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Absolute and Relative Time-Response Models in Radiation Risk Estimation

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Introduction

Radiogenic risks are generally expressed in terms of absolute units (excess cancers per population, dose and time) or as some multiple of the underlying natural risk. These expressions of radiogenic risks are called absolute risks (AR) and relative risks (RR), respectively. Both AR and RR are used in dose-response models and also in time-response models. The present paper is concerned primarily with time-response models that describe the distribution of radiation-induced events over time after exposure. Dose-response models are useful in interpolating from high-dose to low-dose risks. Time-response models are useful not only to describe the distribution of radiation-induced events over the period of observation, but also to project risk beyond that period, hence the "projection" models in the 1980 BEIR report [1]. When levels of radiogenic risk are compared in different populations, or among tumor sites, dose-specific comparisons may be in absolute or

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relative terms, but they gain in precision if time after exposure is taken into account as well as other factors, especially sex and age at exposure. It should be stressed, however, that while the terms “absolute” and “relative” risks are used for both time-response models and risk estimation in populations, the topics are distinct and need to be discussed separately.

Time-Response Models

In view of the multifactorial, multistage nature of the carcinogenic process [2], no model currently in use for time response or dose response can be considered more than a crude approximation of what is surely an extremely complex process. We have no reason to believe that any single time-response model, or any single dose-response model, is appropriate for risk assessment in every instance. Clearly, susceptibility to radiation-induced cancers can vary markedly with age at exposure, age at observation, type of neoplasm, cell type, physiological condition, and concomitant exposure to other physical or chemical agents as well as to other biological modifiers of response [3]. Susceptibility also differs with respect to many characteristics of radiation exposure, whether sparsely or heavily ionizing, fractionated or protracted, and perhaps even dose distribution, whether partial body or whole body, and whether partial organ or whole organ.

Because of the diverse mechanisms through which radiation may cause cancer, and because of the multistage nature of carcinogenesis, it is not surprising that a variety of dose-response relationships have been observed in laboratory, animal and human studies. Similarly, it should not be surprising that no general time-response model is appropriate for all situations.

Definitions. Time-response models can be used to describe the pattern of radiation-induced cancers over time since exposure, as well as to predict future risks beyond the period of observation. Such models to predict future risks beyond the follow-up period of exposed populations have been used by the 1972 and 1980 NAS Committees on the Biological Effects of Ionizing Radiations (BEIR) [1], and have been discussed in detail by Land and Tokunaga [4]. These models make assumptions about the induction or latent periods of radiation-induced cancers, i.e., the distribution of risk over time since exposure. It is assumed that (1) a minimum time is required after exposure before the appearance of radiogenic cancer, (2) excess risk is distributed over time in some manner that may or may not be related to the

underlying cancer rate, and (3) the duration of effect is either limited or continues throughout life. The simplest mathematical models used are the so-called absolute-risk (AR) model and the relative-risk (RR) model (Figure 1). The AR model assumes that radiation exposure *adds* to the natural risk of cancer a dose-dependent increment which may depend on age at exposure, but not on the level of spontaneous or natural cancer incidence during the period of expression. This model has traditionally been used in radiation carcinogenesis for risk prediction. The RR model, on the other hand, assumes that the risk of radiogenic cancer depends on age at observation as well, i.e., the natural cancer risk at any given age is *multiplied* by a relative risk factor whose magnitude depends on dose and age at exposure. For cancers other than leukemia, the 1972 and 1980 BEIR committees assumed a minimum latent period of 10 years. Under the absolute risk model, they assumed that radiogenic cancers were uniformly distrib-

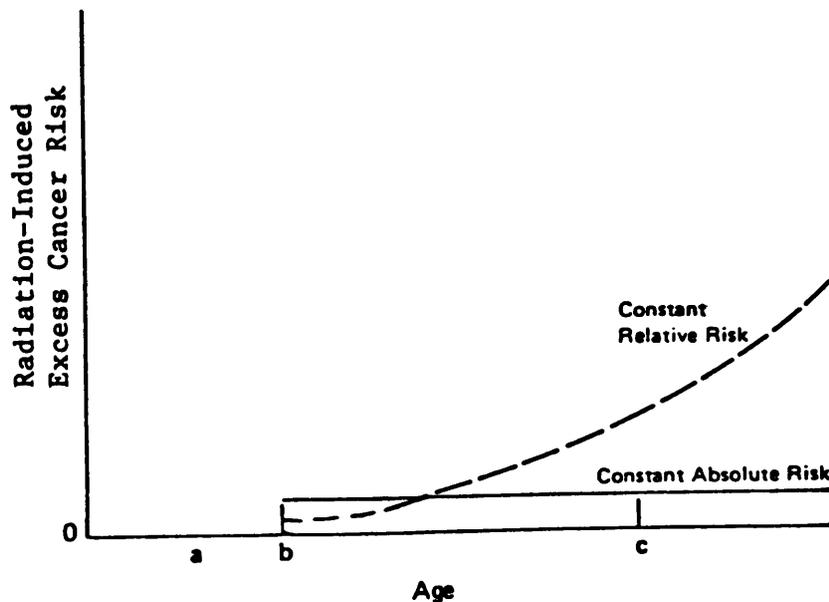
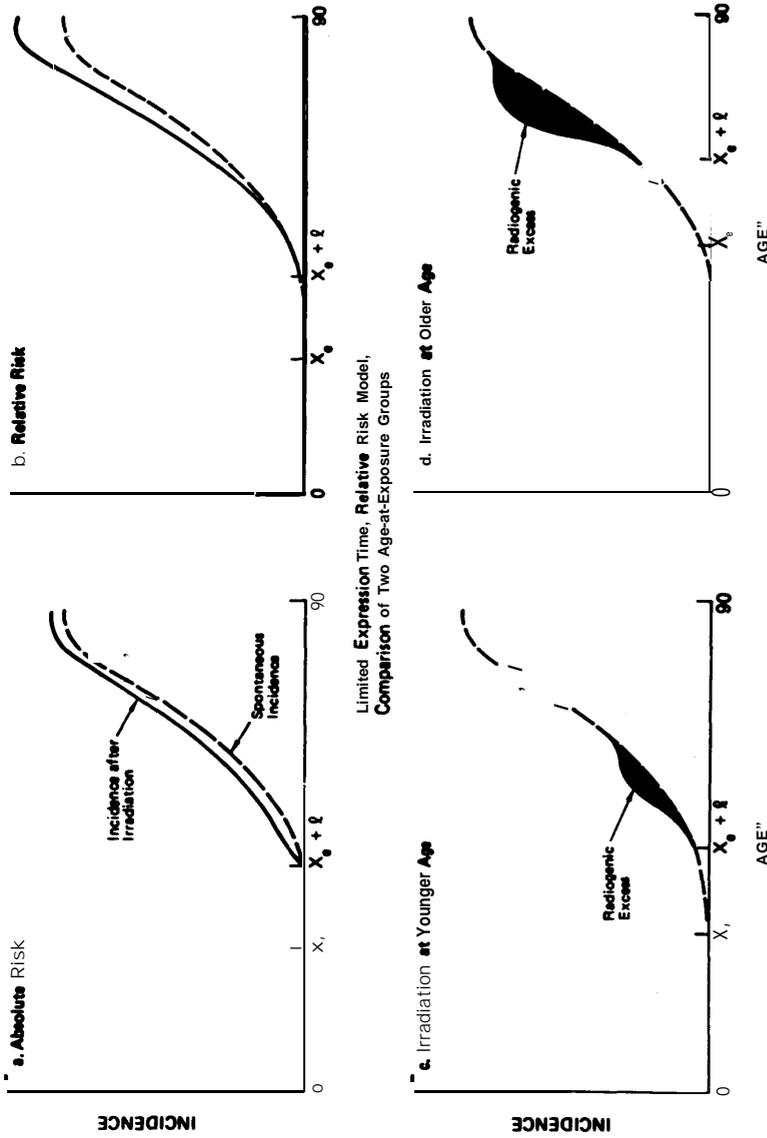


