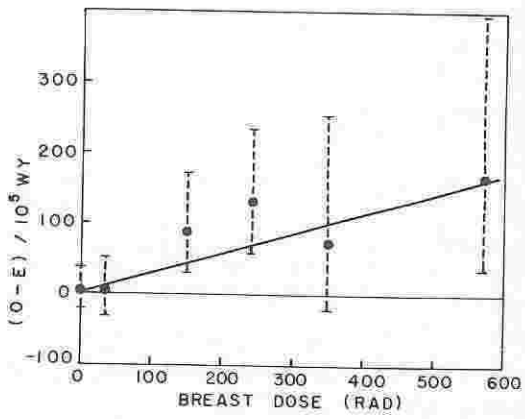


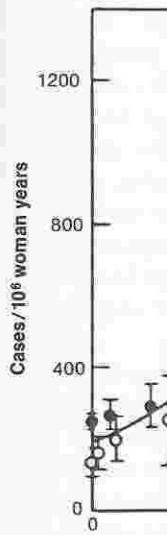
Figure 7. Excess breast cancer vs. dose in fluoroscopy series with 80% confidence intervals. Reproduced with permission from Boice and Monson [32].

a linear dose-response was reasonably consistent with the data (Figure 7). A linear dose-response implies that risk is directly proportional to cumulative dose. Schellabarger et al.[33] have provided data on mammary tumors in rats which lend additional support to this hypothesis.

The major uncertainty in the fluoroscopy studies, in addition to sampling variation, is lack of precise dose estimates. Although an elaborate methodology was developed to estimate dose, the time required for a physician to perform each exam is not known and this is the primary factor in determining risk to a patient.

Breast Cancer in Japanese Atomic Bomb Survivors. MacKenzie's work prompted Wanebo and coworkers[34] to study breast cancer incidence in Japanese women who survived the bomb. This work has been updated for the period 1950–1969 by McGregor et al.[35] and for the period 1950–1974 by Tokunuga et al.[36] The later publication reports on 360 cases of breast cancer occurring in 63,000 Japanese women. There were 288 of these cases residing in Hiroshima or Nagasaki at the time of bombing. Risk estimates for breast cancer in atomic bomb survivors have been lower than those reported in American studies, probably due to differences in genetic and lifestyle factors in Japanese versus American women. Loewe and Mendelsohn[37] have revised the dose estimates used in these studies based on corrections to Japanese building shielding factors. These revisions render previously published work out of date and eliminate some of the anomalies previously noted in the Japanese data.

Straume and Dobson[38] have examined the implications of the revised dose estimates. Breast cancer incidence in both Hiroshima and Nagasaki are now well represented by a single curve (Figure 8). Relative risk is reported to be 1.1 for a dose of 10 rads, 2.4 for a dose of 100 rads, and 4.4 for a dose of



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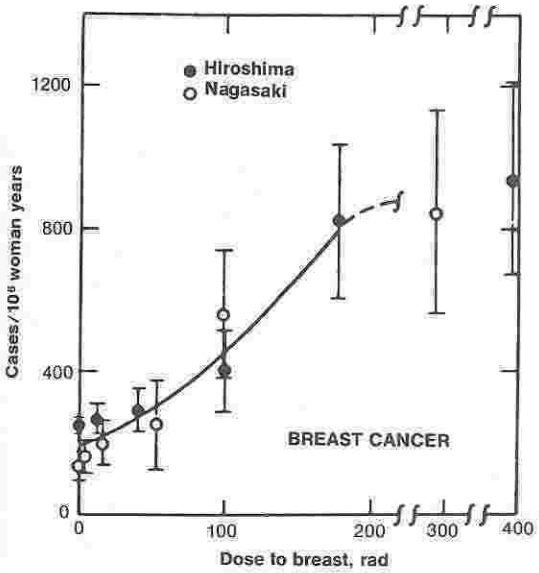


Figure 8. Breast cancer dose-response curve in Japanese atomic bomb survivors using revised dose estimates of Loewe and Mendelsohn [37]. Reproduced with permission from Straume and Dobson [38].

200 rads. Dose-response for a single high-dose exposure appears nonlinear. However, overall relative risk estimates for low doses are consistent with American studies. Absolute risk estimates are 1.4 cases per million WY-rad at a dose of 10 rads, 2.4 cases per million WY-rad at a dose of 100 rads, and 3.3 cases per million WY-rad, which are still much lower than those estimated from American studies.

It should be noted that since Japanese women have a low incidence of breast cancer compared to U.S. women, a similar increase in relative risk for both populations produces less absolute risk for the Japanese. In addition, absolute risk estimates depend on length of followup of the study population and are always low if followup is less than the entire life span. The maximum length of followup for the Japanese is 29 years, whereas some of the U.S. fluoroscopy patients mentioned above were followed for as long as 44 years. Finally, the Japanese sample consists only of women who survived until 1950 after abnormal exposure to radiation in 1945. This sample may be quite different from the U.S. population.

Despite problems associated with interpretation of the Japanese data, it is of interest that revised dose estimates produce a dose-response curve that appears to have a quadratic component. Since the Japanese sample consists of a substantially larger number of women with breast cancer in comparison with other studies, the Japanese data should provide the most precise estimate of the *shape* of the dose-response curve, even though absolute risk estimates may not be applicable to U.S. women.

Breast Cancer in Mastitis Patients Treated with Radiotherapy. In 1969, Mettler et al.[39] reported increased risk of breast cancer in 606 postpartum mastitis patients treated with radiotherapy in Rochester, NY. More recently, Shore et al.[40] followed up 571 of these women by mail survey. In addition, three nonirradiated control groups were examined to determine whether genetic predisposition to breast cancer, having mastitis, or geographic area of residence could account for high risk of disease in the irradiated women. The distribution of age, person years at risk, and length of followup intervals was very similar in the case and control groups. In addition, risk of breast cancer was similar across control groups so controls were combined in the analysis of results.

