THE AGE DISTRIBUTION OF HUMAN CANCER FOR CARCINOGENIC EXPOSURES OF VARYING INTENSITY

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The time and age dependence of cancer incidence rates resulting from various types of carcinogenic exposure are calculated and compared with observed cancer incidence rates. Implications for the detection of increased cancer incidence are discussed. The calculations assume that exposure affects one of several changes necessary for malignant cell transformation.

Key words: carcinogenesis, extra incidence rate, k-stage theory, relative risk

1. Introduction

A number of questions can be raised about the time and age dependence of cancer incidence rates resulting from various temporal patterns of carcinogenic exposure. One is the question which age groups are most vulnerable to such exposure. The issue is important not only for the prevention of cancer, but also for the early detection of increased incidence in a population subjected to additional carcinogenic exposure. For example, one might ask whether restricting study to a subgroup of the exposed population can decrease the time required to demonstrate a significantly high cancer rate. Restriction of study to those under age fifty, for whom background rates are relatively low, may be more sensitive for detection of increased incidence.

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One might also inquire about the sensitivity of cancer incidence rates to increased population exposures. If background levels are increased for a population, how much time must elapse before a significant number of excess cancers can be observed? How much later will the full effect of the increased exposure be apparent?

The answers to such questions depend upon the way the additional agent induces cancer, and on the interactive effects of additional and background exposures. We examine here some implications of the k-stage theory under various assumptions of additional exposure. The predictions of the theory, which are derived in the appendices, are compared with observed human cancer incidence rates.

The background or spontaneous incidence rate for cancer of a particular site among individuals aged $x$ at time $t$ in the absence of increased exposure is denoted by $b(x,t)$. Denote by $h(x,t)$ the exposed incidence rate among those subjected to additional carcinogenic exposure. The difference $e(x,t) = h(x,t) - b(x,t)$ between the exposed and background rates will be called the extra incidence rate due to the additional exposure. The relative risk $r(x,t)$ is the ratio of exposed to background rates: $r(x,t) = h(x,t)/b(x,t) = 1 + e(x,t)/b(x,t)$.

2. The k-stage Theory

The k-stage theory of cell transformation was first proposed by Muller [1] and Nordling [2] to account for their observations that the mortality rates for many forms of adult human cancer increase as the fifth or sixth power of age. According to this theory, a cell generates a malignant neoplasm after it has suffered a certain number, say $k$, of changes. Armitage and Doll [3] assumed that the $k$ changes have different
transition rates and that they must occur sequentially. We further assume that the time required for clonal growth to tumor is negligible, so that the rate of tumor occurrence in a tissue of age \( x \) at time \( t \) equals the rate of cell transformation in the tissue. The consequences of altering this assumption are discussed in Section 5.

When loss of cells through transition to the next stage or due to lethality from carcinogenic exposure is neglected, the above assumptions predict a background rate which is independent of calendar time and proportional to the \((k-1)^{\text{st}}\) power of age. This agrees with the observed data when \( k = 6 \) or 7. For exposures of constant intensity, the exposed and extra rates are also independent of time and proportional to the \((k-1)^{\text{st}}\) power of age. In this case the relative risk is a constant independent of age and time.

In the next section we examine the extra rate as a function of age and time under more general assumptions than that of constant exposure. Expressions for the exposed and extra rates corresponding to variable carcinogen intensity, and derivations for the above results, can be found in Appendix A.

3. Consequences of the k-stage Theory with One Dose-dependent Stage

Suppose that exactly one transition rate is affected by the carcinogen. Then for constant exposures the extra incidence rate \( e(x) \) is proportional to the concentration \( c \) of additional carcinogen:

\[
e(x) = cx^{k-1}.
\]  

(3.1)
There is considerable epidemiological evidence [4] to support the proportionality of extra incidence rate with dose rate, as opposed to, say, the square of dose rate. Doll studied the incidence of lung cancer in physicians in England and its relation to cigarette smoking. He found that the incidence rate of bronchial carcinoma is approximately proportional to the number $c$ of cigarettes smoked per day, and to the fourth power of smoking duration $x$ [5]. This result indicates that $e(x)$ is proportional to $cx^4$ in agreement with (3.1) when $k=5$, provided that the background rate is neglected. The incidence rates are shown in Figure 1.