Figure 1. Absolute-risk (AR) or relative-risk (RR) time-response models may be used to describe the pattern of excess cancer risk over time since exposure. The AR model assumes that radiation exposure adds to the natural risk of cancer a dose-dependent increment which may depend on age at exposure, but not on the levels of natural cancer incidence during the period of expression. The RR model assumes that the risk of radiogenic cancer depends on age at observation as well, that is, the natural cancer risk at any given age is multiplied by a relative risk factor whose magnitude depends on dose and age at exposure. "a" denotes age at irradiation; "b" age at end of minimal latent period; "c" any age after age 6 [1].

uted beyond the interval of observation until the end of life; under the relative risk model, the distribution was assumed proportional to age-specific population rates for the appropriate cancer. The 1972 BEIR committee also presented a "plateau" model under which the expression time for radiation-induced cancers was limited to the period 10 to 40 years after exposure. The ICRP [5] and the UNSCEAR [6] reports present absolute risk estimates. UNSCEAR estimates of lifetime risk are based on an average expression time of about 25 years. If complete lifetime observations were available, the AR and RR models would both describe the same overall excess, although its distribution over time would differ. Few epidemiologic studies, however, have observed exposed populations for life and, furthermore, cancer incidence and cancer mortality rates vary appreciably by age. Thus, the two models generally predict different future excess risks. For example, the 1980 BEIR committee estimate of lifetime risk was 3 to 5 times higher for the RR projection model than for the AR projection model for a single exposure.

In the 1980 BEIR report, some possible patterns were presented by which excess cancers might be distributed with respect to the natural incidence (Figure 2). If the AR model is essentially correct, the index of absolute risk (excess cancers/ 10^6 persons/year/rad) would show little variation as subjects grow older, whereas relative risks (the multiplicative index) would fluctuate, varying with underlying natural age-specific rates. Conversely, if the multiplicative model is essentially correct, the absolute risks would fluctuate across various ages at observation more than the relative risks. Cancer incidence and mortality rates generally increase with age for most cancers [7] and, if the risk of radiogenic cancer is assumed to continue for life, the RR model would predict usually many more extra cancers beyond the period of observation than the AR model. If the duration of effect is finite, as appears to be true for radiation-induced leukemia and bone cancer by brief exposure to radiation, a wave-like distribution of risk is seen, and a third time-dependent model different from both the AR or RR model is necessary to describe the pattern of excess risk.

Minimum latent period, length of follow-up, age at exposure, duration of effect, and radiation dose are extremely important considerations when one attempts to derive or interpret time-response models from existing epidemiologic studies. If exposure occurs at an age when the expectation of life is less than the minimum latent period, then the excess risk for these elderly people must approach zero; any excess will occur only in those who lived longer than the minimum latent period. If the duration of follow-up is less than the minimum latent



X_1 is age at exposure, t is the minimal latent period.

Figure 2. Some possible patterns by which excess cancers might be distributed with respect to the natural incidence. "a," lifetime expression and AR model. "b," lifetime expression and RR model. "c," limited expression period, young age at exposure, and RR model. "d," limited expression period, older age at exposure, and RR model [1]

period, then no radiation risk will be apparent. If the duration of follow-up is less than the duration of effect, then information will be incomplete, and projected estimates will depend upon assumptions that should be interpreted with caution. It is not always possible to validate time-response assumptions using the data to which they are to be applied. For example, if the radiation dose was so low that few radiogenic cancers were induced, then there can be very little information with which to evaluate the appropriateness of any particular time-response model.

A time-response model can work well for a particular cancer site, or for each of a group of cancer sites taken separately, to a particular age-at-exposure cohort, to a particular sex and to a particular level of natural incidence. A time-response model can fail if applied to rates for combined tumors, age cohorts, sexes, or populations. Difficulties may arise, for example, in projecting risks that are not tumor specific, e.g., risks for all malignancies taken as a group. For such an undifferentiated set of tumors, risk coefficients obtained at young ages might represent one subset of cancer types, but because other types predominate at older ages, they might give a very misleading prediction of risk occurring in later life. For example, in the 1972 BEIR report approximately half the predicted lifetime excess mortality from solid tumors following a lifetime exposure of one rad per year derived from risk coefficients estimated from persons exposed under age 10 years and observed for only 25 years. The 1980 BEIR committee recognized this difficulty, and for lifetime risk projection for this group used the coefficients of those exposed between the ages of 10–19 years and followed for 30 years. The 1980 BEIR committee also eliminated from risk projection certain cancers of later life not known to be increased following low-dose radiation, such as melanoma, other skin cancers and prostate cancer. A case also could be made, perhaps, for eliminating certain malignancies such as cancers of the bone, uterus, cervix, brain, liver, pancreas and others that are not clearly elevated following low-level exposure to sparsely ionizing external radiations.

It is often stated that there are no epidemiologic studies in which follow-up has been carried out to the end of life for the entire exposed population. This is strictly correct and implies that any projection of risk over the lifetime of exposed persons involves considerable uncertainty. However, it should be noted that for several studies persons over the age of 50 years at exposure have, in fact, been followed now for their entire life spans; and that for some cancers, such as leukemia, bone cancer, and childhood cancers following prenatal x ray, the exposed populations have likely been followed for the entire period of

risk for which radiogenic neoplasms might be expected. In view of the uncertainties associated with making inferences from epidemiologic studies with incomplete follow-up as well as studies with few radiogenic cancers in excess of the natural incidence, it may be informative to evaluate the evidence from several epidemiologic studies on the relationship between the temporal distribution of radiation-induced cancers and the underlying spontaneous incidence of cancer.

Leukemia and bone cancer. Several large-scale studies [8–11] have indicated that the risk of radiogenic leukemia does not continue throughout life, but is exhausted after about 20 to 30 years (Figure 3). The minimum latent period appears to be about 2 years, and several populations have been followed for up to 30 years. It appears, however, that the studies of the atomic bomb survivors and the British patients treated with radiation for spondylitis support neither the AR nor the RR time-response model (Table 1). Neither model fits when specific risks are distributed over time by age at exposure. The lack of congruence of the cumulative distributions of leukemia following high dose versus low dose exposure over time also suggest that radiogenic leukemia tends to occur earlier than spontaneous leukemia, at least for survivors exposed at young ages (Figure 4). The wave-like nature of the response suggests that radiogenic leukemia risk is neither constant over time nor distributed in a manner proportional to the spontaneous incidence, i.e., risk is independent of the underlying population rates, but depends on time after irradiation. Also, there are apparent differ-

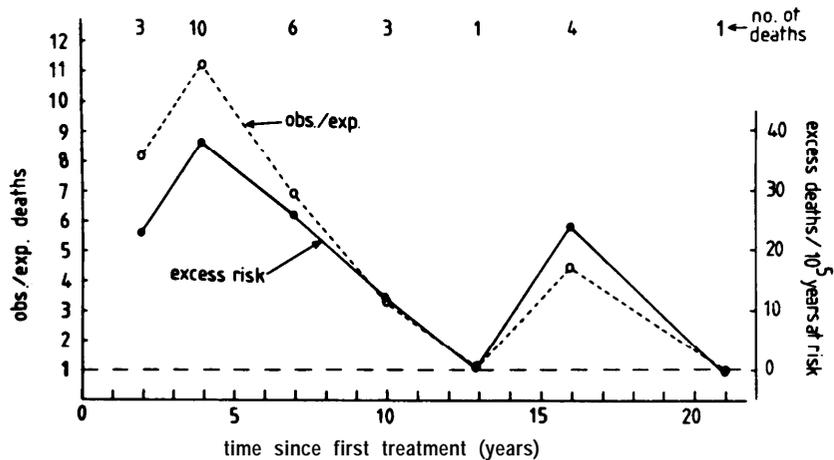


Figure 3. Observed and expected numbers of deaths from leukemia according to the time since first radiation treatment for spondylitis [43].

