

# Calculating Excess Lifetime Risk in Relative Risk Models

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When assessing the impact of radiation exposure it is common practice to present the final conclusions in terms of excess lifetime cancer risk in a population exposed to a given dose. The present investigation is mainly a methodological study focusing on some of the major issues and uncertainties involved in calculating such excess lifetime risks and related risk projection methods. The age-constant relative risk model used in the recent analyses of the cancer mortality that was observed in the follow-up of the cohort of A-bomb survivors in Hiroshima and Nagasaki is used to describe the effect of the exposure on the cancer mortality. In this type of model the excess relative risk is constant in age-at-risk, but depends on the age-at-exposure. Calculation of excess lifetime risks usually requires rather complicated life-table computations. In this paper we propose a simple approximation to the excess lifetime risk; the validity of the approximation for low levels of exposure is justified empirically as well as theoretically. This approximation provides important guidance in understanding the influence of the various factors involved in risk projections. Among the further topics considered are the influence of a latent period, the additional problems involved in calculations of site-specific excess lifetime cancer risks, the consequences of a leveling off or a plateau in the excess relative risk, and the uncertainties involved in transferring results from one population to another. The main part of this study relates to the situation with a single, instantaneous exposure, but a brief discussion is also given of the problem with a continuous exposure at a low-dose rate.

## Introduction

The motivation for the present investigation has been the analysis by the Radiation Effects Research Foundation (RERF) of the cancer mortality of the A-bomb survivors in Hiroshima and Nagasaki (1-3); this is, to some extent, reflected in the issues selected for discussion here. However, calculation of excess lifetime risk and related risk projection methods are also relevant when evaluating the impact of exposure to various environmental and occupational hazards (4,5), and it is believed that some of the results given here might prove useful in this broader setting.

Analyses of the follow-up of the A-bomb survivors in the Life Span Study (LSS) cohort have shown that for most cancer sites the excess mortality rates have continued to increase until the present time. Moreover, this increase is modeled remarkably well by age-constant relative risk models over the current follow-up period (1-3). It should be emphasized that the term "age-constant relative risk" here refers to constancy in age-at-risk rather than age-at-exposure. The type of models

that describe the data will involve excess relative risks that are, for a given age-at-exposure, constant in regard to age-at-risk over the follow-up but they decrease substantially with age-at-exposure. For all cancers except leukemia, which is considered as one group, these excess relative risks also depend markedly on the sex, but to a large extent this sex dependence simply offsets the sex ratio in the background cancer rates.

When presenting results on the excess cancer mortality in this cohort, it has been common practice to express the ultimate conclusions in terms of excess lifetime cancer risks, also denoted the lifetime cancer risk from exposure (3,6-10). Note however, that in most of these references a different measure of excess risk called here "the risk of untimely cancer death" was computed, but the name "excess lifetime risk" was used (C. Land, private communication).

As a measure of excess cancer deaths, the excess lifetime risk has several drawbacks largely related to the fact that since everybody must die, excess cancer mortality can only occur by decreasing the mortality to other causes; this has important implications for calculation of site-specific excess lifetime risks after whole-body exposure. In particular, if it had been found that radiation increases the rate of all major causes of death by the same factor, then there would be no excess lifetime cancer risk at all (but, of course, the life expectancy would be shortened). Some of these complications are discussed in this paper. Although it might be an ad-

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vantage to put more emphasis on presenting the final conclusions in terms of age-specific excess relative risks, considerations of lifetime risks are important, even if only to put current results in the perspective of what has been given in the past.

Computation of excess lifetime cancer risks is usually based on rather complicated life-table calculations. Such detailed calculations are certainly important, but they are not very helpful in understanding the relative importance of the different factors entering the calculations. In this paper some simple approximate expressions are derived and evaluated by comparing them with the detailed life-table calculations. The approximate expressions highlight the important issues involved in excess lifetime risk calculations for relative risk models.

Three aspects of the excess mortality are clearly important in any risk projection, namely the length of the latent period, the magnitude of the effect, and the duration of the effect. The first two of these are incorporated in the general developments. For the duration aspect most of the results given presume a lifelong excess relative risk, but deviations from this pattern are also considered.

Briefly, the organization of the paper is as follows: In the next section the terminology is introduced and the basic competing risks model is described. An explicit relation for the excess lifetime cancer risk is derived in the section entitled "Results Based on Assuming Proportional Mortality Rates." This relation is based on the assumption that the age-specific mortality rates for all causes and for cancer are proportional in age. Using Japanese life-tables for 1965 and 1985 and nonleukemia cancer risk associated with acute radiation exposure, the general validity of this expression is investigated by comparing the results with those based on the detailed life-table calculations. The section "Approximation under Weaker Assumptions" contains some further theoretical developments. In the general setting, bounds for the excess lifetime risks are given, showing that for low-exposure levels the simple approximation is expected to perform well in a wide range of situations. The proof of these results is sketched in Appendix C. The additional problems that occur when more than one cause of death is related to the exposure are addressed in the section dealing with exposure-related causes of death. Finally, the section "Some Further Issues" tries to cover some other major issues and uncertainties involved in lifetime risks calculations such as the importance of age at exposure, the implications of a plateau in the excess relative risk, and transferring results from one population to another.

The main part of the results relate to a situation with a single, instantaneous exposure. This is partly because the present paper grew out of our work on the analysis of the follow-up of the A-bomb survivors but also because the mathematics are simpler for this type of exposure. However, in the sixth section the problem with continuous exposure at a low-dose rate is briefly addressed and a simple approximate relation for the excess lifetime risk is suggested.

## The Competing Risks Model

The basic model used here is a competing risks model, or multiple decrement model, with two causes of deaths, cancer and noncancer (11,12). Cancer as a cause of death is assumed to be related to the level of exposure, whereas the noncancer mortality is assumed to be independent of the exposure. These assumptions mirror the findings in the LSS cohort where a radiation-related excess mortality is found for most cancer sites, but no excess mortality has been established for the other major causes of death (13,14).

Let us first develop the basic relations for the unexposed (background) population. The cause-specific mortality rates in the unexposed population as a function of age,  $a$ , are denoted by  $m_c(a)$  for cancer and  $m_n(a)$  for noncancer. The total mortality rate at age  $a$  is then

$$m(a) = m_c(a) + m_n(a)$$

These rates will in general also depend on the sex and to some extent on the birth cohort and the calendar period, but to avoid a complex notation, this dependence is ignored here. The main results are not affected by this simplification. It is also convenient to introduce the corresponding integrated mortality rates  $M_c(a)$ ,  $M_n(a)$  and  $M(a)$  where, e.g.,

$$M_c(a) = \int_0^a m_c(x) dx$$

and  $M_n(a)$  and  $M(a)$  are defined in a similar way.