A generally linear increase in risk with dose was observed up to 400 rads (Figure 9) although the data are not inconsistent with a quadratic dose-response in the 0–200 rad region. The irradiated group was exposed to an average dose of 247 rads and had double the expected cumulative incidence of breast cancer after 32 years of study (Figure 10). Increases in breast cancer risk were found only in irradiated breasts and not in nonirradiated breasts in women treated with radiation therapy.

In this series, younger women did not appear to be at higher risk from exposure to radiation. The authors speculated that this might be due to the fact that breasts were actively lactating when irradiated. Serum levels of prolactin are highly elevated in postpartum women and prolactin has been shown to be a powerful tumor promoter in animals.[41]

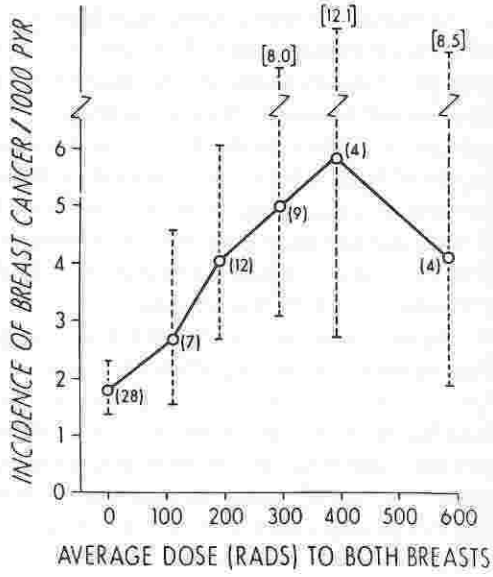


Figure 9. Breast cancer does-response curve in Rochester mastitis series with 80% confidence intervals. Numbers in parentheses are cases in each dose interval. Reproduced with permission from Shore et al. [40].

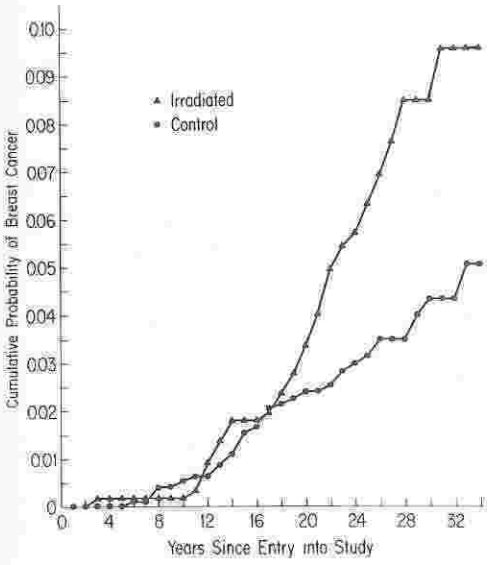


Figure 10. Cumulative breast cancer incidence in Rochester mastitis series by years since entry into study. Reproduced with permission from Shore et al. [40].

Increase in relative risk per rad was estimated to be 0.47% and absolute risk was 8.3 excess cases per million WY-rad. The followup period for women studied was 10–34 years. The minimum latent period was 10–15 years and increased risk was observed for the entire length of the followup period (34 years). Results were, therefore, very similar to results in fluoroscopy studies.

Swedish Study of Breast Cancer in Irradiated Patients. During 1927–57, 1115 Stockholm women were given radiotherapy for nonneoplastic breast conditions.[42] After followup for 6–42 years, 115 breast cancers were observed in irradiated breasts versus 28.7 expected. In nonirradiated breasts, 20 cancers were observed versus 19.9 expected. Median doses to the breast varied with length of treatment from 550–2000 rads. Doses in this study were much higher than those reported in American studies. The BEIR III Committee[13] calculated an absolute risk of 6.2 excess cases per million WY-rad from this series and concluded that since risk from this unfractionated-exposure study was similar to risk in fractionated-exposure studies, risk of breast cancer was proportional to cumulative radiation dose.

Summaries of Human Data on Breast Cancer Risk. Boice et al.,[43] Land et al.,[44] and the BEIR III Committee[13] have provided summaries of the implications of studies discussed above. None of the summaries incorporate revised dose estimates for Japanese atomic bomb survivors. However, all have agreed that studies of American women are most relevant to assessment of risk from

TABLE 1. NO. OF RADIATION-INDUCED BREAST CANCERS AMONG 1,000,000 WOMEN EXPOSED TO 0.01 GY (1 RAD)

Age (yr) at Exposure	Linear Dose Response[a]		Linear Dose Response + Cell Killing at High Dose Levels[b]	
	Absolute Risk Model	Relative Risk Model	Absolute Risk Model	Relative Risk Model
35	234	312	307	425
40	202	288	266	391
45	172	257	226	350
50	143	226	187	307
55	115	191	151	259
60	88	154	116	208
65	64	117	84	158
70	42	79	55	108

[a]An absolute risk of 6.6 cancers/10^4 WY-Gy and a 0.42% increase in relative risk per centigray (rad) were used in the computation.
[b]An absolute risk of 8.7 cancers/10^4 WY-Gy and a 0.57% increase in relative risk per centigray (rad) were used in the computation.

mammographic screening, particularly since Japanese women have a much lower spontaneous incidence of breast cancer.

Major conclusions are: (1) risk is proportional to cumulative dose, (2) women under 20 years of age are at increased risk, (3) breast cancer risk did not decrease during the maximum followup times of any of the studies (30-45 years), and (4) the multiplicative or relative risk model is probably the most appropriate for assessing breast cancer risk.