TABLE 1.—Absolute and relative risks of leukemia over time since exposure among patients irradiated for spondylitis [19], and atomic bomb survivors [13].

	A. Ankylosing spondylitis								Total
	Years After Treatment								
	0-	3-	6-	9-	12-	15-	18-	21+	
Leukemias	6	10	6	3	1	4	1	0	31
Absolute Risk ^a	1.5	3.8	1.6	1.2	0.0	2.4	0.6	(-.9)	1.8
Relative Risk	6.0	11.2	6.9	3.3	1.0	4.4	1.8	0.0	4.8

^a per 10⁶PY

	B. Atomic bomb survivors							Total
	Years After Exposure							
	5-	10-	14-	18-	22-	26-	30+	
Leukemias ^b	23	13	10	6	7	4	3	66
Absolute Risk ^c	4.1	2.2	1.8	0.9	1.1	0.4	0.4	1.7
Relative Risk ^d	17	14	10	10	7.2	2.9	1.1	7.4

^b 100+ rad

^c Linear Regression Estimate (10⁶PY-rad), all doses

^d 100+ rad vs 0 rad

ences by cell type. Chronic lymphocytic leukemia is known not to be increased after irradiation; and for acute leukemia, the induction period varies by age at exposure while the induction period for chronic granulocytic leukemia does not [9]. The wave-like distribution of leukemia risk over time since exposure does, however, appear compatible with log-normal models [4]. Bone cancers following radium-224 injection follow a similar wave-like distribution of risk over time since exposure [12]. For leukemia and bone cancer, therefore, neither the RR nor the AR time-response model is appropriate.

Cancers other than leukemia and bone cancer. A-bomb survivors. Can any conclusions be drawn from the distribution of an undifferentiated set of cancers, other than leukemia, over time since exposure? For the A-bomb survivors [13], there appears to be a clear pattern of increasing risk of death from cancer under the AR model (Table 2A), even after the minimum latent period is passed, but much less variation under the RR model. This, however, is a somewhat age-confounded interpretation since the young at the time of the bombings appear to be of high sensitivity to radiation-induced cancers and are the most likely ones to survive beyond 30 years. This becomes evident when excess risk is examined simultaneously by age at exposure and age at observation (Table 2B). For the youngest cohorts, the information is limited since they are just now entering the ages when most spontaneous cancer risks increase rapidly. It is also conceivable that the RR time-response model might fit each particular tumor individually but not a particular mix of tumors.

LEUKEMIA MORTALITY

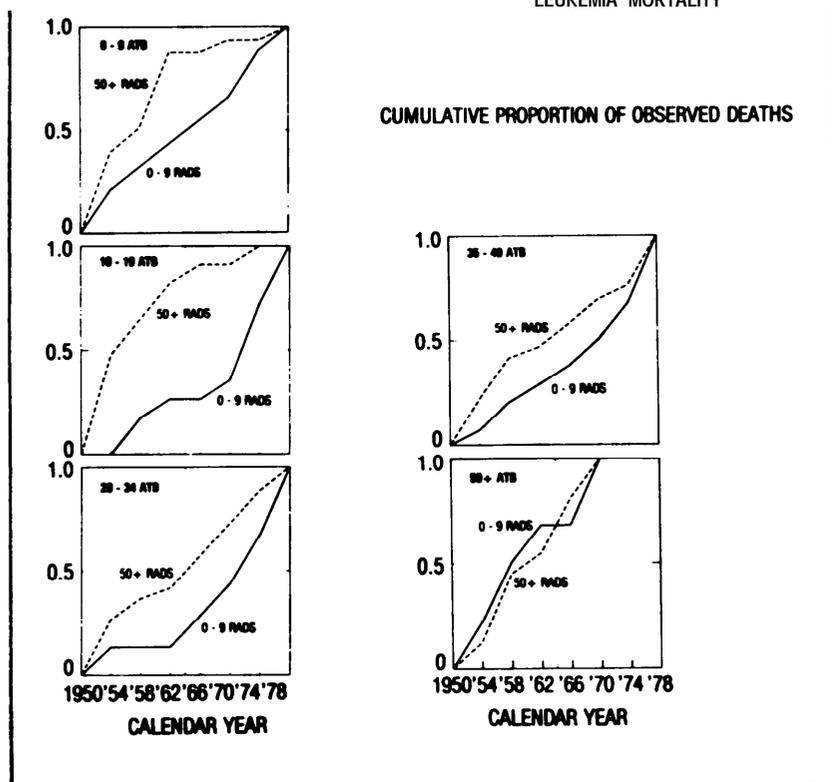


Figure 4. Cumulative proportion of leukemia deaths occurring over time since exposure in atomic bomb survivors according to age-at-time-of-bombing (ATB) and dose ($50 + \text{rads}$ vs. $0-9 \text{ rad}$). The dissimilarity between the high dose and low dose curves suggest that radiogenic leukemia tends to occur earlier than spontaneous leukemia, at least for survivors exposed at young ages [4].

Spondylitis patients. Similarly, for the spondylitic patients [8] the RR model appears to be more adequate than the AR model to describe the risk over time since exposure for cancers of heavily irradiated sites near the spine (Table 3). Interestingly, it is frequently overlooked that this important study of radiogenic effects suggests that the risk decreases after 20 to 27 years of follow-up (Figure 5). Although not statistically significant, this decrease supports the need for caution in the application of projection models beyond the follow-up periods of observation.

TABLE 2.—Absolute risks (AR)^a and relative risks (RR)^b of all cancers except leukemia by age at exposure and age at death and years after exposure among atomic bomb survivors [13].

2A. All ages.								
	5-	10-	14-	Years After Exposure			30+	Total
				18-	22-	26-		
Total Cancers	38	33	58	54	66	81	102	432
Absolute Risk ^a	1.6	-0.1	2.6	3.0	3.2	3.7	9.2	3.0
Relative Risk ^b	1.1	0.8	1.3	1.0	1.3	1.4	1.7	1.3

2B. Age Specific.								
Age at Exposure		<30	30-39	Age at Death			70+	Total
				40-49	50-59	60-69		
<10	AR	1.2	4.4	13.4	—	—	—	
	RR	15	5.0	6.8	—	—	—	
10-19	AR	0.0	1.7	4.6	20.7	—	—	
	RR	1.0	2.5	2.4	8.2	—	—	
20-34	AR	—	1.4	1.0	8.0	10.3	—	
	RR	—	1.8	1.9	2.0	1.6	—	
35-49	AR	—	—	0.3	-1.0	2.1	12.7	
	RR	—	—	1.2	1.1	1.3	1.4	
50+	AR	—	—	—	17.4	0.5	18.3	
	RR	—	—	—	2.2	1.0	1.4	

^a Linear regression estimate (10⁶PY-rad), all doses, 1950-78

^b 100+ rad vs 0 rad

TABLE 3.—Absolute risks (AR)^a and relative risks (RR) of cancers of heavily irradiated sites near the spine by age at first treatment and years after treatment among ankylosing spondylitis patients [8].