The survivor function gives the probability of being alive as a function of the age  $a$ . This probability can be expressed as

$$S(a) = \exp\{-M(a)\}.$$

In particular,  $S(0) = 1$ . The conditional probability of being alive at age  $y$ , given alive at age  $x$ , is denoted by  $S(y:x)$  and is obtained as

$$S(y:x) = S(y)/S(x) = \exp\{-[M(y) - M(x)]\}.$$

This survivor function gives the proportion still alive at age  $y$  among those alive at age  $x$ .

The lifetime cancer risk for someone alive at age  $x$ ,  $B(x)$ , can now be obtained as the integral of the product of the survivor function and the cancer mortality rate over all ages  $y$  greater than  $x$ , i.e.,

$$B(x) = \int_x^\infty m_c(y)S(y:x) dy \quad (1)$$

The lifetime risk  $B(x)$  is the proportion of all eventual deaths among those alive at age  $x$ , which are due to (background) cancer. The calculations needed to derive the lifetime risk from a particular life-table are briefly reviewed in Appendix A.

Next, the impact of exposure on a population of individuals exposed at age  $e$  or a population with a given age distribution is considered. By assumption the noncancer mortality rate is unchanged. Let  $m'_c(a:e)$  and  $m'(a:e)$  denote the cancer mortality rate and the total

mortality rate at age  $a$  for someone exposed at age  $e$ . Also, for the other measures to be considered, a prime will be used to indicate that the particular function refers to the exposed population. In general  $m'_c(a:e)$  might be a rather complicated function of the dose received, the age, the age at exposure, the time since exposure, and the background cancer mortality rate  $m_c(a)$ . The statistical methods for estimating this relationship is not the issue here. When calculating excess lifetime risks, one will normally consider the implications of a specified dose to an individual or a population of individuals. This will also be the approach taken here. Thus, the problem to be considered involves a comparison of the cancer risks in two populations, an unexposed and an exposed. The individuals in the latter population all receive the same dose and the excess lifetime risk to be computed is only relevant for this exposure level.

We shall focus on the following age-constant relative risk model

$$m'_c(a:e) = [1 + r(e)] m_c(a) \quad a > e \quad (2)$$

and consequently,

$$m'(a:e) = m(a) + r(e)m_c(a)$$

where  $r(e)$  is the excess relative cancer risk for an individual exposed at age  $e$ . It should be emphasized that this model allows the excess relative risk to depend on age-at-exposure, but not on age-at-risk. The models used in the recent analyses of the current follow-up of the cancer mortality in the LSS cohort are of this type, but they also include a latent period (typically 10 years). The modifications needed to deal with a latent period are described at the end of this section. Note also that risk projections based on Eq. (2) assume that the exposure-induced excess in the form of a constant excess relative risk continues to the end of life. This is a very strong assumption; in the study of the long-term effects of radiation, no exposed human population has been followed for more than 40 years. The implications of a leveling-off or a plateau in the excess relative risk for the excess lifetime risk will be considered in the next to the last section of this paper.

The survivor function,  $S'(a:e)$ , for a population of individuals exposed (and alive) at age  $e$ , can now be obtained as

$$S'(a:e) = S(a:e) \exp\{-r(e)[M_c(a) - M_c(e)]\}.$$

The second factor represents the additional decrement of the population caused by the excess cancer risk. The lifetime cancer risk for someone exposed at age  $e$  becomes

$$B'(e,r(e)) = \int_e^\infty m'_c(y:e)S'(y:e)dy. \quad (3)$$

Finally, the excess lifetime cancer risk in a population exposed at age  $e$  is obtained as the difference between the lifetime risks among exposed and unexposed:

$$\text{ELR}(e,r(e)) = B'(e,r(e)) - B(e) \quad (4)$$

The excess lifetime cancer risk can be interpreted as

the increase in the proportion of all eventual cancer deaths in a population of individuals exposed at age  $e$ . It is often presented as the expected number of additional cancer cases per million (or thousand) individuals per unit dose. Appendix A gives some further details on the computations necessary to derive the excess lifetime risk.

Let us also briefly introduce two other summary measures of the lifelong excess risk due to the exposure, which are occasionally used in risk projections. The first summary measure is here called the risk of untimely cancer death, although one may well question the appropriateness of this terminology. The risk of untimely cancer death for someone exposed at age  $e$ , RUD( $e,r(e)$ ), is defined as a weighted integral of the excess cancer mortality rates with weights given by the background survivor function

$$\text{RUD}(e,r(e)) = \int_e^\infty [m'_c(y:e) - m_c(y)]S(y:e)dy.$$

In the relative risk model Eq. (2) this simplifies to the product of the excess relative risk and the lifetime risk from the background cancer

$$\text{RUD}(e,r(e)) = r(e)B(e). \quad (5)$$

The risk of untimely death and the excess lifetime risk differ on which survivor function is applied to the exposed population. For the former measure the survivor function used does not include an allowance for the additional decrement of the population caused by the excess cancer cases. An interpretation of the risk of untimely death may be given by considering the following hypothetical situation. The risk of untimely cancer death is the increase in the proportion of ultimate cancer deaths if all individuals dying from exposure-induced cancer are replaced immediately after death by someone of the same age and sex. Note that a given person may be replaced several times in this hypothetical replacement scheme; this is also reflected in the fact that the risk of untimely death is a linear function of the excess relative risk. Hence values larger than 1 can, in principle, occur. As mentioned in the introduction, the risk of untimely death has been used under the name "excess lifetime risk" in several publications on risk projections (3,6,7,9).

The loss of life expectancy for someone exposed at age  $e$  is defined as the difference between the expected remaining lifetime for an individual exposed at age  $e$  and the expected remaining lifetime if unexposed and alive at age  $e$ . The loss of life expectancy can be calculated as

$$\text{LLE}(e,r(e)) = \int_e^\infty S(y:e)dy - \int_e^\infty S'(y:e)dy. \quad (6)$$

So far we have introduced the excess lifetime risk, the risk of untimely death, and the loss of life expectancy for an individual exposed at age  $e$  or, equivalently, for a population of individuals all exposed at age  $e$ . The analogous measures for a population with some distri-

bution of the age at exposure are simply obtained as a weighted average of these age-specific measures with weights proportional to the age distribution in question. The choice of age distribution may have a large impact on the resulting average excess lifetime risk. Risk projections for the LSS cohort beyond the current follow-up period are naturally based on the present age distribution of the survivors, but in other situations the choice is more arbitrary. The risk projections in the BEIR III report (7) were based on the 1969–1971 U.S. life-tables. Age-at-exposure specific excess lifetime risks were not given in that report, but only the average value in the so-called life-table population; this is a hypothetical population with the distribution of age at exposure proportional to the survivor function.

