MASTER

EPIDEMIOLOGIC MEASURES OF RISK AS A BASIS FOR LEGAL COMPENSATION*

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ABSTRACT

The scientific basis for compensation of persons developing cancer who have a documented history of exposure to radiation or other carcinogens is an important legal issue. The measure Relative Attributable Risk (RAR) has been proposed as a basis for determining eligibility for compensation. The purpose of this report is to present results of an analysis of the magnitude and sources of uncertainty in the RAR measure. The range of $1/10^6$/rad-year to $6/10^6$/rad-year was chosen as a reasonable range of excess-risk estimates for thyroid cancer based on published estimates. The use of such a range in risk estimates produces very wide variability in RAR estimates. Uncertainty in underlying incidence levels and in dosimetry are other major factors contributing to large variability in estimated RAR levels.

Introduction

Means by which individuals with known exposures to ionizing radiation might be legally compensated upon development of a cancer is a challenging issue in the legal application of scientific findings. Legislation has been proposed, and proposals have been made in other sectors, which would change current legal procedures in at least two ways: Legal eligibility for compensation would be entirely or partly determined outside of court by the construction of tables outlining the percentage of an individual's risk attributable to exposure on the basis of the estimated dose, cancer site, sex of the individual, and the age at which cancer developed. Second, the rule that causation must be "more probable than less probable" could be altered to a lower (or conceivably higher) percentage of risk required to be attributable to the exposure. At least two major scientific issues would enter into the suggested legal process: First, precisely how shall increased risk be measured in the exposed population? Second, how uncertain is the resulting estimate of risk which determines compensation?

Measurement of risk attributable to exposure

Increased risk of a disease in an exposed population may be measured as the _multiplicative_ increase in risk over the baseline incidence (relative risk) or the _additional_ risk added to the baseline incidence (excess risk).

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In symbols, if I_o is baseline incidence of a particular disease of interest and I_e is the incidence rate in the exposed population at a particular dose, Relative Risk = RR = I_e/I_o and Excess Risk = ER = $I_e - I_o$.

Both these measures apply to all individuals in an exposed population. Suppose of N_e exposed individuals, $D_e = I_e N_e$ develop cancer. Then the proportion of diseased cases considered to be radiation-caused is logically estimated as $(I_e N_e - I_o N_e)/D_e = (I_e - I_o)/I_e$. This measure is referred to as Relative Attributable Risk (RAR), and its potential for use in determining compensation has been discussed by Bond (1).

RAR is a function of the Relative Risk in the exposed, since

$$RAR = 1 - \frac{1}{RR} = \frac{RR-1}{RR} \;.$$

If it is assumed that Excess Risk is a linear function of dose, then a simple expression for the dose needed to produce a given RAR may be written. Let $I_e(d)$ represent incidence in the exposed at dose d, and k be excess risk per unit dose. Then $I_e(d) = kd + I_o$ and

$$RAR = \frac{I_e(d) - I_o}{I_e(d)} = \frac{kd}{kd + I_o} \quad \text{or} \quad d = \frac{I_o}{k} \cdot \frac{RAR}{1 - RAR}$$

Figure 1 shows the dose required to produce a particular RAR value for several choices of I_o and k.

DOSE REQUIRED TO PRODUCE AN RAR VALUE FOR VARIOUS CHOICES OF
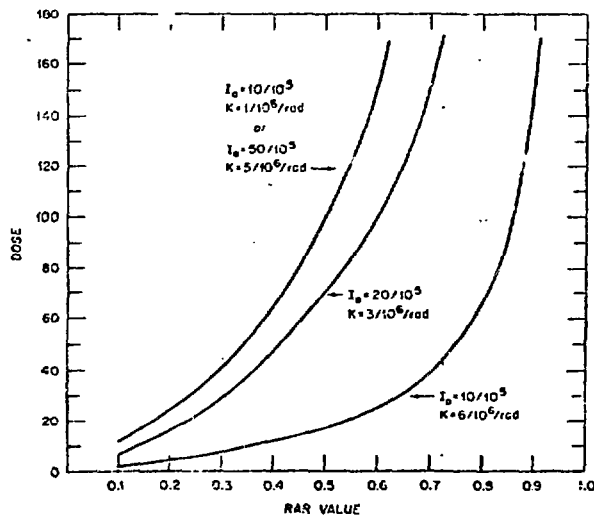BASELINE INCIDENCE AND EXCESS RISK

FIGURE 1

An examination of the sources and magnitudes of uncertainty involved in estimating RAR levels for radiation-related cancer sites has been carried out, using a computer program designed to estimate RAR levels for a life table population under various conditions. Thyroid cancer is used as the example in this manuscript. The next sections describe briefly the program and the range of underlying risk estimates and assumptions made for thyroid cancer.