Age at First Treatment		0-2	3-8	Years After Treatment			Total
				9-14	15-20	21+	
<25	AR		0.8	(-1.4)	10.1	(-6.4)	1.6
	RR		2.0	0.0	4.7	0.0	1.9
25-34	AR		(-1.2)	3.0	8.6	4.3	2.5
	RR		0.3	1.7	2.0	1.2	1.5
35-44	AR		4.8	17.1	14.6	11.8	11.1
	RR		1.7	2.1	1.5	1.3	1.7
45-54	AR		4.1	31.1	15.7	(-3.6)	15.1
	RR		1.2	1.8	1.3	1.0	1.4
55+	AR		13.1	38.8	41.6	34.8	25.4
	RR		1.3	1.6	1.5	1.4	1.4
Total Cancers		33	51	91	69	15	259
AR (×10 ⁻⁴)		4.0	2.5	12.2	12.5	3.9	6.8
RR		1.7	1.3	1.8	1.6	1.1	1.6

^a Absolute Risk (× 10⁻³PY)

Cervical cancer patients. A recent large epidemiologic study of women treated with radiation for cervical cancer [10] suggests that both relative and absolute risks increase over time since exposure for cancers of heavily irradiated sites near the pelvis, but the increase is

much more dramatic for absolute risks. Age-specific risks over time are more nearly constant under the RR model, and there is a suggestion that the relative risks might remain elevated until the end of life (Table 4). Much of this excess, however, is associated with sites that

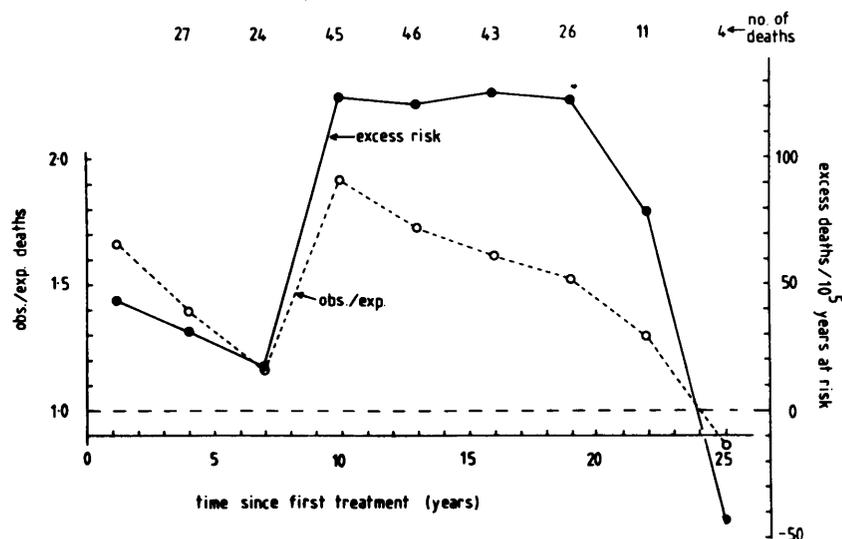


Figure 5. Observed and expected deaths from cancers of “heavily irradiated” sites near the spine, according to time since first radiation treatment among spondylitics [43].

TABLE 4.—Observed cancers and relative risks of cancers of heavily irradiated sites near the cervix by age at exposure and years after exposure among patients receiving radiotherapy for cervical cancer [10].

Age at Exposure		Years After Exposure					Total
		10–	15–	20–	25–	30+	
<30	Observed Cancers	5	3	4	3	1	16
	Relative Risk	5.2	2.5	3.4	4.5	5.3	3.7
30–39	Observed Cancers	33	37	23	5	11	109
	Relative Risk	1.3	1.7	1.6	0.7	2.9	1.5
40–49	Observed Cancers	83	74	45	28	7	237
	Relative Risk	1.1	1.4	1.4	1.8	1.4	1.3
50–59	Observed Cancers	133	68	30	19	4	254
	Relative Risk	1.4	1.2	1.1	1.9	2.6	1.3
60–69	Observed Cancers	75	38	12	2	0	127
	Relative Risk	1.1	1.3	1.4	1.5	—	1.2
70+	Observed Cancers	20	5	1	0	0	26
	Relative Risk	1.1	1.5	2.0	—	—	1.2
Total Cancers ^a		374	232	120	61	24	1,622
Absolute Risk ($\times 10^{-4}$)		7.1	11.5	13.3	35.8	81	2.6
Relative Risk		1.2	1.3	1.3	1.7	2.1	1.1

^a Includes tumors near the cervix for which age distributions were not available.

received extremely high radiation doses, such as the bladder, rectum, and genital organs for which generalizations to situations involving low-level exposures may not be appropriate.

Childhood cancer patients. A recent study of over 9,000 persons treated for childhood cancer [14] suggests that a RR time-response model would be more appropriate than an AR model to describe the pattern of excess cancers over time since treatment (Table 5). These children were all treated at a comparable age, most under age 15, although only about 80 percent received radiotherapy. The very low underlying expected rate of cancer, however, only 11 expected cancers, creates imprecision in the risk estimates by years after treatment. In addition, these patients also received cytotoxic drugs which could interact synergistically with radiation [15] and certain childhood cancers appear to be associated with an extreme radiosensitivity to the development of second malignancies [16]. Conceivably, time to response could be quite different in irradiated populations more representative of the general population.

Specific cancer sites. Mechanistically, the RR time-response model seems consistent with a multistage model of carcinogenesis in which cellular changes caused by ionizing radiation may result in cancer provided that subsequent "promoting" influences cause the affected cell or cells to replicate uncontrollably. The RR model might be expected to describe time to response if non-radiogenic cancers reflect the influence of agents other than radiation initially, but the same promoting factors that influence radiogenic cancers. Because tissues vary in their sensitivity to radiation carcinogenesis, and because different promoting factors may influence the time of appearance of cancers of different tissues, the model makes sense theoretically only in terms of single cancer sites or groups of cancers having similar patterns of change in risk with increasing age at observation. Table 6 [17] gives an example of how the RR model might hold exactly for three cancer sites considered singly, but grossly distort the lifetime risk projection when applied to the three cancer sites as a group.

Breast. Studies of radiation-induced breast cancer support the validity of the RR time-response model [4]. The relative risks over time

TABLE 5.—*Absolute and relative risks of all second cancers over time since treatment for childhood cancer [14].*

	Years After Treatment					Total
	2-	5-	10-	15-	20+	
Observed Cancers	35	52	42	24	14	167
Absolute Risk ($\times 10^{-3}$)	1.5	2.7	5.1	7.5	15	3.1
Relative Risk	12	15	17	15	17	15

since exposure, given a latent period that appears inversely related to age at exposure, appear more constant than do the absolute risks over time (Table 7). The congruence of the cumulative distributions of radiogenic and spontaneous breast cancers over time for all ages at exposure in the recently updated A-bomb series of 564 cases further suggests that the radiation-induced breast cancers develop only after

TABLE 6.—Example of absolute and relative risk projections forward in time for radiogenic cancers of the thyroid, breast, and digestive organs, individually and grouped together. The example assumes a 1-rad exposure at age 15 years among 100,000 women, a 30-year follow-up, and a 10-year minimal induction period [17].