The final problem to be considered in this section is the impact of a latent period or induction period on the summary measures introduced above. To this end, assume that the excess cancer mortality does not show up until  $t$  years after the exposure, i.e., the relative risk model in Eq. (2) is replaced by

$$m'_c(a:e) = \begin{cases} m_c(a) & a < e + t \\ [1 + r(e)] m_c(a) & a > e + t \end{cases} \quad (7)$$

Straightforward calculations show that in this case, the excess lifetime risk becomes

$$S(e + t:e) ELR(e + t, r(e)).$$

The first term gives the probability of surviving the latent period and the second term is the previous defined excess lifetime risk [Eq. (4)] for someone alive at age  $e + t$  when the excess relative risk is  $r(e)$ .

Similarly, including a latent period of length  $t$  leads to the following risk of untimely death

$$S(e + t:e) r(e) B(e + t)$$

and the loss of life expectancy now becomes  $LLE(e + t, r(e))$ .

## Results Based on Assuming Proportional Mortality Rates

Based on a given life-table and the relations derived in the previous section, it is not too complicated to devise a program that computes the excess lifetime risk (Appendix A). When used, such a program would return the appropriate answer, but one would have to consider a large number of situations in order to gain insight into the relative importance of the various aspects of the problem. To obtain such insight, an alternative approach is taken here. It turns out that a simple, explicit expression for the excess lifetime risk is available if it is assumed that in the background (unexposed) population the cancer mortality rate and the total mortality rate are proportional as a function of age, i.e.,

$$m_c(a) = B m(a). \quad (8)$$

This is, of course, not exactly true in any population,

but it will be demonstrated later that the relationship obtained in this setting is a useful approximation to the more elaborate life-table calculation. Furthermore, this approximation provides very important guidance in understanding the major issues and uncertainties involved in computing excess lifetime risks.

The relation in Eq. (8) is equivalent to assuming a constant proportion of cancer deaths for all ages at death. Moreover, a simple calculation shows that the lifetime cancer risk in the unexposed population for someone alive at age  $x$  reduces to independent of the value of  $x$ , i.e.,

$$B(x) = B. \quad (9)$$

It is noteworthy that when the ratio of the cancer mortality rate to the total mortality rate is constant throughout life, this constant is also the lifetime cancer risk. Moreover, this result will be true irrespective of the particular shape of the overall survivor function.

Turning now to the exposed population, the lifetime cancer risk [Eq. (4)] can be expressed explicitly as a function of the (constant) lifetime cancer risk in the unexposed population and the excess relative risk

$$B'(e, r(e)) = B [1 + r(e)] / [1 + B r(e)]. \quad (10)$$

Finally, the excess lifetime cancer risk becomes

$$ELR(e, r(e)) = r(e) B [1 - B] / [1 + r(e) B]. \quad (11)$$

Details on the derivation of relation between Eqs. (10) and (11) can be found in Appendix B. The denominator in Eq. (11) is negligibly different from 1 for small values of the excess relative risk, and indicates, usefully, the extent to which excess lifetime risks are nonlinear in  $r(e)$  for larger values. The factor  $[1 - B]$  reflects the point made in the introduction that the excess cancer mortality can only be taken from mortality to other causes. Note that this simple expression holds for any shape of the overall survivor function as long as the proportionality assumption [Eq. (8)] is fulfilled.

The relation in Eq. (11) also reveals, rather surprisingly, that the excess lifetime risk depends on age at exposure only through the dependence on the excess relative risk. This means that the excess lifetime risk would take the same value for all ages at exposure if the excess relative risk did not depend on  $e$ .

If a latent period of length  $t$  is present, the expression in Eq. (11) should be multiplied by the probability  $S(e + t:e)$  of surviving the latent period. This will introduce some additional dependence on age at exposure. However, the comment above on the constancy of the excess lifetime risk will then apply to the excess lifetime risk given survival of the latent period.

The developments above suggest that for small values of the excess relative risk the following approximation to the excess lifetime risk may be used:

$$r(e) B [1 - B].$$

This approximation turns out to be very useful. For the Japanese mortality rates (details later) the approximation is within about 6 to 7% of the life-table calcu-

lations for an exposure of 0.1 Sv, and the approximation is even more accurate for an exposure of 1.0 Sv. To make the approximation less dependent on the additional assumption in Eq. (8), we allow for the fact that the lifetime risk, in general, depends on the age of exposure. Thus, for low levels of exposure, the following approximation to the excess lifetime risk is proposed

$$r(e) B(e) [1 - B(e)]. \quad (12)$$

Note that this approximation also yields an approximate standard error (SE) for the excess lifetime risk. If for example the excess relative risk  $r(e)$  has an 40% SE, then this will lead to a 40% SE for the excess lifetime risk (ignoring any uncertainty in the determination of  $B(e)$ ).

A comment on the risk of untimely death seems appropriate here. Somewhat surprisingly, a comparison of relation between Eqs. (5) and (12) shows that the risk of untimely death and the proposed approximation differ by a factor of  $1 - B(e)$  as the excess relative risk tends to zero. This implies that even for very low exposure levels the risk of untimely death for all cancers except leukemia will be approximately 25% larger than the corresponding excess lifetime risk.

If a constant latent period of length  $t$  is present the approximation becomes

$$S(e + t:e) r(e) B(e + t) [1 - B(e + t)]. \quad (13)$$

Dropping the first factor in Eq. (13) gives an approximation to the excess lifetime risk given survival of the latent period.

The performance of the approximation in Eq. (12) will now be studied in the context of estimating the excess lifetime risk to all cancers except leukemia for individuals receiving an instantaneous exposure to ionizing radiation. The mortality in the unexposed population will be taken as that of the Japanese population in 1965 and 1985 (15-17).