The model

The general approach used in this sensitivity analysis is to simulate as closely as possible the experience of a radiation-exposed population with respect to thyroid cancer, using a reasonable range of relevant input variables. The model has two phases: First, the experience of a population exposed to a single dose is compared to a nonexposed population by the construction of a life table for each of these populations, and the combination of certain information from both life tables. The dose estimate for that single population is incorporated into the excess risk estimate used. Second, the model is used to estimate the experience of an actual population exposed at a single point in time by using the dose and age distribution of the actual population to combine information from a series of life tables. Because of space limitations, no attempts will be made to provide a detailed description of the construction of the life table estimates. Greater detail is available in Zeighami, et al. (2).

This simulation program uses a single exposed life table and the nonexposed life table to create the following output:

(a) For each exposed population the RAR at each age at observation, denoted by RAR(x), is computed as $k(x)/[I_o(x) + k(x)]$.

(b) The distribution of RAR values over each age beginning two years after exposure is given for the exposed population.

(c) The number of excess cases occurring during a lifetime due to the exposure is calculated by substracting total lifetime cases in the nonexposed cohort from those occurring in the exposed. The value in the life table is expressed as a number of excess cases per 100,000 persons entering at the age of exposure. In subsequent applications the number of excess cases occurring following an age at exposure has been adjusted for the proportion of an initial life table population of 100,000 actually remaining at the age of exposure.

Second, the program simulates the experience of an actual population by doing the following: Given input including (1) the age and dose distribution for the actual population, (2) excess risks for each dose, and (3) the expected (baseline) disease incidence, the simulation program calculates,

(a) the distribution of RAR at each age of observation,

(b) the distribution of RAR values over the lifetime of the
     exposed population,

(c) the excess cases occurring during the remaining lifetime for
     each age at exposure and dose category, and

(d) the excess number of cases expected to occur during the
     exposed population's lifetime.

At present the program requires that the distributions of dose and age at
exposure be independent so that each age group must be assumed to have
the same dose distribution. However, the generalization of dependence of
the distributions of dose and age at exposure is a direct one, and can
be easily made if needed.

The factors included in the simulation which contribute to variation
in the RAR estimates for thyroid cancer are: (a) level of baseline
incidence, (b) response at a given dose, (c) magnitude of dose, (d) length
of time following exposure during which maximum excess risk occurs, and
(e) age at exposure.

Thyroid cancer

Baseline (nonexposed) annual incidence rates for thyroid cancer were
estimated using 1973-77 general population rates for U.S. white males and
females reported by SEER (3). Figure 2 shows the rates for U.S. white
females.

A single straight-line fit to the data was inadequate, because of
the steady or declining rates after approximately age 35. A segmented
linear fit did provide an adequate fit, with the point at which the line
segments meet being a variable in the weighted least-squares fit. A
single straight line fit did provide an adequate fit to the data for
males.

Thyroid cancer in most populations is a rare tumor, particularly in
males. In order to investigate the effects of baseline incidence on RAR
levels, all simulations were made at the levels defined by the curves fit
to U.S. white male and female rates (designated as low incidence), at age-
specific rates twice that level (designated as medium incidence) and
at age-specific rates three times the national average (designated as high
incidence).