Cancer Site	Estimate of risk exposure at age 15 to age 45			Projected lifetime risk		
	Naturally Expected Cancers	Radiogenic Excess	RR	Naturally Expected Cancers	Radiogenic Excess AR Model	RR Model
Thyroid	160	11.3	1.0706	400	28	29
Breast	910	14.2	1.0156	7,300	36	114
Digestive	200	2.0	1.0100	6,700	4.9	65
Total	—	—	—	14,400	69	207
Grouped Sites	1,270	27.5	1.0217	14,400	69	312

TABLE 7.—Absolute risks (AR)^a and relative risks (RR) of breast cancer by age at exposure and age at observation among patients irradiated because of tuberculosis or mastitis, and atomic bomb survivors [18].

Age at Exposure	Series		Age at Observation		40–	50–	60–	70+
			20–	30–				
10–19	TB-Fluoroscopy	AR	3.2	12.0	24.8	32.7	—	—
		RR	9.0	4.1	3.1	3.1	—	—
	A-Bomb	AR	0.6	4.6	7.7	—	—	—
		RR	8.8	4.9	3.1	—	—	—
20–29	TB-Fluoroscopy ^b	AR	—	0.4	7.6	3.1	19.5	—
		RR	—	1.1	1.7	1.2	2.1	—
	Mastitis	AR	—	8.2	13.9	28.6	—	—
		RR	—	3.0	1.9	2.5	—	—
	A-Bomb	AR	—	1.1	3.4	7.0	—	—
		RR	—	2.0	1.9	3.4	—	—
30–39	Mastitis	AR	—	—	11.5	41.6	41.2	—
		RR	—	—	1.7	3.1	2.8	—
	A-Bomb	AR	—	—	(-2.6)	3.9	0.5	—
		RR	—	—	0.3	2.4	1.2	—
40–49	A-Bomb	AR	—	—	4.4	(-0.5)	0.1	(-0.9)
		RR	—	—	2.2	0.8	1.0	0.7
50+	A-Bomb	AR	—	—	—	(-2.9)	2.3	1.5
		RR	—	—	—	0	1.8	1.6

^a × 10⁻⁴PY

^b 20–39 Years of Age

women attain the age at which the cancers normally develop, and in a manner proportional to the natural incidence (Figure 6). Furthermore, these generalities appear to hold not only for atomic bomb survivors, but also for women who received multiple chest fluoroscopies for tuberculosis, and for women who received radiotherapy for post-partum mastitis [18]. Breast cancer, however, differs from practically all other cancers in that there is little evidence that women over age 40 at exposure are at much, if any, risk of radiogenic cancer. In contrast, among A-bomb survivors [13], spondylitic patients [8], and cervical cancer patients [10], persons exposed after age 40 years are at appreciable risk of developing radiation-induced cancers of

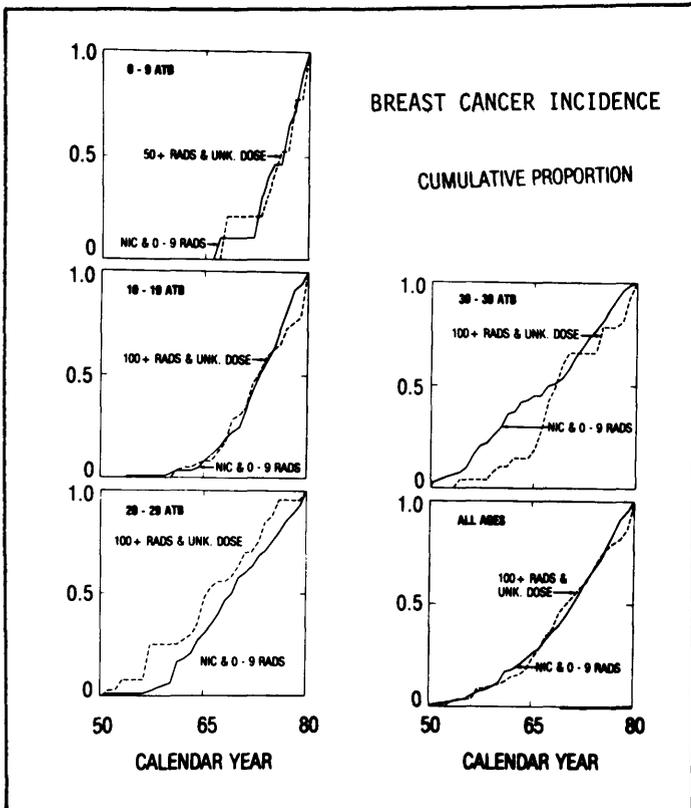


Figure 6. Cumulative proportion of 564 breast cancer cases occurring over time since exposure in atomic bomb survivors according to age-at-time-of-bombing (ATB) and dose. The similarities between the cumulative distributions of radiogenic (high dose) and spontaneous (low dose) breast cancers suggest that radiogenic breast cancers develop only after women attain the age at which the cancers normally develop, and in a manner proportional to the natural incidence [4].

other sites. If breast cancer is atypical in this sense, it may also be atypical with respect to time response.

Stomach and Lung. Stomach and lung cancers are observed radiogenic effects among spondylitics and A-bomb survivors. Among the spondylitics [19], the pattern of risk over time is not well defined for the small stomach cancer series; for the lung, however, the RR model is clearly superior (Table 8). The cumulative distributions of risk over time among atomic bomb survivors [13] suggest that the RR model is more appropriate for cancers of both lung and stomach, as well as breast (Figure 7). These comparisons are based on combined ages at exposure. Age-specific comparisons based on the atomic bomb survivor data, however, yield similar results for both types of cancer [4]. These conclusions conceivably could change, however, after more data have been gathered for both studies. It might also be noted that when the number of radiogenic cancers is small in comparison to the natural incidence, the cumulative distributions of low-dose and high-dose cases are necessarily similar, and thus not very informative.

Thyroid. For children irradiated for enlarged thymus glands [20], the AR time-response model for radiation-induced thyroid cancers appears very consistent with the observed data (Table 9). As was the case for the childhood cancer study, however, the very low number of expected thyroid cancers, less than 1 over all, makes the estimates of relative risk over time very imprecise. Nonetheless, when one compares these absolute risk estimates with normal age-specific incidence rates, it is clear that relative risks are declining sharply over time. On the other hand, thyroid cancer is normally an indolent tumor, and time to diagnosis depends strongly upon the level of diagnostic effort. In a closely monitored population, like the thymically-irradiated children, in which an excess risk is already known to exist, it might be expected that diagnoses would tend to be shifted to earlier ages as compared to the general population. Thus, the apparent flatness of the time to response data could, in part, be an artifact of diagnostic effort.

TABLE 8.—Absolute risks (AR)* and relative risks (RR) of stomach cancer and lung cancer by years after treatment among spondylitics [19].