Let us first see how much the Japanese cross-sectional mortality statistics for the years 1965 and 1985 depart from the assumption of proportionality Eq. (8). To this end it is convenient to reexpress the lifetime risk  $B(x)$  for someone alive at age  $c$  as

$$B(x) = \int_x^\infty (m_c(y)/m(y)) f(y:x) dy, \quad (14)$$

where  $f(y:x) = m(y) S(y:x)$  is the probability density function of the lifetime distribution for someone alive at age  $x$ . The ratio  $m_c(y)/m(y)$  gives the proportion of cancer deaths among those dying at age  $y$ , and it is seen that the lifetime risk is obtained as a weighted average of these age-specific proportions with weights equal to the probability of dying for the corresponding age. In the special case where the cancer mortality rate is proportional to the total mortality rate, this ratio is a constant,  $B$ , independent of the age, and as noted earlier, the lifetime risk then equals this constant.

Figure 1 displays for each sex separately the relative frequency of nonleukemia cancer deaths among all deaths in 1965 and 1985, with the age at death grouped

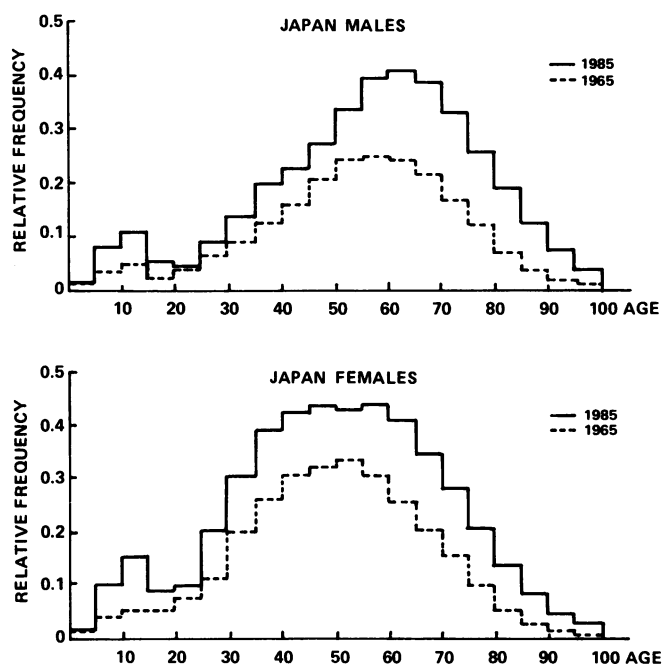


FIGURE 1. The proportion of nonleukemia cancer deaths among all deaths with same age at death. Age at death grouped in 5-year intervals. Calculations are based on Japanese mortality statistics for 1965 and 1985.

in 5-year intervals. A rather similar pattern is seen: After an initial rise to a peak in the age group 10 to 14 years of age, the proportions decline until age 25, then rise to an overall maximum around age 60 and finally decrease markedly for the older age groups. For both sexes the relative frequencies in 1985 are substantially higher than those in 1965. If leukemia were included the early peak would be doubled, but for ages above 40, only minor changes would be seen. The pattern seen in Figure 1 may seem far from the constant proportion predicted by the proportionality assumption in Eq. (8), but the ages below 55 carry almost no weight when the lifetime risk is computed as the weighted average in Eq. (14). Therefore, the lifetime risk  $B(x)$  for someone alive at age  $x$  is essentially constant for all values of  $x$  less than 55. This is illustrated in Figure 2 where the lifetime risk to the nonleukemia cancers for someone alive at age  $x$  is shown as a function of  $x$  for both sexes based on the Japanese national mortality statistics for 1965 and 1985. Note also the higher values for males in both years and that the lifetime risk has increased considerably between 1965 and 1985.

In connection with Figures 1 and 2 it should be noted that a recent investigation of the LSS autopsy data (Jablon, private communication) has shown that the detection rate of cancer as the cause of death as determined death certificates decreases markedly at older ages; this is true for specific sites and for all cancers except leukemia together. Thus, the drop-off seen in Figures 1 and 2 for old ages may, in part, be the consequence of such a decrease in the detection rate; the true rates may actually comply better with the assumptions of the approximation.

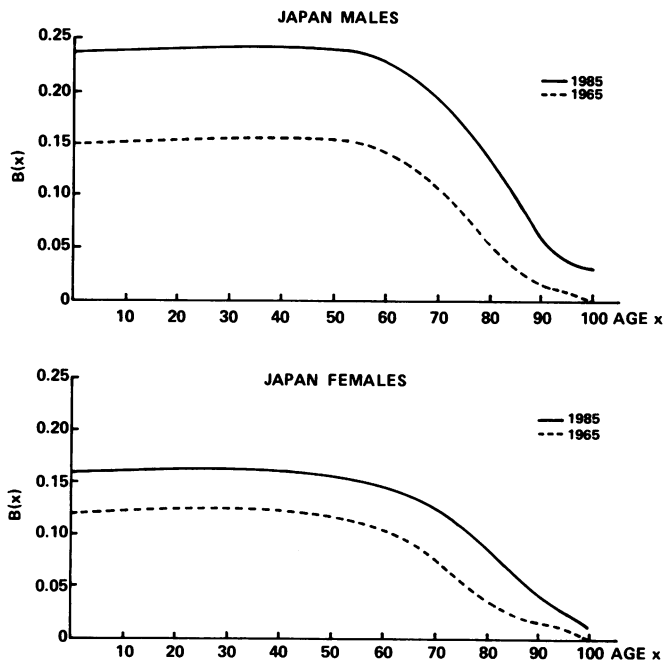


FIGURE 2. The lifetime risk of all cancers except leukemia for someone alive at age  $x$ . Calculations are based on Japanese mortality statistics for 1965 and 1985.

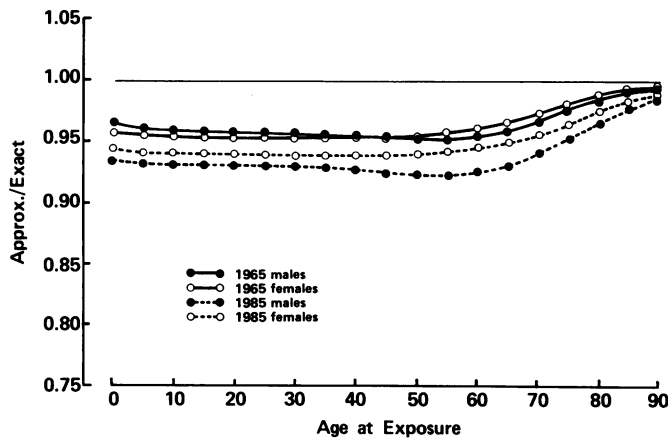


FIGURE 3. Evaluation of the proposed approximation to the excess lifetime risk: the ratio of the approximate value to the exact value as a function of age at exposure for an excess relative risk of 0.05.