SEGMENTED LINEAR FIT TO AGE-SPECIFIC THYROID CANCER
INCIDENCE RATES, FEMALES
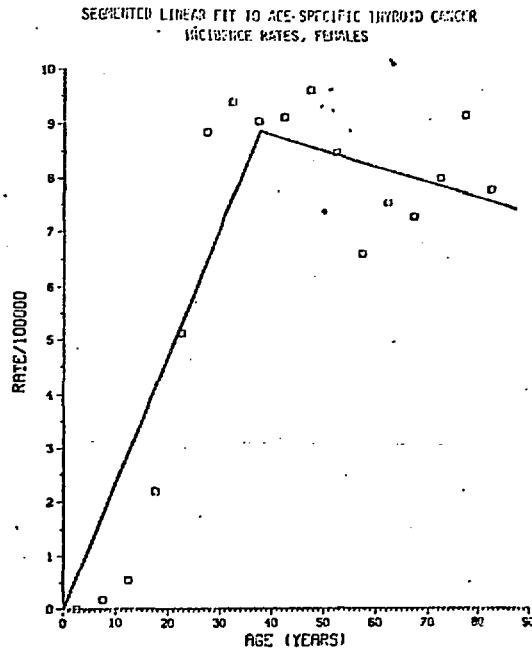
U. S. WHITE FEMALES
THYROID CANCER INCIDENCE, 1973-77

Figure 2

Baseline incidence rates for males are roughly half those for females, and the two sexes exhibit an age pattern which is clearly different. All simulation runs are therefore made separately for the two sexes. Incidence rates by single years of age were taken from the functions fit to the curves.

The evidence relating external radiation to subsequent risk of thyroid neoplasms comes principally from studies of persons therapeutically irradiated in the head and neck in infancy and childhood. Since the primary interest in this report is in the estimation of risk at low dose levels, the human studies most useful in obtaining low dose estimates are briefly summarized.

(1) Atomic Bomb Survivors. No excess was observed in this group among persons irradiated at whole body doses of less than 40 rads (kerma). Among those irradiated at 50+ rads, the estimate of excess risk was 2.4 cases/10^6/ rad-year in females and 0.92 cases/10^6/rad-year in males (4). The estimates covered the period from 5 years until 26 years after exposure and included all age groups.

(2) Israel Tinea Capitis Population (5). A total of 10,902 Jewish children immigrating into Israel received an estimated thyroid dose of 6-9 rads during scalp irradiation for Tinea capitis. An excess of 10 cases was observed in this group (based on the control population's risk). Neither the exact distribution of ages at irradiation nor the distribution of length of followup was given.

(3) Thymus Irradiation During Infancy. Hempelmann et al. (6) followed a group of 2,872 individuals given x-irradiation to the thymus during infancy. Estimated doses to the thyroid were quite high on the average. Among those persons with estimated thyroid doses below 100 rads (estimated average dose = 17.2 rads) the incidence rate for thyroid cancer was 2.6 per 100,000 per year (1 case in 35,028 person-years). Since this is based on one event, the confidence limits are clearly large. The difference between the rate observed and that expected in either males or females of the same ages is not significant.

(4) New York Tinea capitis Study. Shore, et al. (7) evaluated a similar population of 2,215 subjects irradiated during childhood for Tinea capitis and compared them to 1,395 nonirradiated control subjects who had Tinea capitis. Thyroid doses were estimated to be 6-10 rem, and follow-up averaged 20 years. No thyroid neoplasms developed in the irradiated group.

(5) Extrapolation from High Doses. Linear extrapolation of risk from high doses to low doses is generally presumed to provide a conservative estimate of the risk at low doses. The population reported by Hempelmann (6) seems to provide the best opportunity to fit a dose-response curve to the incidence rates in an exposed population since the population included persons with a wide range of doses. A population of 2,872 males and females receiving x-irradiation during infancy for enlargement of the thymus was compared with a control group which included 5,000 non-irradiated siblings.

Shore et al. (7) fit both quadratic and linear models to the data set reported by Hempelmann. They found both a significant dose-squared component and linear dose component in the dose-response relationship for the data. The weighted linear estimate of risk per rad was 5.2 per 10^6 population per rad ($\pm$ 0.48) for females and 1.8 per 10^6 population per rad ($\pm$ 0.29) in males. They noted that these estimates obtained from a linear fit to the data were 2 to 3 times higher at low doses than estimates obtained using the quadratic fit to the data.