Site		Years After Treatment							
		0-	3-	6-	9-	12-	15-	18-	21+
Stomach	Number	6	3	5	7	12	6	4	2
	AR	0.3	(-.7)	1.6	1.3	4.4	0.9	1.4	(-.6)
	RR	1.2	0.7	1.1	1.5	2.4	1.3	1.3	0.9
Lung	Number	13	10	13	26	16	21	15	10
	AR	1.4	0.3	1.2	1.3	4.3	4.8	7.5	5.4
	RR	1.5	1.1	1.2	2.1	1.1	1.4	1.6	1.4

* $\times 10^{-4}$ PY

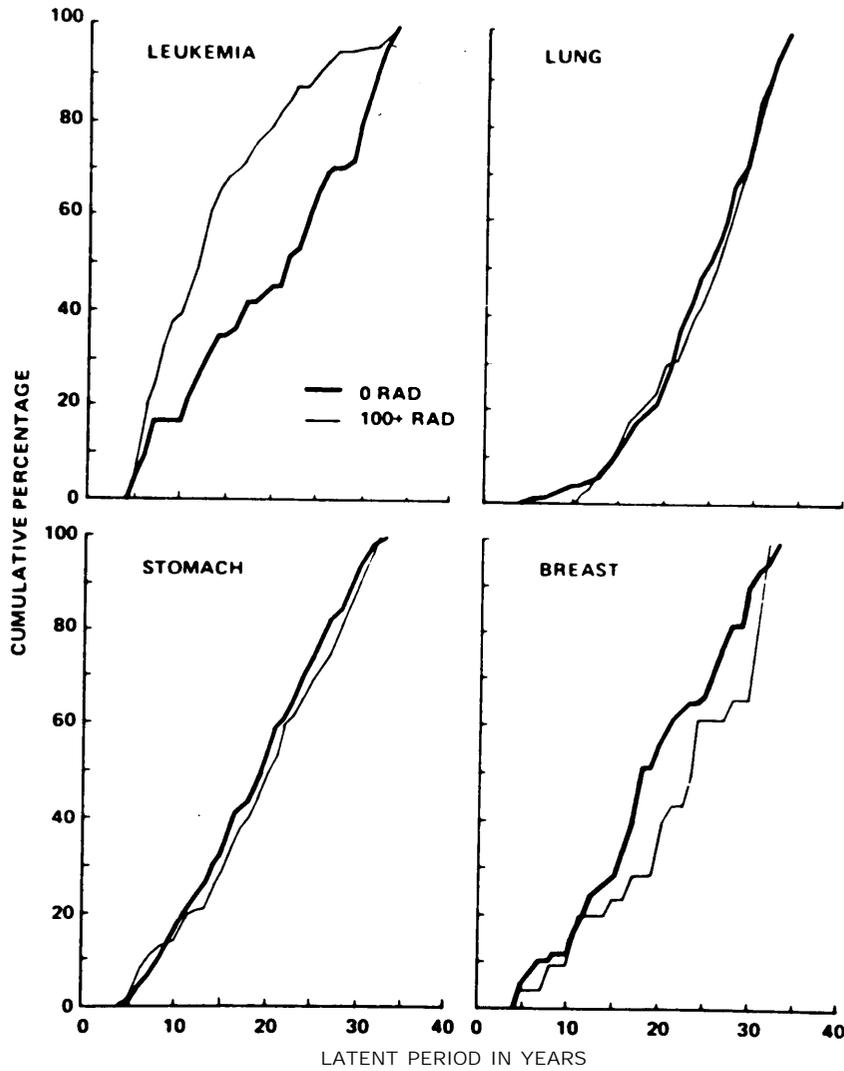


Figure 7. Cumulative proportions of deaths due to leukemia and cancers of the lung, stomach, and breast occurring over time since exposure in atomic bomb survivors according to dose (100+ rad vs. 0 rad). Radiogenic leukemias occur earlier than spontaneous leukemias and appear to have a finite expression period. The expression of radiogenic lung cancer and stomach cancer appear to be similar to that of radiogenic breast cancer as discussed in Figure 6, i.e., they develop in a manner proportional to the natural rates [13].

TABLE 9.—*Absolute risks of thyroid cancer by years after exposure among persons irradiated for enlarged thymus glands in early life [20].*

	Years After Exposure				Total
	5-14	15-24	25-34	35-49	
Thyroid Cancers	6	12	8	4	30
Absolute Risk*	2.6	5.7	5.2	5.6	

* $\times 10^{-4}$ PY; Adjusted for sex, Jewish ethnicity and dose

Discussion. What can be concluded from the foregoing survey of epidemiologic studies about the appropriateness of various time-response models for radiation induced cancer? One conclusion that seems clear is that there is no universally applicable model. Neither the AR nor the RR model is appropriate for cancers, like leukemia following external irradiation or bone sarcoma following x-ray or brief radium exposure, whose excess is of limited duration. The RR model seems to hold for a number of cancer sites, but the best evidence comes from studies of female breast cancer, an unusual cancer in that irradiation seems ineffective after about age 40. It is reassuring that lung cancer also seems to correspond to the RR model, but supporting evidence with respect to stomach cancer is weak. Other supporting evidence is based upon comparisons of combined cancer sites and ages at exposure, and we have seen that such evaluations can be deceptive (see Table 6). The apparent consistency of radiogenic thyroid cancer with the AR time-response model may be an artifact associated with medical surveillance. However, the data on thymically-irradiated children are reasons for caution in concluding that the RR model is universally applicable to radiogenic cancers with long expression periods.

For most cancer sites, underlying risk increases markedly with increasing age at observation. In general, populations exposed to ionizing radiation as children have now been observed for only the first few years of the age range during which most of this increase takes place. We have seen enough to conclude that for some sites there is an excess risk, and that it tends to be higher, relative to background, than in populations irradiated at older ages. But we have no way of knowing whether or not these high relative risks will continue well into the age ranges at which cancer risk is normally highest. That is, although the RR model, or perhaps, in the case of thyroid cancer, the AR model may appear to hold in midlife, it does not necessarily follow that the pattern will continue. The question is of more than theoretical interest because, while relative risks tend to be high in persons irradiated in childhood, absolute risks tend to be low compared to

those estimated for older exposure cohorts, and the difference between lifetime projections by the RR and AR models is large.

Comparison of One Population with Another

It is essential that risks derived from exposed populations be applied, perhaps with suitable adjustments, to other exposed populations to estimate the magnitude of possible hazards involved and to make decisions based upon the benefits associated with such exposures. Such radioepidemiology has been applied in the mammography evaluations in the 1970s [21], and is currently being developed to give guidance to courts concerned with compensation cases involving prior radiation exposure [22,23]. Time-response as well as dose-response models must be used to develop probability tables to estimate the chances that a cancer arising in an individual was "caused" by a prior radiation exposure. Since there is a practical and continuing need to apply risks from one population to another, is there an appropriate way in which this should be done?

No two exposed populations are as similar as we might like, and it is always difficult to generalize findings from one epidemiologic study to another when the conditions of exposure and of the populations studied are different. Most epidemiologic studies on which current estimates are based involved exposures 30 to 50 years ago when conditions differed dramatically from those of today. The reasons why cancer risks in one population may differ from those in another are unclear, but must be related to the types of exposures, to concomitant influences of physical, chemical or biological co-factors for disease, or to differences in sex, age at exposure, and age at observation. If radiation does, in fact, interact with other environmental or biological factors associated with increased cancer risk, then conceivably radiogenic risk could be greater in one irradiated population than another simply because of a different level of exposure to some other factor.

It is also possible that different kinds of radiation exposure may interact differently with certain other risk factors. For example, radiation appears to interact in a multiplicative manner (Table 10) with cigarette smoking among uranium miners [24]. In a recent evaluation of lung cancer data among atomic bomb survivors, however, cigarette smoking was found to interact in a manner consistent with an additive model; that is, the effect of radiation and cigarette smoking together was not greater than expected if they were acting independently as causes of lung cancer [25].

TABLE 10.—Relative risks according to smoking and radiation exposure among uranium miners and atomic bomb survivors [25].

Population		Uranium Miners		Atomic Bomb Survivors	
		Smoking Level Low	High	Smoking Level Low	High
Radiation Level	Low	1.0	7.7	1.0	9.7
	High	18.2	146.8	6.2	14.0

It is generally accepted that radiation may be a universal carcinogen. However, in no animal system or human epidemiologic study have all varieties of cancer been found to increase following radiation exposure. The single most informative population for radiation risk estimation is the atomic bomb survivors, but even here not all cancers have been found to be increased. Thus far, cancers of the uterus, cervix, brain, skin, bone and prostate have not been increased above expectation, nor has Hodgkin's disease, melanoma or chronic lymphocytic leukemia [13]. A few of these cancers have been found in excess in other irradiated populations. Thus, generalizing from one population to another should be done cautiously.