The BEIR III Committee[13] concluded that the risk estimates of Boice et al.[43] were the best currently available (see Table 1). Since data on Rochester mastitis patients treated with radiotherapy suggested that a cell-killing effect existed at high doses, risk estimates were calculated based on both a simple linear dose response and a linear dose response plus cell-killing term. These risk estimates are higher than the estimate published by Bailar[27] in 1977. However, average mammography dose has decreased. The net effect is that risk from mammography is still approximately the same as the Bailar estimate.

Risk-benefit analysis of mammography screening is a complex subject which requires extensive mathematical modeling for meaningful results. Although many models have been proposed, the analysis of Eddy[45] represents the state-of-the-art in this field. A physical exam alone is estimated to increase the expected life span of the average 50 year old woman by 37.55 days. An annual mammography exam in addition to the physical exam increases

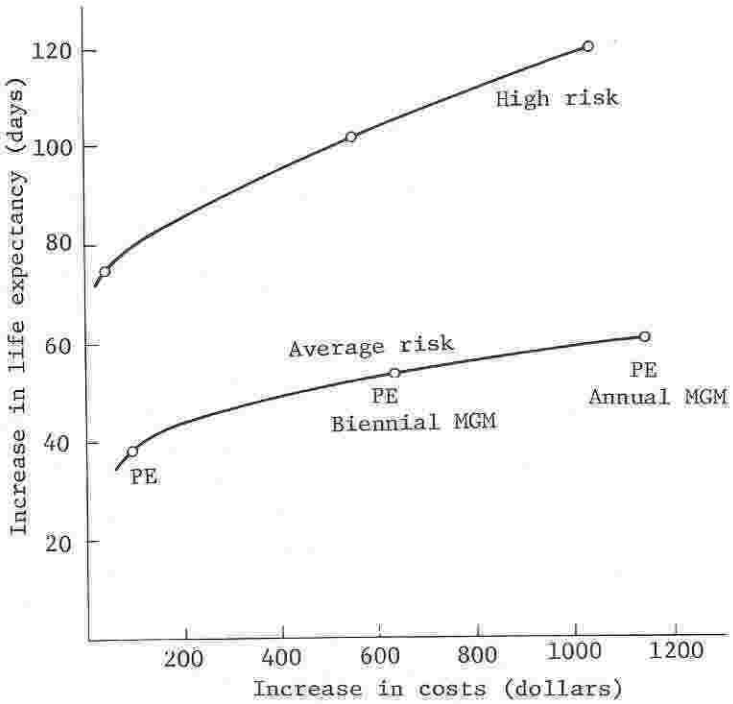


Figure 11. Life expectancy vs. program costs for difference breast cancer screening strategies in 50-year-old average risk and high-risk woman. PE is physical exam and MGM is a mammographic exam. Reproduced with permission from Eddy [45].

the average life span by an additional 23.05 days (Figure 11). Women at high-risk of breast cancer have about double the benefit in terms of expected increase in life span. Radiation effects are estimated to decrease average life-span by 0.8 days in a 50 year old woman. Eddy's analysis is based on the assumption that each mammographic exam provides a dose of 1 rad to the breast and that 6 cancers per million WY-rad will be induced after a latent period of 10 years. The use of absolute estimates of radiation risk probably underestimates the radiation hazard. However, doubling the radiation risk decreases the expected life-span of a 50 year-old woman by only 1.6 days.

LOW-DOSE EXTRAPOLATION FROM BREAST CANCER INCIDENCE DATA

Radiation dose-response data from U.S. tuberculosis patients examined by fluoroscopy and mastitis patients treated with radiotherapy (Figures 7 and 9) are not inconsistent with a linear dose-response hypothesis, but both cases (see

TABLE 2. SAMPLE SIZE REQUIRED TO ASSURE THAT ACCEPTANCE OF THE NULL HYPOTHESIS OF NO INCREASE IN RISK IS NOT IN ERROR.[a]

Relative Risk	Cases	Critical No.	Sample Size
2.00	78	47	940
1.80	103	78	1241
1.60	158	119	1904
1.50	212	158	2554
1.40	306	226	3687
1.30	501	367	6036
1.20	1034	750	12458
1.15	1758	1267	21181
1.10	3776	2706	45494
1.08	5789	4138	69747
1.06	10097	7198	121651
1.04	22281	15842	268446
1.02	87397	61971	1052976

[a] Relative risk of radiation-induced breast cancer in an exposed versus unexposed group is listed in column 1. The total number of cases that must be observed to assure a power of 0.90 is shown is column 2. Column 3 indicates the number of cases that must be observed in the exposed group to reject the hypothesis of no increased risk at a significant level of 0.05. The cumulative incidence (0–74) of breast cancer in the U.S. is 8.3% [19]. The total number of women (half exposed, half unexposed) required to yield the number of cases in column 2 after lifetime followup is listed as the sample size in column 4. *(Adapted from Gail M: Power computations for designing comparative poisson trials.* Biometrics *1974; 30; 231–237.)*

also the Japanese data in Figure 8) appear to have a quadratic component in the 0–200 rad region. While these data may be useful for establishing upper bounds on the risk of low-level radiation exposure, they remain inadequate for determining the precise shape of the dose-response curve in the low-dose region.

Consider the sample size requirements of an experiment designed to test the hypothesis that there is no increase in risk of breast cancer after exposure to low-dose radiation. In the fluoroscopy series, the estimated increase in relative risk per rad was 1.11%. In the mastitis series it was 0.43%. For ten rads of exposure, relative risk would increase 4.3–11.1%. To state with a 90% probability that 10 rads of exposure does not increase relative risk by 10% would require observation of 3776 cases of breast cancer in exposed and control groups, of which fewer than 2706 occur in the exposed group (using the experimental design of Gail[46]). Since the current U.S. cumulative incidence of breast cancer for women aged 0–74 is 8.3%, 45,494 women would need to be followed for their entire life span (see Table 2). If an increase of 2% in relative risk were under study, 1,052,976 women would need life-span followup. The largest currently available data set consists of 360 cases of breast cancer in exposed and nonexposed Japanese women. This sample size is

only capable of detecting a 40% difference in relative risk between case and control groups.