The performance of the proposed approximation for the excess lifetime risk when applied to radiation-induced nonleukemia cancers is shown in Figures 3 and 4. The dependence on the age at exposure for a fixed value of the excess relative risk is considered in Figure 3. Here the ratio of the approximate value from Eq. (12) to the exact value obtained from Eq. (4) using the life-table method is plotted against age-at-exposure for each sex in 1965 and 1985. The value 0.05 has been chosen for the excess relative risk. This corresponds roughly to the estimated average excess risk in the LSS cohort for a dose of 0.1 Sv. The values shown are those obtained when no latent period is present, but the introduction of a latent period will only result in a translation of the age scale. The relation in Eq. (12) is seen

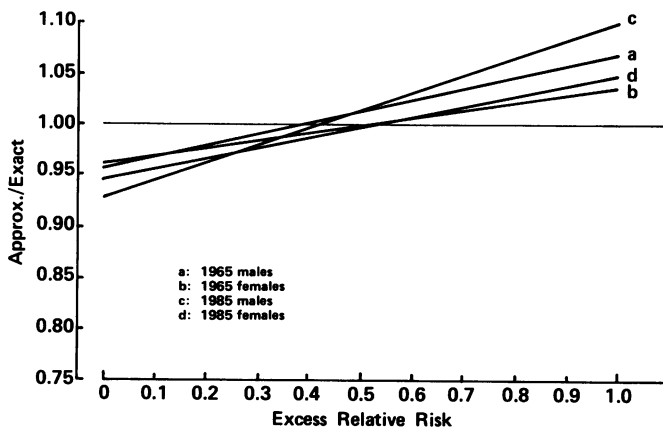


FIGURE 4. Evaluation of the proposed approximation to the excess lifetime risk: the ratio of the approximation averaged over age at exposure to the similarly averaged exact value as a function of the excess relative risk. See the text for further explanation.

to underestimate the excess lifetime risk by, at most, 4.5% in the 1965 life-table. For the 1985 life-table the underestimation is around 6% for females and 7.5% for males for ages below 55.

The behavior of the approximation over a range of excess relative risk values is displayed in Figure 4. Weighted averages of the age-at-exposure-specific values of the proposed approximation and the life-table calculation were computed by applying the age distribution of the life-table population to the age at exposure. Figure 4 gives the ratio of these weighted averages as a function of the excess relative risk for each sex in 1965 and 1985. It is seen that the approximation stays within  $\pm 7\%$  of the life-table calculation for excess relative risks smaller than 0.8. However, by far, the most remarkable feature of this figure is the almost-perfect linearity of the ratio of the approximation to the life-table-based value when plotted against the excess relative risk. Note that this ratio would be exactly linear if the proportionality assumption [Eq. (8)] was satisfied [Eq. (11)]. This pattern suggests that an extremely accurate approximation to the excess lifetime risk will have the form

$$r(e) B(e) [1 - B(e)] / [a + b r(e)].$$

It is actually possible, quite generally, to devise a refined approximation of this form, but this will not be pursued further, since the emphasis here is on simple and easily interpretable approximate relations. Moreover, such improved approximations offer no computational advantages relative to the life-table method.

### Approximation under Weaker Assumptions

In this section results are given for the age-constant relative risk model [Eq. (2)], but without the assumption in Eq. (8) that cancer and total mortality rates are proportional. In this general setting no explicit expression for the excess lifetime risk similar to Eq. (11) is avail-

able. However, an approximate expression can still be obtained. Write  $B(e)$  as the average of the background lifetime risk  $B(e)$  with respect to the distribution of age at cancer death where all these quantities are conditional on being alive at age  $e$ . That is,

$$\bar{B}(e) = \frac{\int_e^{\infty} B(y) f_c(y:e) dy}{\int_e^{\infty} f_c(y:e) dy},$$

where

$$f_c(y:e) = m_c(y) S(y:e)$$

is the density of time to cancer death for those alive at age  $e$ .

Then for small  $r(e)$  an approximation without relying on assumption in Eq. (8) is

$$r(e) B(e)[1 - \bar{B}(e)]. \quad (15)$$

This and the following results are developed in Appendix C. In fact, the approximation in Eq. (15) is an upper bound for the excess lifetime risk, and moreover it is shown that the ratio of Eq. (15) to the exact value is bounded between  $1 - r(e)B(e)/[1 - \bar{B}(e)]$  and 1. Thus Eq. (15) is a very good approximation for the values of  $r(e)$  in the range of interest. A modification to deal with the latent period can easily be devised along the lines given at the end of the second section.

It is emphasized that the approximation in Eq. (15) is based on the age-constant relative risk model (but is otherwise general). For small values of the excess relative risk, it is negligibly different from results of exact life-table calculations. Actual use of the approximation is of little value, however, since calculation of  $\bar{B}(e)$  is essentially as difficult as the life-table calculation. The point of this more general approximation is to better understand the error in approximation in Eq. (12) and the one preceding it.

It is seen that the general result in Eq. (15) is very similar to the proposed approximation in Eq. (12), and unless the lifetime cancer risk varies markedly with age, especially on the range of ages where cancer deaths typically occur, the last factor in Eq. (15) will be close to  $1 - B(e)$  for the age at exposure in this age span. Thus, for small values of the excess relative risk  $r(e)$ , the ratio of the approximate expression in Eq. (12) to the exact life-table calculation is essentially equal to  $[1 - B(e)]/[1 - \bar{B}(e)]$ . Moreover, this ratio will tend to be smaller than one if most of the cancer deaths occur in the age groups where cancer is becoming a less important cause of death. When the ratio  $[1 - B(e)]/[1 - \bar{B}(e)]$  is slightly smaller than one, the approximation will underestimate the excess lifetime risk for  $r(e)$ -values close to zero, but this may actually increase the range of  $r(e)$ -values for which an acceptable approximation is obtained (Fig. 4).

In conclusion, the existence of a general approximation of the form in Eq. (15) clearly indicates that the simple expression in Eq. (12) is a useful approximation

to the excess lifetime risk for low exposure levels, not only when the cancer and total mortality rates are proportional.