As another example, Cutchis [6] analyzed incidence data on a basal cell epithelioma in adult males in New York City. He found, after controlling for susceptibility to sunburn, that the incidence rate is proportional to daily rate of outdoor exposure. Assuming that outdoor exposure is a measure of ultraviolet radiation dose to the skin, and that the spontaneous occurrence of this skin cancer is negligible, his finding is also in agreement with (3.1).

We shall now examine the time and age dependence of the extra rate when exactly one of several stages is affected by the additional carcinogen. We consider examples corresponding to various temporal patterns of additional exposure. The mathematical derivations are contained in Appendix B.

i) First suppose that additional exposure begins at a particular time $t_0$. Then the individuals who are older at onset of exposure will have higher extra incidence rate at any later time $t_0 + \tau$, provided the carcinogen related transition is not the first.
This is because they have had longer background exposure and thus more cells in the previous stage ready for the carcinogenic effect of the agent. When the affected stage is the first, the extra incidence rate at a fixed time after exposure onset is independent of age. Thus the relative risk decreases with age, provided that cancer occurs in more than one stage. If it occurs in one stage, the relative risk is independent of age.

The increase in incidence with age at onset of additional exposure is demonstrated by the data of Court-Brown and Doll [7] on excess nasal sinus cancer among men employed in the nickel refining industry in South Wales, shown in Figure 2. It is also suggested by the data of Case et al. [8], which show that bladder tumor incidence among men in the dyestuff industry increases slightly with age at start of employment.

The opposite finding was reported by Hoover and Cole [9] in their study of bladder cancer among men employed in the paint, leather, dye-stuff, and organic chemical industries in eastern Massachusetts. After standardizing for occupational category, calendar year of first employment and duration of employment, they find that men first employed in one of these occupations by the age of 24 have a risk 2.4 times that of men never so employed, while men employed after age 25 show virtually no excess risk. This appears to contradict the theory. However the authors do not report standardizing for total time elapsed since start of employment. Thus it is possible that those who were aged 24 or younger at start of employment have had more background exposure subsequent to leaving the industry than those employed after age 24. If so, this could account for the apparent discrepancy.
Decreased vulnerability with increasing age at onset of exposure is also reported by Kahn [10] for lung cancer incidence among cigarette smokers. He finds that for each category of smoking duration for which data suffice to make a comparison, persons who begin smoking under age 20 have a greater risk than those who start later. This association, which holds at all smoking levels, is also inconsistent with the above theory. A possible explanation, conjectured by Kahn, is that early smokers include a higher proportion of inhalers than those who start after age 20. Another explanation for the disagreement will be discussed in Section 5.

ii) As a second example, suppose that additional exposure terminates at some time $t_1$. If the carcinogen related stage is the last, then the extra incidence rate is zero for all age groups at all times subsequent to $t_1$. (Of course this neglects the time between transformation and cancer detection. Actually the extra rate would be zero only after all those cancers generated prior to $t_1$ have been detected.) If the $(k-1)^{st}$ stage is affected, then the extra rate at any time after termination is independent of the time elapsed since termination of exposure. The fact that extra rates for lung cancer cease to rise in former cigarette smokers [7], as shown in Figures 3 and 4, suggests that the penultimate stage is affected by the carcinogenic components of cigarette smoke. However, because of the large variation indicated by the confidence limits in Figure 3, other temporal patterns cannot be excluded.

iii) We next consider the extra rate resulting from single or brief exposures. Since this is a special case of each of the first two examples, all of the above comments apply. If the exposure affects the $j^{th}$ of $k$ cellular changes, then the extra rate varies as the first
power of exposure intensity, as the \((j-1)^{st}\) power of age at exposure, and for \(j < k\), as the \((k-j-1)^{st}\) power of time since exposure. An agent affecting the last stage induces a single pulse response. Note that an agent affecting the first of two changes induces an extra rate that is independent both of exposure age and of time since exposure.