IMPROVEMENT OF RISK ESTIMATION PROCEDURES

Precise estimation of the effects of low-doses of radiation (below 40-80 rads) requires extrapolation from effects at high doses. Such extrapolation requires a mathematical model based on relevant biological data. Future research should, therefore, be directed towards a more detailed understanding of the process of carcinogenesis and evaluation of mathematical models relevant to our understanding of that process.

The Multihit Model of Carcinogenesis

Dethlefsen et al.[14] have summarized the general aspects of mammary carcinogenesis in animals. Recent work[47,48] indicates that breast cancer induction in MuMTV-infected mice involves four stages. A cell undergoes mutation and then proliferates under proper conditions (promotional stage). A cell in the resulting clone then undergoes mutation and proliferates. Radiation may be involved in stages 1 and 3 (initiation), as well as stages 2 and 4 (promotion). Similar multistage sequences in tumor development have been observed in a wide variety of animal and human cancers.[49-51]

The multiple mutation theory or multihit model of carcinogenesis was originally proposed by Muller[52] in 1951. An extensive literature has developed from this idea during the past 30 years.[49,53,54] In the past decade, the multihit model has gained dramatically increased acceptance due to (1) Fialkow's demonstration that virtually all cancers arise from a single cell[55,56] and (2) Ames' demonstration that almost all carcinogens are mutagens.[57,58]

The present conception of this model[59,60] assumes that a normal cell is initiated (rendered potentially malignant) through alteration of cellular DNA by radiation, chemicals, viruses, or other factors. Initiation may be retarded by DNA repair or accelerated by promoting agents. Farber[61,62] suggested that a malignant cell is the result of an evolutionary process in which a normal cell and/or its progeny pass through several rate-limiting steps, some of which may be mutations. From a mathematical standpoint, "hits" may be either mutations or nonmutational rate-limiting events and the terms may be used interchangably. Breast cancer may be viewed as a four-hit process. The first and third hits may be mutations. The second and fourth hits could be epigenetic events that cause proliferation of clones of cells.

Recently, Holliday[63] unraveled two puzzling phenomenan that lend greater credence to the model. Many researchers have viewed carcinogenesis as an epigenetic process since programs imbedded in cellular DNA, which cause rapid prenatal cellular proliferation and which are normally dormant,

could give rise to malignancy if triggered by mutation or other factors in the cellular environment. In addition, if hits cause malignancy, it was not clear why animals with short life spans are prone to tumor incidence similar to humans who have an extensive life span. Holliday proposed that "damage to DNA followed by repair can trigger epigenetic changes in gene expression which are responsbile for malignancy." Since DNA repair is more efficient in large long-lived animals, tumors occur over a more extended time span.

Tumor Growth After Induction of a Malignant Cell

After the induction of a malignant cell, tumors grow at a rate dependent on the promotional environment. It may require many years for a cell to produce a clinically observable tumor.[64] In the case of colon cancer, Sutherland and Bailar[65] have estimated that the time between a single initiated cell and an observable tumor is typically 21–40 years. This is the so-called latent period, a term used very loosely in the radiation research literature.

Minimum latent periods for human radiation-induced breast cancer were as low as 6–8 years at doses over 1000 rads (Figure 12). This suggests that at very high doses, cells may be rendered malignant and grow directly to form a clinically observable tumor 6–8 years later. Breast tumor doubling times have been observed to average 95.8 days.[66] Typical tumor size at clinical detection was 3.5 cm in a 1970–1975 study of breast cancers diagnosed in a

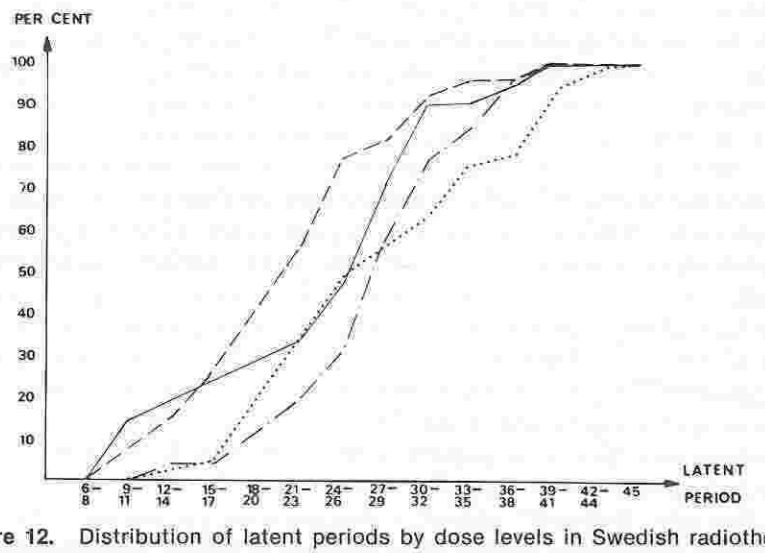


Figure 12. Distribution of latent periods by dose levels in Swedish radiotherapy series. Highest dose levels produced shortest latencies. Dose levels are 500-3999, 1000-1499, 500-999, and 1-499 rads, respectively. Reproduced with permission from Barel et al. [42].

Denver hospital. Approximately 35 doublings are required for a cell 10μm in diameter to grow into a 3.5 cm tumor.[64] Under the assumption of exponential growth, a typical breast tumor would require 9.2 years to become clinically apparent. However, tumors typically grow more quickly, often in half the time expected under the exponential assumption.[67] An average latent period of 4.6 years would be expected simply to provide enough time for tumor growth. The fact that median latent periods are greater than 10 years in all reported studies implies that in most cases, the radiation exposure begins, but does not complete, the process of induction of a single malignant cell.