## Several Exposure-Related Causes of Deaths

In the basic competing risk model introduced in the second section, the cause of death information is aggregated into two main causes: those related to exposure, called cancer; and those unrelated to exposure, called noncancer. In the major reviews of the long-term effects of ionizing radiation (6,7) much attention is given to estimating lifetime risks of dying from radiation-induced cancers of specific sites. There are additional problems arising in such an endeavor.

First it must be realized that site-specific excess lifetime risk calculations depend on whether one is considering site-specific exposure or whole-body exposure. This is particularly important if one expects the sum of the site-specific excess lifetime risks to represent the excess lifetime risk for a collection of sites in whole-body exposure. Technically speaking, in calculations for a given site the problem is whether or not the survivor function of  $S'(a:e)$  is decremented for the excess mortality rate of other radiogenic cancers. Either possibility is correct but relates to different situations: for site-specific exposure the additional decrement is not appropriate, whereas for whole-body exposure it is required.

It is convenient to base the arguments on the approximate relationship for the excess lifetime risk when trying to quantify the order of magnitude of these problems. Moreover, for the points to be made here it is necessary to expand the competing risks model to include three causes of death, two of which are related to exposure. To fix the terminology we shall refer to these two causes as "lung cancer" and "other cancers," with the understanding that the results are not restricted to this particular subdivision of all cancers. For both of these causes the effect of exposure will be described by an age-constant relative risk model of the form in Eq. (2).

Among unexposed let  $B_1$  and  $B_2$  denote the lifetime risks of lung cancer and other cancers, respectively. The corresponding excess relative risks are denoted  $r_1$  and  $r_2$ . The  $B$ 's and the  $r$ 's will depend on age at exposure, but this dependence has been suppressed in the notation since it is not central to the developments here.

For site-specific exposure the excess lifetime risk of death to lung cancer is approximately

$$r_1 B_1 [1 - B_1].$$

This follows directly from the results in the second and third sections since deaths to other cancers and non-cancer deaths may be pooled together as causes unrelated to the site-specific exposure. For whole-body exposure calculations similar to those given in Appendix B lead to the following approximate excess lifetime risk

$$r_1 B_2 [1 - B_1] - r_2 B_1 B_2, \quad (16)$$

showing that for a given site the excess lifetime risk is, in general, smaller for whole-body exposure. The sum of a number of site-specific excess lifetime risks each based on site-specific exposure will therefore be larger than the excess lifetime risk for the collection of sites in whole-body exposure. Note also that the excess lifetime risk in Eq. (16) may in certain situations become negative even though the excess relative risk  $r_1$  is positive. This will happen if the excess relative risk  $r_2$  associated with other cancers is larger than  $r_1 [1 - B_1]/B_2$ . The relation in Eq. (16) may alternatively be expressed as

$$r_1 B_1 [1 - B_1 - B_2] + (r_1 - r_2) B_1 B_2. \quad (17)$$

Excess relative risk estimates are very similar for most solid tumors indicating that the second term in Eq. (17) typically contributes little, if anything, to the excess lifetime risk. Thus, the important difference between the excess lifetime risk from site-specific exposure and that from whole-body exposure shows up in the factor one minus the background lifetime risk for the radiation-related causes of death. For site-specific exposure this is  $1 - B_1$ , and for whole-body exposure it becomes  $1 - (B_1 + B_2)$ .

Summing Eq. (17) and the corresponding (approximate) expression for the excess lifetime risk to death from other cancers gives the excess lifetime risk to all cancers from whole-body exposure

$$[r_1 B_1 + r_2 B_2] [1 - B_1 - B_2]. \quad (18)$$

Introducing the total background lifetime cancer risk  $B = B_1 + B_2$ , this may be written as

$$r B [1 - B]$$

where

$$r = [r_1 B_1 + r_2 B_2] / [B_1 + B_2] \quad (19)$$

is a weighted average of the site-specific excess relative risks with weights proportional to the site-specific lifetime risks. Thus, the expression in Eq. (18) is formally identical to the approximate relation derived in the third section. The weighting in Eq. (19) is equivalent to using weights proportional to the number of deaths from the different causes in the background population. An excess relative risk analysis of the mortality data for a collection of cancer sites by maximum likelihood methods implicitly uses a similar weighting of the data from the individual sites, indicating the results obtained from separate site-specific calculations will be consistent with those found when analyzing the collection of sites together. There are some complications here that should be recognized: the validity of excess relative risk models for the individual sites does not, in general, ensure that an excess relative risk model will be appropriate when the sites are aggregated into a single cause of death (e.g., all cancers). If cancers occurring late in life generally have a smaller excess relative risk, one would expect to find an excess relative risk decreasing with

follow-up time for all cancers together. It is not clear to what extent this will invalidate the consistency result outlined above.

## Some Further Issues

For radiation-induced cancers, no epidemiological study exists in which the entire cohort has been followed until all members have died. Therefore, risk projection methods giving a summary of lifelong excess risk inevitably involve some sort of extrapolation of effects in time and age beyond our current knowledge. In a discussion of the uncertainties involved in such projections it is necessary to distinguish between two types of applications: determination of the ultimate number of excess cancer cases (or lifetime risk) in a specific study cohort of exposed individuals, and computation of the excess lifetime risk in some theoretical population assumed exposed to a single dose of radiation.

The former situation is conveniently discussed by considering the LSS cohort. Here the excess number of cancer cases in the first 40 years of follow-up is mainly a question of finding suitable models to describe existing data, so the extrapolation concerns only those below 45 to 50 years of age at exposure. The extrapolation involves both the future background cancer mortality and the future excess relative cancer risk. As shown in the section "Results Based on Assuming Proportional Mortality Rates," the background cancer mortality in Japan has increased substantially from 1965 to 1985, indicating that this aspect of the extrapolation will require a modeling of the time trend in the background mortality rates.

In the latter type of application one will usually assume that the total mortality and the cancer mortality are as specified by some life-table, and extrapolation of this background mortality is handled by assuming that these rates prevail for the whole life span. Extrapolation of the excess relative risk for those under 45 to 50 years of age at the time of exposure remains an important issue. Moreover, the relevance of applying the excess relative risks found in the LSS cohort to the population in question needs also to be considered, especially if this population has a very different pattern of cancer mortality. Instead of transferring the excess relative risk estimates, one may contemplate computing the (time- and age-dependent) absolute excess risk in the LSS cohort and add this excess to the background cancer rate of the population life-table. An approach of this type was adopted by the BEIR III committee in their calculations (?).