The average yearly excess cancer risk per person exposed to a given dose of radiation and followed for a specified number of years after exposure can be expressed simply in absolute terms, in numbers of excess cases or deaths, or relative to background or natural risk (e.g., percentage of baseline risk). We have dealt above with the problem of how that average yearly risk is distributed over time after exposure. Here we are concerned with whether it makes more sense to use one measure or the other (or perhaps some other measure) when comparing risk in different irradiated populations or when transferring risks from one population to another which may have different background levels of risk. As in the case of time to response, the data are most informative when considered site-specifically.

- A simple example of the computation of absolute and relative risks is presented for the study of tuberculosis patients exposed to multiple chest fluoroscopies in Table 11. Among 877 women who survived 10 or more years after first fluoroscopy, 38 breast cancers developed compared with 20.9 expected. The absolute risk can be computed as the difference between the observed and expected values divided by the woman-years of follow-up and the average breast dose of 150 rads: 6.2 excess cancers per million women per year per rad. The percent increase in relative risk per rad can be computed as the excess relative risk, 82 percent in this case $(O/E-1)$, divided by the average dose, for a value of 0.55 percent per rad.

TABLE 11.—Example of a simple computation of absolute risks and relative risks per rad among women with tuberculosis who received multiple chest fluoroscopies and subsequently developed breast cancer [38].

Assume 10 year minimum latent period	
Number of women surviving 10 years	877
Observed Breast Cancers after 10 years (O)	38
Expected Breast Cancers after 10 years (E)	20.9
Woman Years at Risk after 10 years (WY)	18,511
Average Breast Dose (D)	150 rad

$$\text{Absolute Risk} = [(O-E)/WY]/\text{Dose} = (RR-1)I_0/\text{Dose} = 6.2 \text{ excess cancers per million women per year per rad}$$

$$\text{Relative Risk (RR)} = O/E = 38/20.9 = 1.82$$

$$\% \text{ Increase In Relative Risk Per Rad: } [(RR-1)/\text{Dose}] \times 100\% = 0.55\%$$

$$* I_0 = E/WY$$

Breast Cancer. Now which radiogenic breast cancer estimate, the absolute risk or the relative risk, is more similar among various populations of exposed women, in particular, the American women with tuberculosis and mastitis and the Japanese atomic bomb survivors? Clearly, the normal age-specific incidence of breast cancer varies between Western women and Japanese women (Figure 8), so it might be very instructive to learn whether absolute or relative risks are more similar across these populations. Unfortunately, not all studies were well represented by subjects exposed at all ages of interest, and only comparisons between ages 10 to perhaps 39 are informative (Table 12). Despite the small numbers, the absolute risks appear definitely more consistent across studies [18,26]. It is further evident from these data that radiation does not merely multiply the underlying or natural breast cancer risk by a constant factor across all ages. If this were so, older women with a much higher natural risk would show much greater absolute risk estimates than younger women, when in fact, the opposite is true.

Thyroid cancer. Radiation-induced thyroid cancer has been reported in several populations exposed during the early years of life, in particular, atomic bomb survivors and children irradiated for enlarged thymus glands, enlarged tonsils or tinea capitis [20]. Once again, the absolute risks are somewhat more consistent among these populations (Table 13). Thyroid cancer is relatively rare in most populations, compared to other cancers, but rates are naturally high among persons living in Israel, Iceland and Hawaii [27].

Leukemia. Leukemia is the form of cancer most commonly found following radiation exposure. Elevated rates have been reported among

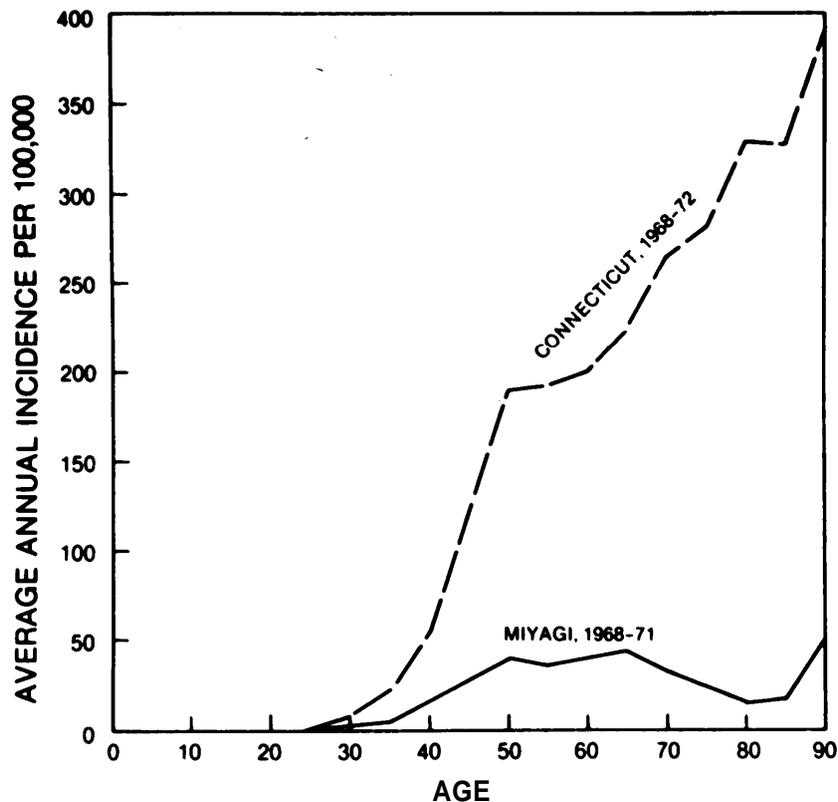


Figure 8. Age-specific population rates for female breast cancer incidence in the United States (Connecticut, 1968-72) and in Japan (Miyagi, 1968-71) [27].

atomic bomb survivors [9], spondylitis patients [8], patients with benign gynecologic bleeding disorders [28], radiologists [29], children exposed to prenatal x ray [11], thorotrast patients [30], thyroid cancer patients given high doses of radioactive iodine [31], and others [1]. The incidence of acute and myelogenous leukemia varies very little around the world [27] and, therefore, it appears that both the AR and RR models yield comparable estimates of effect across studies of atomic bomb survivors, patients treated for spondylitis, and women treated for benign bleeding disorders (Table 14). Since the expression period of radiogenic leukemia is less than the period of observation, these similarities are not surprising. Surely then, similar findings from so many studies must be easily generalizable to other exposed populations. Not necessarily.

Cervical cancer patients who received very large localized exposures for the treatment of their disease have been found to be at very low

TABLE 12.—Absolute risks and percent increases in relative risk per rad of breast cancer among three exposed populations [18, 39].

Age at Exposure	Study	No. Cancers Among Exposed	% Increase RR/rad	Absolute Risk 10 ⁶ WY-rad
0-9	A-Bomb	18	4.5	2.8
10-19	TB-Fluoroscopy	13	0.8	8.7
	Mastitis	2	—	(28) ^a
20-29	A-Bomb	40	3.0	9.0
	TB-Fluoroscopy	18	0.2	3.8
	Mastitis	18	0.4	6.3
30-39	A-Bomb	36	0.9	2.9
	TB-Fluoroscopy	4	(2.4) ^a	(7.0) ^a
	Mastitis	13	0.4	9.4
40-49	A-Bomb	28	1.5	4.9
	TB-Fluoroscopy	1	(0.6) ^a	(7.7) ^a
	Mastitis	3	(1.6) ^a	(52.1) ^a
50+	A-Bomb	15	-.3	-1.0
	A-Bomb	15	1.0	3.3

^a Estimate based upon small numbers and is associated with a large uncertainty

TABLE 13.—Absolute risks and percent increases in relative risk per rad of thyroid cancer among four exposed populations [20].