Implications of the Multihit Model

The mathematical implications of this model are (1) cancer incidence increases as a power function of age minus the average tumor growth time, (2) age is simply an indicator of cumulative exposure, and (3) the slope of the curve of log incidence versus log (age − tumor growth time) is one less than the number of hits required to induce malignancy. Actual cancer incidence data departs from this curve due to artifacts induced by inaccurate reporting of disease (particularly in older age groups), changes in incidence of disease over time, age-related factors influencing disease occurrence, and exposures to carcinogenic agents at higher than background levels for portions of the life span.

Fitting the Multihit Model to Breast Cancer Data

It can be shown that the probability distribution of time to induction of a malignant cell is a Weibull distribution under multihit model assumptions.[65] Cancer incidence can be modeled by the Weibull hazard function since the hazard function is the probability of a cancer at time t, given no cancer before time t. Therefore,

$$h(t) = km^k t^{k-1},$$

where k is the number of hits required to create a malignant cell, m is the average probability of a hit, and t is the time from the beginning of exposure to the appearance of a malignant cell.

In order to allow for time between appearance of a malignant cell and clinical diagnosis of cancer (tumor growth time), we can make the simplifying assumption that t is age minus average tumor development time (4.6 years). However, in the case of breast cancer, females are probably at the same risk as males prior to puberty. This risk is virtually zero, since cumulative incidence of breast cancer over the male life span is 0.1%.[19] If we assume age at puberty averages 11.5 years,

$$t = \text{age} - 11.5 - 4.6.$$

Breast cancer incidence curves change slope dramatically at about the age of menopause (see Figure 4). However, we can fit the Weibull hazard function to the premenopausal incidence in Figure 4 and find that the number of hits required to induce malignancy (k) is 4 and the average annual probability of a hit (m) is 0.01091.

Fitting Postmenopausal Incidence Data

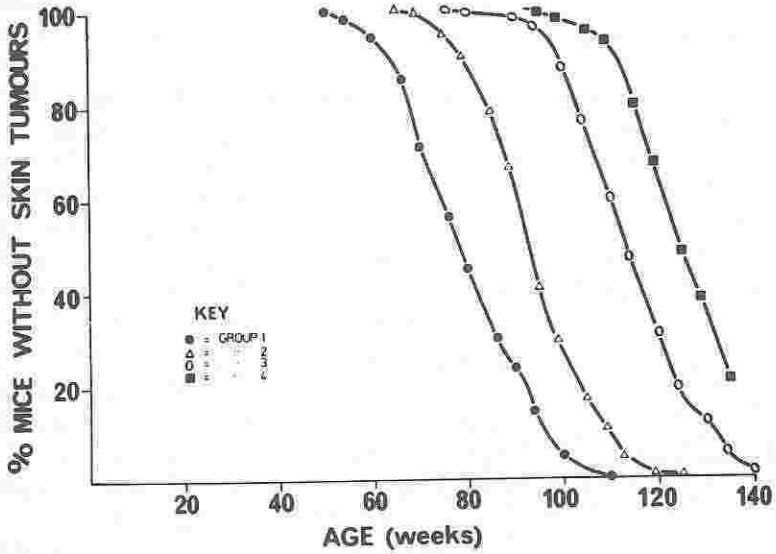
Two competing models have recently been fitted to breast cancer incidence data. Manton and Stallard[68] provide a model that fits U.S. female breast cancer mortality for 1969 under the assumption that both a pre- and postmenopausal type of breast cancer exist. Moolgavkar et al.[23] argue that breast cancer is a single two-stage disease with clonal proliferation between stages and that changes in the slope of the breast cancer incidence curve can be explained by variation in the number of breast cells at risk in the average breast at different ages.

The two-stage model of Moolgavkar and coworkers is consistent with observations in animal models,[14] whereas the Manton and Stallard model is not well supported by animal or epidemiologic data. However, the assumption that risk decreases at menopause solely because the breast decreases in size is not consistent with data which relate changes in endocrine function to cancer incidence. For example, radiation-induced mammary gland cancer in the rat can be substantially reduced by ovariectomy.[69] It seems unlikely that this affect can be accounted for simply by loss of mammary gland tissue. More likely, the combined effect of changes in endocrine function and reduction in breast size cause a decrease in risk. Let us assume that both of these factors reduce the probability of a hit at menopause, but that the disease remains a four-hit phenomenon consisting of two stages of mutation and two stages of clonal proliferation. The multihit model is analogous to the two-stage model of Moolgavkar in that a hit may be viewed as the probability of a mutation or as the probability of cellular proliferation after a mutation occurs.

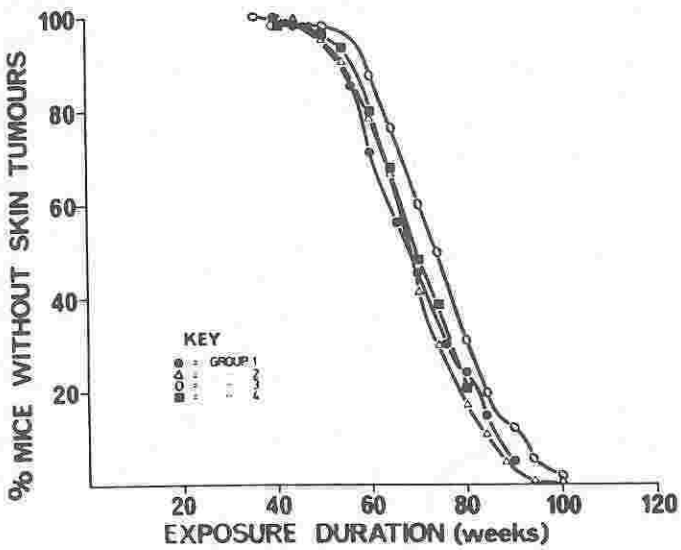
An important implication of multihit model assumptions is that age is a surrogate variable for cumulative risk caused by continuous exposure to background levels of carcinogens. Peto et al.[70] performed an elegant animal experiment which provides support for this assumption (Figure 13). This phenomenon allows for a simple graphical interpretation of the effect on changes in risk on the shape of the breast cancer incidence curve.