The lack of knowledge about the future behavior of the excess relative risk for those exposed as young is the source of considerable uncertainty in both types of risk projections. This is illustrated in Table 1, where the implications on the excess lifetime nonleukemia cancer risk of three different models for the duration of the excess risk are compared. The results are given for four different values of age at exposure for both males and females. Calculations are based on the 1985 Japanese



**Table 1. Excess lifetime nonleukemia cancer risks from a radiation exposure of 0.1 Sv for different choices of length of the plateau in the excess relative risk.\***

	Males			
	Age at exposure, yr			
	15	30	45	60
ERR at 0.1 Sv	0.075	0.050	0.025	0.025
Lifetime risk	0.238	0.241	0.242	0.231
ELR infinite plateau	0.015	0.010	0.005	0.004
ELR 40-yr plateau	0.003	0.007	0.005	0.004
ELR 30-yr plateau	0.001	0.004	0.004	0.004
	Females			
ERR at 0.1 Sv	0.150	0.100	0.050	0.050
Lifetime risk	0.162	0.162	0.159	0.147
ELR infinite plateau	0.021	0.014	0.007	0.005
ELR 40-yr plateau	0.005	0.009	0.007	0.005
ELR 30-yr plateau	0.002	0.004	0.006	0.005

\* Calculations are based on the 1985 Japanese life-table and a latent period of 10 years is assumed.

life-table, and all models include a 10-year latent period. The first model assumes a lifelong excess relative risk, whereas the second and third models have a plateau in the excess risk lasting for 40 years and 30 years, respectively. The excess relative risk estimates are essentially those given by Pierce et al. (18) for all cancers except leukemia. These estimates are obtained by fitting an age-constant excess relative risk model linear dose. The dose was taken as the DS86 dose to the large intestine using a low-LET dose equivalent based on an assumed relative biological effectiveness (RBE) of 10 for neutrons. A 10-year latent period is assumed. Their estimation procedure allows for random errors in the dose estimates, and the analysis is based on follow-up until the end of 1985. The slope of the dose response depends on sex and age at exposure, the latter factor being categorized as 0 to 19, 20 to 34, and 35 and older. The SE of estimated excess relative risks is approximately 40%.

Table 1 summarizes the consequences of a single radiation exposure of 0.1 Sv. Since the excess relative risk estimates are based on a linear dose-response model, one might consider a further adjustment to allow for a possible nonlinearity of the dose response in the low-dose range. This has not been attempted here, but it may well lead to a reduction of the excess relative risk by 30 to 50% (19). Also, the BEIR III committee (7) used a correction factor of 1.23 to adjust for incomplete death-certificate ascertainment of cancer as the cause of death.

The results in Table 1 clearly indicate the major uncertainty in the risk projection for those exposed as children or young adults. The first and the third model probably represent two extreme modes of extrapolation and the results differ by more than a factor 10 for those exposed at ages below 20. The large excess relative risk found in this group in the current follow-up should never be used uncritically in risk projections. At best, very strong (and untestable) assumptions are required to make any useful estimates from LSS regarding lifetime

risks for this group. Viewed in this perspective the modest underestimation resulting from the approximation proposed in the third section is, indeed, a minor issue.

As a crude approximation to the effect on the excess lifetime cancer risk of a plateau in the excess relative risk one may use the following simple rule: multiply the excess lifetime risk obtained for lifelong excess risk by the probability of dying during the period with increased risk given survival of the latent period.

Finally, let us briefly consider projections of risk from continuous exposure. The calculation of excess lifetime risks in this setting is potentially much more complicated. First of all, there is an additional parameter, the dose rate, to take into account. Moreover, the problem of how to model the dependence of the age-specific excess relative risk on the previous exposure history is not an easy one. Here, we shall restrict ourselves to the simplest possible situation, that of an exposure with a constant dose rate  $d$  starting at age  $e$  and continuing throughout the rest of life. Furthermore, it will be assumed that the excess relative risk is linear in the cumulative dose, such that the excess relative risk at age  $a$  becomes  $b(e)d(a - e)$ , where  $b(e)$  is the excess relative risk per unit (cumulative) dose. Under these circumstances (and for a low dose rate) one may consider using

$$b(e) d \text{MRL}(e) B(e) [1 - B(e)]$$

as an approximation to the excess lifetime risk associated with the exposure. Here  $\text{MRL}(e)$  is the mean remaining lifetime for someone alive at age  $e$ . Under the further assumption of proportional mortality rates in Eq. (8), one may show that this relation gives an upper bound for the excess lifetime risk. An empirical investigation, similar to those reported in the third section but on a much smaller scale, gave the following results for nonleukemia cancer: for age-at-exposure below 80 years the ratio of the approximation to the value derived from a life-table calculation varied between 1.01 and 1.23 for males in 1985 and between 1.05 and 1.25 for females in 1985. The corresponding values based on the 1965 life-table were 1.00 to 1.23 for males and 1.06 to 1.33 for females. These values are all derived in a situation with no latent period, and the excess relative risk per year  $b(e) \times d$  was 0.005 Sv. This corresponds roughly to a dose rate of 0.01 Sv/year, assuming that the average excess relative risk found in the LSS cohort at this dose level can be applied in the present setting.

The approximation is obviously less satisfactory than those obtained for a single exposure, but it may still be useful when assessing the order of magnitude of the excess lifetime risk from continuous exposure at low-dose rates.

## Concluding Remarks

In an area like lifetime risk projections that clearly involves speculations about events yet to occur, it is critical to make the structure of the relationships as clear as possible. It is felt that an approach using the simple approximation described in this paper is a useful

alternative to the less-transparent life-table calculations. This approximation is based on an age-constant excess-relative risk model. By now, the only serious doubt about the appropriateness of this type of model for the cancer mortality in the LSS cohort is for those who were exposed as children and young adults. The uncertainty in the risk projection for this group, especially for the children, is extremely large, though, and any serious assessment of excess lifetime risks should address this problem. The most appropriate approach here seems to be to investigate the sensitivity of the excess lifetime risk to various models for the future magnitude and duration of the excess mortality in this group. Some preliminary calculations along these lines are presented in Table 1; more realistic models will probably involve a gradually leveling off of the excess relative risk.

## Appendix A

This appendix describes how the lifetime risk and the excess lifetime risk are derived from a life-table and the corresponding cancer mortality statistics. Such information is always provided for each sex separately, but to simplify the discussion this distinction will be made explicit here.