Study	No. Persons	No. Cancers	% Increase RR/rad	Absolute Risk (10 ⁶ PY-rad)
A-Bomb ^a	4,377	26	6.4	3.4
Thymus ^b	2,651	30	30.3	3.5
Tonsil ^c	2,578	181	11.5	3.6
Tinea Capitis ^d	13,060	23	26.5	6.3

^a [40], <30 yrs ATB, ≥50 rad

^b [20]

^c [41]

^d [42]

TABLE 14.—Absolute risks and percent increases in relative risk per rad of leukemia among three populations exposed after age 10 [1].

Study	No. Persons	No. Leukemias	% Increase RR/rad	Absolute Risk (10 ⁶ PY-rad)
A-Bomb	19,472	62	2.0-3.1	0.8-1.2
Spondylitis	14,554	52	2.3	0.9
Menorrhagia	2,068	6	2.7	1.2

risk of radiogenic leukemia in many well-conducted studies [10]. Whereas hundreds of excess leukemias might have been expected, only a handful have been found. Cell-killing effects of high-dose radiotherapy have been postulated as a possible explanation. Although American radiologists [29] practicing in the early years of this century were

at increased risk of leukemia, British radiologists were not [32]. Were the exposures different because the British began taking precautions earlier? Radium dial workers [33] and German patients [12] who ingested or received high doses of radium have been found to be at increased risk of osteosarcoma, but not leukemia. Uranium miners are at high risk of lung cancer associated with exposures to radon gas, but no leukemia excess has ever been reported [34]. Prenatal x ray is associated with increased leukemia deaths in childhood, atomic bomb survivors exposed *in utero* did not experience any leukemia deaths [35]. Tuberculosis patients who received hundreds of multiple chest fluoroscopies have been found to be at high risk for breast cancer development, but no leukemia excess has been reported [36].

Some of the above differences can be partially explained in terms of dose-response models (high-dose cell killing among the cervical cancer patients, for example) or because some studies were not of particularly high power due to low bone marrow dose levels, inadequate sample size, or both. It is sometimes forgotten that, even as low statistical power (and statistical variability generally) can be responsible for failure to detect an existing excess risk, it can also lead, for the same reasons, to overestimation of an effect. Thus, differences in risk among exposed populations are to some extent to be expected. On the other hand, many of the above differences, and others that are seen with respect to other sites, are sufficiently great to remind us, forcibly, that efforts to impose order on our knowledge of radiation carcinogenesis in man through modelling and analogy are based on imperfect understandings.

Discussion. Once again, it is not clear how best to apply risks derived from one population to another. For most cancers, it appears that the age-specific absolute risks might be more consistent. However, for other cancers for which the spontaneous rates are similar in exposed populations and for which the period of observation exceeds the expression period for radiogenic disease, both the RR and the AR estimates appear equally useful.

It should be mentioned, however, that when the underlying patterns, as opposed to absolute levels, of variations in cancer incidence by age at observation are appreciably different between populations, a logical inconsistency occurs. If relative risks are constant over time within populations, as suggested from the previous time-response evaluations, the absolute risks cannot be invariant among populations exposed at similar ages, at least not at all ages at observation. This contradiction has been remarked upon for breast cancer [18], for which age specific rates increase steeply in the U.S. but level off after about age 50 among

Japanese. Moolgavkar and colleagues [37], however, have argued persuasively that this apparent leveling off merely reflects rapid increases in breast cancer risk over time, and that within younger birth cohorts the dependence of risk on age at observation strikingly parallels that seen in the U.S. Thus, the apparent contradiction may be an artifact of looking at population rates across birth cohorts. Nevertheless, it is well to remember that we are dealing with extremely simple, ad hoc extrapolation models whose intrinsic biological plausibility has yet to be established. Care must thus be taken in transferring absolute risk estimates across the Pacific, from Japan to the United States, and then projecting relative risks forward in time to predict future risks. It is hoped that further follow-up of atomic bomb survivors and medically irradiated populations will yield additional insights into the appropriateness of AR versus RR estimates.

Comparison of One Cancer with Another

From the data already presented, it should be clear that organ-specific risk estimates bear little relation to the level of natural incidence (Table 15), and this is true for both AR and RR estimates. Some cancers of high natural incidence, for example colon and prostate, have low or zero relative risk per rad coefficients. Some cancers of high natural incidence, for example breast, have high relative risk coefficients. Some cancers of low natural incidence, for example thyroid, also have high relative risk coefficients. And some cancers of low natural incidence, for example esophagus, have low relative risk coefficients. These observations also indicate that the doubling dose of radiation (100 percent divided by the RR percentage increase per rad) is not the same for all cancers. There is no basis for extrapolating

TABLE 15.—Radiation risk coefficients and natural incidence of selected cancers

Type of Cancer	Natural Incidence* (Cases/10,000 per year)	Radiation Risk Coefficients	Percent Increase RR/Rad	Absolute Risk (10 ⁶ PY-rad)
Prostate	High (6.9)	Low	0.0 ^b	0.0 ^b
Breast	High (8.5)	High	0.4–1.0 ^b	5.8 ^b
Thyroid	Low (0.4)	High	6–30 ^c	3–6 ^c
Esophagus	Low (0.4)	Low	0.4 ^d	0.3 ^d

* Age-adjusted, sex specific; [7]

^b [1]

^c [20]

^d [8]

routinely from one cancer to another using either the RR or the AR model.

Conclusion

Granted that exposed populations are dissimilar, that epidemiologic studies have not followed exposed persons for their entire life spans, and that the natural incidence for many malignancies is changing over time, can any conclusion be drawn with respect to time-response, projection or extrapolation models or to the better form of risk estimates to be used to compare populations or different sites of cancer? Because of the multicausal, multistage nature of carcinogenesis, it is unlikely that the appropriateness of either an AR or RR model for projection of risk forward in time, or for comparing one population to another, will soon be definitely established. Both of these models are simple mathematical constructs being applied to explain complex phenomena. Clearly, caution must be exercised in projecting risks forward in time and in using risks derived from one population for another population, and from one cancer for another. Some tentative conclusions, however, can be made based on current information: (1) neither the absolute- nor the relative-risk model is well-suited to all estimation purposes; however, (2) the relative risk model appears more useful to describe the distribution of radiogenic solid tumors over time in the same population; (3) the absolute risk model appears useful to transfer the risk of some tumors from one population to another of different natural incidence; and (4) neither risk model is valid to project the risk of one cancer to that of another cancer. Despite the serious limitations of current models, they nonetheless are useful in providing guidance on the hazards associated with medical, occupational, and environmental exposures to ionizing radiation.

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Discussion

C. W. MAYS: Congratulations John, on a superbly clear description on both of these models. The take home message that I get is that neither model in its simple-minded form is likely to be universally right and that what will end up will be something more complex. The other take home message that I get is that it is absolutely essential that the follow-up of these irradiated populations exposed to high doses and medium doses be followed out until the time of extinction, until all or virtually all of these patients have died, because only when this is done can you be sure which model correctly gives the right expectation for total cancer risk.

J. D. Boice: I would agree with you on both counts.