It is obvious from Equation 5.1 that a large risk over a short period of time can generate the same age-specific incidence as a small risk over a large period of time. Fitting the postmenopausal data in Figure 4, while constraining the number of hits to be 4, produces an estimate of the probability of a hit of 0.00426. In order for this level of risk to produce the observed age-specific incidence of breast cancer at age 47.5, it is necessary to view this level of

Figure 13. various ages cating that r from Peto et



(a)



(b)

Figure 13. Life-table curves of tumorless mice after exposure to benzo (a) pyrene at various ages. Age and exposure duration do not affect the shape of the curves indicating that risk is a function only of cumulative dose. Reproduced with permission from Peto et al. [69].

exposure as occurring over (age − 11.5 − 4.6 + 78.5) years. Therefore, breast cancer incidence can be modeled using Equation 5.1 with,

$$m = 0.01091, t = \text{age} - 11.5 - 4.6, t < 47.5; \text{ and}$$
$$m = 0.00426, t = \text{age} - 11.5 - 4.6 + 78.5, t >= 47.5.$$

This model yields a virtually perfect fit to the data. Changes in risk of a hit which produce an apparent change in the slope of the log incidence curve can be viewed simply as an expansion or contraction of time of exposure due to a decrease or increase in probability of a hit.

Introducing Radiation Risk into the Model

Consider now, adding radiation risk to the equation due to annual mammography exams. This has the effect of increasing the probability of a hit at the age that screening starts. It has an effect similar to menopause, but in the opposite direction. The slope of the incidence curve will increase, rather than decrease.

The effect of radiation exposure may be assumed to be proportional to background level of risk. This assumption is supported by the fact that increase in relative risk from a specific radiation dose is about the same for American and Japanese women, while the increase in absolute risk for the Japanese is lower in proportion to their lower level of background risk.

Figure 14 provides a graphic display of the effect. The shaded areas

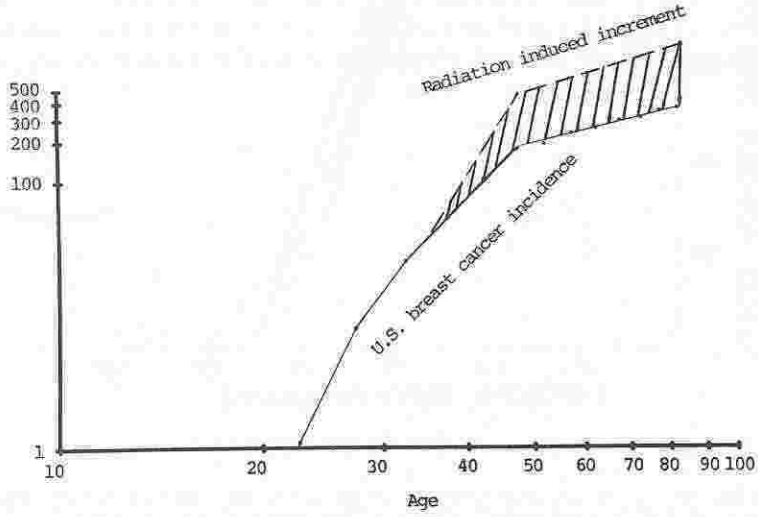


Figure 14. Log-log plot of U.S. female age-specific breast cancer incidence with hypothetical increment in risk induced by radiation exposure. Data from Young et al. [19].

represent additional breast cancers induced by the radiation hazards of screening. It is obvious that this model estimates higher risk if radiation exposure is begun prior to menopause, consistent with the findings of Boice et al.,[43] that risk is higher for exposure at younger ages.

A detailed analysis of the data on radiation-induced breast cancer in mastitis patients treated with radiation therapy and tuberculosis patients undergoing multiple fluoroscopies is beyond the scope of this paper. However, the model outlined above indicates the general method of approach. The cumulative incidence of breast cancer over the life span is the area under the incidence curve, or the integral of the hazard function,

$$c(t) = (mt)^4.$$

Since the probability of a hit (m) multiplied by time (t) is an indicator of dose, the model implies that the dose-response curve is curvilinear. If radiation only affects two of the four hits (perhaps only mutation, and not promotion phases) then the dose-response curve should be quadratic. If radiation affects cellular proliferation as well, the dose-response curve will be a cubic or quartic function. The Japanese atomic bomb survivor dose-response data (with revised dose estimates) are clearly nonlinear (see Figure 8).

SUMMARY AND CONCLUSIONS

Ethical, economic, and experimental design contraints force investigators to obtain in vivo carcinogenesis data from animal experiments or human epidemiologic studies which yield precise estimates of risk only at high exposure levels. Direct and precise estimation of low-dose radiation effects is not possible due to inherent statistical problems associated with extrapolation from high-dose data into the low-dose region. However, indirect estimation of low-dose radiation hazards is possible using the multihit model of carcinogenesis. This model is based on cancer incidence data collected over many decades on tens of millions of people. Available data on human radiation effects can be introduced into the modeling process without the requirement that these data precisely define the model to be used. This reduction in the information demanded from the limited data on human radiation effects allows a more rational approach to estimation of low-dose radiation hazards and helps to focus attention on research directed towards understanding the process of carcinogenesis, rather than on repeating human or animal experiments that cannot provide sufficient data to resolve the low-dose estimation problem. Assessment of the risk of radiation-induced breast cancer provides an excellent example of the utility of multihit modeling procedures.