A life-table for a given population for a given period describes how a hypothetical cohort of 100,000 newly born individuals is diminished by normal mortality from all causes under the assumption that the age-specific mortality is identical to that found in the total population in the period. The life-table gives the number of individuals still alive at each subsequent birthday (i.e., at age 1, 2, 3, etc.) until the whole cohort has died. Cause-specific mortality statistics are usually given as the cause-specific mortality rate for 5-year age groups (i.e., 0-4, 5-9, etc.).

To obtain the lifetime cancer risk for someone unexposed and alive at age  $e$  from Eq. (1) using this information, one may proceed as follows: the integral on the right hand side of Eq. (1) is written as the sum of the integral from age  $e$  to age  $e + 1$ , the integral from age  $e + 1$  to  $e + 2$ , the integral from age  $e + 2$  to  $e + 3$ , etc. Each of these integrals is then computed as the cancer mortality rate for the age in question times the average cohort size at that age divided by the size of the cohort at age  $e$ . The lifetime cancer risk is then obtained as the sum of these expressions.

The lifetime cancer risk for some exposed at age  $e$  is derived in a similar way from Eq. (3). The cancer mortality rate is here  $1 + r(e)$  times that of the background population [Eq. (2)]. The values of the survivor function  $S'(a:e)$  are obtained recursively for  $a = e, e + 1, e + 2, \dots$  from the relation

$$S'(a + 1:e) = S'(a:e) S(a + 1:a) \exp\{-r(e)m_c(a)\},$$

where  $S'(e:e) = 1$  and  $S(a + 1:a)$  is the ratio of the life-table cohort size at age  $a + 1$  to that at age  $a$ . The lifetime cancer risk for someone exposed at age  $e$  given in Eq. (3) may now be evaluated as a sum of the terms

$$(1 + r(e)) m_c(a) [S'(a + 1:e) + S'(a:e)]/2$$

for  $a = e, e + 1, e + 2, \dots$ . Finally, the excess lifetime cancer risk is found as the difference between the lifetime risk for the exposed and the lifetime risk for the unexposed [Eq. (4)].

## Appendix B

Derivation of relation Eqs. (10) and (11): From Eq. (3) we have

$$B'(e, r(e)) = \int_e^\infty m'_c(y:e) S'(y:e) dy.$$

For the age-constant relative risk model this becomes

$$B'(e, r(e)) = \int_e^\infty (1 + r(e)) m_c(y) \exp\{-[M(y) - M(e)] - r(e)[M_c(y) - M_c(e)]\} dy.$$

If the additional assumption in Eq. (8) is fulfilled, we get

$$\begin{aligned} &= \int_e^\infty (1 + r(e)) B m(y) \\ &\quad \exp\{-1 + r(e)B[M(y) - M(e)]\} dy \\ &= \frac{(1 + r(e))B}{1 + r(e)B} \int_e^\infty (1 + r(e)B) m(y) \\ &\quad \exp\{-[1 + r(e)B][M(y) - M(e)]\} dy \\ &= \frac{(1 + r(e))B}{1 + r(e)B} \end{aligned}$$

since the integral equals one. The relation in Eq. (11) is finally obtained by subtracting off  $B$ .

## Appendix C

The following result is shown in this appendix: for an age-constant relative risk model the excess lifetime risk ELR ( $e, r(e)$ ) is always smaller than

$$r(e) B(e) [1 - \bar{B}(e)]$$

and always larger than

$$r(e) B(e) [1 - \bar{B}(e)] - B(e) \bar{B}(e) r(e)^2,$$

where  $\bar{B}(e)$  is the lifetime risk averaged over the distribution of age at cancer death among unexposed alive at age  $e$ . Note that the simple approximation in Eq. (10) does not necessarily stay within these bounds. Note also that the ratio of these bounds tends to one as the excess relative risk approaches zero. This implies that the bounds are very tight for exposure levels leading to only small excess relative risks.

A proof of this result is here given for age at exposure  $e = 0$ . The proof for general  $e$  is quite similar. To simplify the notation let  $r$  denote the excess relative cancer risk if exposed at age 0.

To find the lower bound for the excess lifetime risk a lower bound for the lifetime risk in the exposed population is first established

$$B'(0,r) = [1 + r] \int_0^\infty m_c(y) S(y) \exp\{-r M_c(y)\} dy$$

$$= [1 + r] G(r),$$

where  $G(r)$  is defined as the integral above. The function  $G(r)$  is a decreasing, convex function (it is actually completely monotone) taking the value  $B(0)$  for  $r = 0$ . Therefore,

$$B(0) + r DG(0) \leq G(r)$$

and

$$[1 + r][B(0) + DG(0)] < B'(0,r), \quad (C1)$$

where  $DG$  denotes the first derivative of  $G$ . It remains to find an expression for  $DG(0)$ . Now

$$DG(0) = - \int_{y=0}^\infty m_c(y) S(y) \int_{x=0}^y m_c(x) dx dy.$$

Interchanging the order of integration leads to

$$= - \int_{x=0}^\infty m_c(x) S(x) \int_{y=x}^\infty m_c(y) S(y:x) dx dy$$

$$= - \int_0^\infty m_c(x) S(x) B(x) dx$$

$$= - B(0) \bar{B}(0),$$

where  $\bar{B}(0)$  is the mean value of the lifetime risk  $B(x)$  in the distribution of time to cancer deaths among those eventually dying from (background) cancer.

The lower bound for the excess lifetime cancer risk is now obtained by inserting this expression in Eq. (C1) and subtracting off the lifetime risk among unexposed.

To derive the upper bound, first note that the lifetime cancer risk is one minus the lifetime noncancer risk. Thus

$$B'(0,r) = 1 - \int_0^\infty m_n(y) S(y) \exp\{-r M_c(y)\} dy$$

$$= 1 - H(r),$$

where  $H(r)$  is the defined as the integral in the preceding line. The function  $H(r)$  is also a decreasing, convex function and takes the value  $1 - B(0)$  for  $r = 0$ , so

$$1 - B(0) + r DH(0) < H(r)$$

and

$$B'(0,r) \leq B(0) - r DH(0), \quad (C2)$$

where  $DH$  denotes the first derivative of  $H$ . Now

$$DH(0) = - \int_{y=0}^\infty m_n(y) S(y) \int_{x=0}^y m_c(x) dx dy.$$

After interchanging the order of integration and some further manipulations similar to those above

$$= - \int_0^\infty m_c(x) S(x) [1 - B(x)] dx$$

$$= - B(0) [1 - \bar{B}(0)].$$

Inserting this in Eq. (C2) and subtracting off  $B(0)$  gives the desired upper bound for the excess lifetime risk.

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