Maxon, et al. (8) combined data from several studies to estimate a linear dose-response function for incidence of thyroid cancer. The estimated function was

$$\text{Incidence} = 0.42 \ (10^{-5})(\text{dose in rem})$$

At low doses, the incidence estimated by this function is in the range of risks for U.S. white males below the age of 30.

The published estimates of risk of thyroid cancer for external radiation fall roughly between $0.5/10^6$/rad-year and $6/10^6$/rad-year. Risk estimates from external radiation for the simulation were accordingly chosen as $1/10^6$ cases/rad-year, $3/10^6$ cases/rad-year, and $6/10^6$ cases/rad-year.

Risk estimates for internal emitters, primarily from uptake of ^{131}I, are also of concern in thyroid carcinogenesis. The precise effectiveness of ^{131}I compared to external radiation is uncertain (9). Potential differences in effectiveness exist, because of differences in dose rate, and because of potential uneven distribution of an internal emitter within the thyroid (10). However, if it is assumed that ^{131}I is a fraction $f \leq 1$ as effective as external radiation, then the RAR estimates developed in the present work for a dose d of external radiation apply to a dose d/f of ^{131}I. For example, if it is assumed that an effectiveness of one-tenth for ^{131}I compared to external radiation holds, then a dose of 50 rads is equivalent to a 500 rad dose of ^{131}I.

One major uncertainty in thyroid cancer is the length of the period of maximum excess risk following exposure. In the present simulation it has been uniformly assumed that excess risk began at an age two years after exposure. Three different scenarios are considered for the length of the period during which maximum excess risk occurs — a ten-year period, a twenty-year period, and a thirty-year period. Following that period, excess risk is assumed to decline linearly to zero at age 80.

Age at exposure to the insult may also affect the level of subsequent risk of thyroid cancer, but the evidence of the effect in the literature is not conclusive. Therefore, we did not choose in the basic life table simulations to change the excess risk levels according to the age at which exposure occurred. Total number of excess cases in a lifetime will be affected by the age at which exposure occurs, so that single life tables have been constructed under four different assumptions concerning the age at which exposure occurred: (a) infancy [assuming exposure at age 0]; (b) child [assuming exposure at age 5]; (c) teen [assuming exposure at age 15]; and (d) adult [assuming exposure at age 30].

RAR value for life table populations

In Tables 1 and 2, the RAR value presented is the median RAR value during a lifetime (i.e., over all ages at observation) for a cohort exposed at birth to the specific dose and having the age-specific baseline incidence rates for thyroid cancer corresponding to those for U.S. white males and females respectively. A twenty-year period of maximum excess risk is assumed.

Table 1. Median Lifetime RAR Value for the Life Table Stationary Population Exposed in Infancy by Sex, Dose, and Excess Risk Level[*]

	FEMALES Excess Risk per Rad[*]				MALES Excess Risk per Rad[*]		
	$1/10^6$	$3/10^6$	$6/10^6$		$1/10^6$	$3/10^6$	$6/10^6$
Dose							
1 rad	0	0.02	0.04		0	0.04	0.08
10 rads	0.07	0.18	0.32		0.13	0.38	0.69
25 rads	0.15	0.38	0.59		0.30	0.62	0.84
50 rads	0.28	0.60	0.76		0.54	0.84	0.92

[*]Assumes that excess risk begins two years following exposure.

The table illustrates the large level of uncertainty which is reflected by the reasonable range of uncertainty in the excess risk estimates for thyroid cancer. For a female estimated to have been exposed to 50 rads at birth, the range in median RAR values is from 0.28 to 0.76, depending on the excess risk estimates.

The other factor which is likely to be most uncertain is the dose estimate. The range in median RAR value for a population which is exposed to a range of 1 rad to 25 rads is large, even within a fixed excess risk estimate.

Other important factors in determining risk are baseline incidence and the length of the period of assumed maximum excess risk. Table 2 shows the effect of baseline incidence level and period of maximum risk on the median RAR value, using females estimated to be exposed to 50 rads at infancy as an example.