REFERENCES

1. Weinberg AM: Symposium: Extrapolation to low doses of ionizing radiation. I. Introduction. *Rad Res* 1982; 90:33–34.
2. Morgan KZ: Cancer and low level ionizing radiation. *Bull Atomic Sci* 1978; Sept: 30–41.
3. Brues AM: Critique of the linear theory of carcinogenesis. *Science* 1958; 128:693–699.
4. Burch PRJ: Radiation carcinogenesis: A new hypothesis. *Nature* 1960; 185:135–142.
5. Shellabarger CJ: Radiation carcinogenesis. *Cancer* 1976; 37:1090–1096.
6. Yuhas JM: Dose-response curves and their modification by specific mechanisms. In: *Biology of Radiation Carcinogenesis.* (Yuhas JM, Tennant RW, Regan JD, eds) New York: Raven Press, 1976; pp 51–61.
7. Upton AC: Radiobiological effects of low doses: Implications for radiobiological protection. *Rad Res* 1977; 71:51–74.
8. Morgan KZ: The linear hypothesis of radiation damage appears to be non-conservative in many cases. *Proc IV Intl Cancer Cong Intl Rad Protect Assoc.* 1977; 1:11–14.
9. Gofman JW: Question of radiation causation of cancer in Hanford workers. *Health Phys* 1979; 37:617–639.
10. Brown JM: Linearity vs. non-linearity of dose response for radiation carcinogenesis. *Health Phys* 1976; 31:231–245.
11. Brown JM: The shape of the dose-response curve for radiation carcinogenesis: Extrapolation to low doses. *Rad Res* 1977; 71:34–50.
12. Schneiderman MA, Mantel N, Brown CC: From mouse to man—Or how to get from the laboratory to Park Avenue and 59th Street. *Ann NY Acad Sci* 1975; 246:237–248.
13. BEIR: The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980. Washington: National Academy Press, 1980.
14. Dethlefsen LA, Brown JM, Carrano AV, et al.: Can animal and in vitro studies give new, relevant answers to questions concerning mammographic screening for human breast cancer? *J Natl Cancer Inst* 1978; 61:1537–1545.
15. Brown CC: Statistical aspects of extrapolation of dichotomous dose-response data. *J Natl Cancer Inst* 1978; 60:101–108.
16. FDA: Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides. *Toxicol Appl Pharmacol* 1971; 20:419–438.
17. Chand N, Hoel DG: A comparison of models for determining safe levels of environmental agents. In: *Reliability and Biometry.* Philadelphia: SIAM, 1974. pp 681–700.
18. Waldren C: Measurement of mutagenesis in mammalian cells. *Proc Natl Acad Sci USA* 1979; 76:1358–1362.
19. Young JL, Percy CL, Asire AJ (Eds): Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973–1977. *Natl Cancer Inst Monogr* 57, 1981.

20. Breslow NE, Day NE: *Statistical Methods in Cancer Research Vol 1—The Analysis of Case-Control Studies.* IARC Sci Pub No 32. Lyon: Intl Agency Res Cancer, WHO, 1980.
21. Waterhouse J, Muir CS, Correa P, et al.: *Cancer Incidence in Five Continents,* Vol III. IARC Sci Pub No 15. Lyon: Intl Agency Res Cancer, WHO, 1976.
22. Haenszel W, Kurihara M: Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst* 1968; 40:43-68.
23. Moolgavkar SH, Day NE, Stevens RG: Two-stage model for carcinogenesis: Epidemiology of breast cancer in females. *J Natl Cancer Inst* 1980; 65:559-569.
24. MacMahon B, Cole P, Brown J: Etiology of human breast cancer: A review. *J Natl Cancer Inst* 1973; 50:21-42.
25. Kalache A: Risk factors for breast cancer: A tabular summary of the epidemiological literature. *Br J Surg* 1981; 68:797-799.
26. Bailar JC III: Mammography: A contrary view. *Ann Intern Med* 1976; 84:77-84.
27. Bailar JC III Screening for early breast cancer: Pros and cons. *Cancer* 1977; 39:2783-2795.
28. Upton AC, Beebe GW, Brown JM, et al.: Report of the National Cancer Institute Ad Hoc working group on the risks associated with mammography in mass screening for the detection of breast cancer. *J Natl Cancer Inst* 1977; 59:481-493.
29. Shrivastava PN: Radiation dose in mammography: An energy-balance approach. *Radiology* 1981; 140:483-490.
30. MacKenzie I: Breast cancer following multiple fluoroscopies. *Br J Cancer* 1965; 19:1-8.
31. Myrden JA, Hiltz JE: Breast cancer following multiple fluoroscopies during artificial pneumothorax treatment of pulmonary tuberculosis. *Can Med Assoc J* 1969; 100:1032-1034.
32. Boice JD, Monson RR: Breast cancer in women after repeated fluoroscopic examinations of the chest. *J Natl Cancer Inst* 1977; 59:823-832.
33. Schellabarger CJ, Bond VP, Aponte GE, et al.: Results of fractionation and protraction of total-body radiation on rat mammary neoplasia. *Cancer Res* 1966; 26:509-513.
34. Wanebo CK, Johnson KG, Sato K, et al.: Breast cancer after exposure to the atomic bombings of Hiroshima and Nagasaki. *N Engl J Med* 1968; 279:667-671.
35. McGregor DH, Land CE, Choi K, et al.: Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki 1950-69. *J Natl Cancer Inst* 1977; 59:799-811.
36. Tokunaga M, Norman JE, Asano M, et al.: Malignant breast tumors among atomic bomb survivors, Hiroshima and Nagasaki, 1950-74. *J Natl Cancer Inst* 1979; 62:1347-1359.
37. Loewe WE, Mendelsohn E: Revised dose estimates at Hiroshima and Nagasaki. *Health Phys* 1981; 41:663-666.
38. Straume T, Dobson RL: Implication of new Hiroshima and Nagaski dose estimates: Cancer risks and neutron RBE. *Health Phys* 1981; 41:666-671.