Table 2. Median Lifetime RAR Values for Females Exposed to 50 Rads in Infancy and Having an Excess Risk of 6 per 10^6/Rad-Year

| | Period of Maximum Excess Risk | | |
	Ten Years	Twenty Years	Thirty Years
Low Incidence	0.75	0.76	0.80
Medium Incidence	0.55	0.59	0.63
High Incidence	0.34	0.38	0.42

The period of time during which maximum excess risk was assumed to occur has a minor effect on the median lifetime RAR value (as well as on the entire distribution of RAR over all ages). In contrast, the estimate of baseline incidence has a major effect on the estimated RAR value.

Estimates of age-specific incidence rates, particularly for rare tumors, such as thyroid cancer, are subject to considerable random variation. Figure 2 illustrated the considerable scatter rates by age group for thyroid cancer in females. For thyroid cancer and other rare tumors, the estimate of baseline incidence rate is subject to considerable random variation, as well as genuine variations in risk among population groups. The estimate used will clearly affect the RAR estimate considerably.

Figure 3 shows the pattern of RAR values by age at observation, for several doses and excess risk estimates. The curves shown in the figure are for females, using the incidence rates estimated from SEER data, and assuming a ten-year period of maximum excess risk. The figure shows again the large uncertainties at each age in the RAR value, even for a known dose.

RAR VALUES FOR THYROID CANCER BY AGE AT OBSERVATION FOR VARIOUS DOSES AND EXCESS RISKS

FEMALES, LOW INCIDENCE, 10 YR. LATENCY

Figure 3
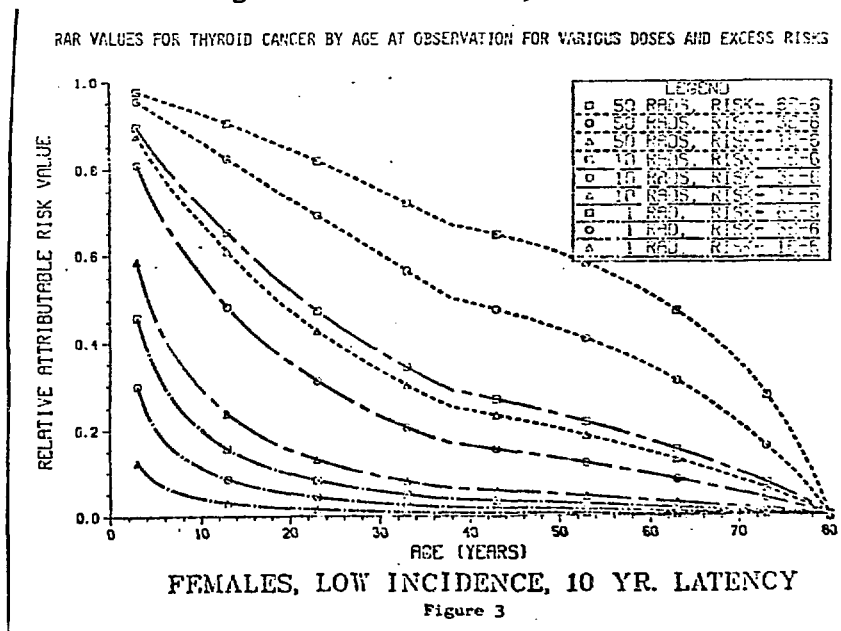
Summary and recommendations

The present simulation illustrates the large uncertainties in RAR estimates for thyroid cancer produced by logical degrees of uncertainty in excess risk levels, baseline incidence, and dose level. Furthermore, when compensation is based on the age at which cancer develops, it is necessary to take into account the nature of increases in risk by age at observation and by period of time elapsed from exposure. The present simulation included only a very limited attempt to consider additional uncertainty produced by such estimates.

Given that large uncertainty exists in levels of increased risk associated with radiation exposure, any measure of risk used for compensation will be highly variable. If compensation is based on scientific literature estimates, however, then it is worthwhile to consider the characteristics of measures which might be used.

Fixing an RAR level at which individuals developing cancer will be compensated is equivalent to fixing the relative risk value at which compensation will occur. Since the likelihood of a causal relationship is most often expressed in terms of relative risk, the direct use of relative risk as a basis for compensation would be more straightforward. Another alternative would be to use some combination of excess risk and relative risk to determine eligibility for compensation.

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