39. Mettler FA Jr, Hempelmann LH, Dutton AM, et al.: Breast neoplasma in women treated with x-rays for acute postpartum mastitis. A pilot study. *J Natl Cancer Inst* 1969; 43:803–811.
40. Shore RE, Hempelmann LH, Kowaluk E, et al.: Breast neoplasms in women treated with x-rays for acute post partum mastitis. *J Natl Cancer Inst* 1977; 59:813–822.
41. Furth J: The role of prolactin in mammary carcinogenesis. In: *Human Prolactin.* (Pasteels JL, Robyn C, Ebling FJG, Eds) New York: American Elsevier, pp 233–248.
42. Baral E, Larsson LE, Mattsson B: Breast cancer following irradiation of the breast. Cancer 1977; 40:2905–2910.
43. Boice JD, Land CE, Shore RE, et al.: Risk of breast cancer following low-dose radiation exposure. Radiol 1979; 131:589–597.
44. Land CE, Boice JD, Shore RE, et al.: Breast cancer risk from low-dose exposures to ionizing radiation: Results of parallel analysis of three exposed populations of women. *J Natl Cancer Inst* 1980; 65:353–376.
45. Eddy DM: *Screening for Cancer: Theory, Analysis and Design.* Englewood Cliffs: Prentice-Hall, 1980.
46. Gail M: Power computations for designing comparative Poisson trials. *Biometrics* 1974; 30:231–237.
47. Miyamoto JM, DeOme KB, Osborn RC: Detection of inapparent preneoplastic cells by in vivo cultivation of dissociated mouse mammary gland. *Proc Am Assoc Cancer Res* 1975; 16:15.
48. DeOme KB, Miyamoto MJ, Osborn RC, et al.: Detection of inapparent transformed mammary gland cells in vivo: Recovery of nodule-transformed cells from virgin female BALB/cfC3H mice. *Cancer Res* 1978; 38:2103–2111.
49. Sutherland JV: The multihit model of carcinogenesis: applications to human colon cancer incidence data. Ph.D. Thesis, Department of Biometrics, Univ. Colorado School of Medicine.
50. Berenblum I: Cancer prevention as a realizable goal. Cancer 1981; 47:2346–2348.
51. Cleton FJ, Simons JWIM (Eds): *Genetic Origins of Tumor Cells.* Boston: Martinus Nijhoff, 1980.
52. Muller HJ: Radiation damage to the genetic material. *Sci Prog* 1951; 7:93–493.
53. Whittemore A, Keller JB: Quantitative theories of carcinogenesis. *SIAM Rev* 1978; 20:1–30.
54. Peto R: Epidemiology, multistage models, and shortterm mutagenicity tests. In: *Origins of Human Cancer.* (Hiatt HH, Watson JD, Winsten JA, Eds) Cold Spring Harbor, New York, 1977. pp 1403–1428.
55. Fialkow PJ: The origin and development of human tumors studied with cell markers. *N Engl J Med* 1974; 291:26–35.
56. Fialkow PJ: Clonal origin of human tumors. *Biochim Biophys Acta* 1976; 458:283–321.
57. Ames BN, Durston WE, Yamasaki E, et al.: Carcinogens are mutagens: A simple test system combining liver homogenates for activation and bacteria for detection. *Proc Natl Acad Sci USA* 1973; 70:2281–2285.

58. Ames BN: Identifying environmental chemicals causing mutations and cancer. *Science* 1979; 204:587–593.
59. Boutwell RK: The function and mechanism of promoters of carcinogenesis. *CRC Crit Rev Toxicol* 1974; 17:419–443.
60. Trosko JE, Chu EHY: The role of DNA repair and somatic mutation in carcinogenesis. *Adv Cancer Res* 1975; 21:391–425.
61. Farber E: Carcinogenesis—Cellular evolution as a unifying thread: Presidential address. *Cancer Res* 1973; 33:2537–2550.
62. Farber E: Sequential analysis of chemical carcinogenesis. Laboratory Workshop In: *Cancer Biology I—Etiology, Diagnosis and Treatment.* Aspen: Given Institute of Pathobiology, 1979.
63. Holliday R: A new theory of carcinogenesis. *Br J Cancer* 1979; 40:513.
64. Collins VP, Loeffler RK, Tivey H: Observations on growth rates of human tumors. *Am J Roentgenol* 1956; 76:988–1000.
65. Sutherland JV, Bailar JC III: The multihit model of carcinogenesis: Application to colon cancer data from the Third National Cancer Survey (abstract). *Proc Am Assoc Cancer Res* 1979; 20:77.
66. Steel GG: *Growth Kinetics of Tumours.* Oxford: Clarendon Press, 1977.
67. Mendelsohn ML: Tumor growth and the cell cycle. Lecture, Univ of Colorado School of Med, Feb. 18, 1977.
68. Manton KG, Stallard E: A two-disease model of female breast cancer: Mortality in 1969 among white females in the United States. *J Natl Cancer Inst* 64:9–16.
69. Cronkite EP, Shellabarger CJ, Bond VP, et al.: Studies on radiation-induced mammary gland neoplasia in the rat. I. The role of the ovary in the neoplastic response of the breast tissue to total- or partial-body X-irradiation. *Rad Res* 1960; 12:81–93.
70. Peto R, Roe FJC, Lee PN, et al.: Cancer and ageing in mice and men. *Br J Cancer* 1975; 32:411–426.