The data of Court-Brown and Doll [7] on excess leukemia incidence among those x-irradiated as treatment for ankylosing spondilitis show an increase in incidence with age at exposure (see Figure 5). This supports the above theory with radiation affecting a late stage in the induction of leukemia.

The findings of Bizzozero et al. [11] on chronic and acute leukemia following the atomic bombings at Hiroshima and Nagasaki are inconsistent with the above conclusions. According to this data, the mean appearance time (time between exposure and leukemia appearance) is a decreasing function of exposure intensity for those under 30 years of age at the time of the bombings. No such decrease of appearance time with the intensity was noted for those of exposure age over 30. This is in disagreement with the above theory, which predicts that for any values of \(k\) and \(j\) the mean appearance time for radiation induced leukemia is independent both of age at exposure and exposure intensity. These data include spontaneous as well as radiation induced leukemia. Thus the findings suggest a theory that atomic radiation induces leukemia independently of the spontaneous mechanisms, and that radiation induced leukemia develops more rapidly among the young.
iv) As a final example, suppose that exposure at constant concentration begins at age $x_0$, and terminates at age $x_1$. This is the case for cigarette smokers who continue smoking at the same rate. Here $x_0$ is, say, 20 years, and $x_1$ is age at death. It is also roughly the case for radiologists, who enter the profession at approximately 35 years of age and retire at about 65 years.

Because of the assumed constancy of extra exposure, the extra rate is independent of time. Expressions for the ratio of excess rate to background rate, corresponding to the k-stage theory with exactly one of k transitions dose related, are given by (A.18) of Appendix B. It follows from analysis of these expressions that the relative risk is increasing in $x$ in the range between $x_0$ and $x_1$, and decreasing in $x$ for $x$ sufficiently greater than $x_1$. This conclusion has been observed [12] as shown in Table 1 among those employed in five industries shown to be associated with a statistically significant excess of bladder cancer (dyestuffs, rubber, leather, paint, and organic chemicals). It has also been observed [13] for all cancers in radiologists, as shown in Table 2. The same increase of relative risk with age can be found in Doll's data on lung cancer incidence in smokers and nonsmokers.

However, it is not apparent in the observations of Case et al. [8] of bladder tumors among British men ever employed in the dyestuffs industry.
Of the 280 such cases reported, the most frequent age of occurrence was 40-50 years (35% of all cases), twenty years earlier than the most frequent age of occurrence in the general Birmingham male population. In Figure 6 the incidence rates for five benzidine exposure duration categories are plotted as percentages of the duration standardized rate. The peak is at exposure durations of 5-10 years, with subsequent decline in risk for those who have been so employed for longer times. This suggests the possible attenuation of a pool of susceptibles.

4. Implications for the Detection of Increased Cancer Incidence

We now consider which age groups are most vulnerable in a population exposed to increased levels of a carcinogen. We also examine the time required to detect the effect of such an increase. As will be seen, the results depend strongly on how the additional exposure interacts with background exposures.

Consider a population which is exposed to a carcinogenic agent at an average level $c(t)$ in excess of background levels, and which is observed for cancer incidence for a particular time period. The population is to be compared with a suitably matched control or unexposed population for which the incidence rate $b(x)$ of a particular cancer is assumed to increase with age $x$, but to be independent of time. Given the background and extra rates and the age distributions of the populations in the observation period, one can calculate the expected numbers $B_x$ and $E_x$ of background and extra cancers among those aged $x$ (see Appendix C).

If the background rate is high, it will be difficult to detect the effect of the additional exposure. Suppose the number of extra cancers
necessary to produce a detectable excess is twice the standard error of the expected number of background cases. This means extra cancers are detected only if $E_x$ exceeds twice the square root of $B_x$. Squaring the quantities involved, we have that the excess cancers can be detected only if

$$\frac{E_x^2}{B_x} > 4. \quad (4.1)$$

Let us consider which age group $x$ maximizes the quantity on the left hand side of (4.1). To illustrate how completely the answer depends on one's assumption about the interaction of the additional carcinogen with background exposures, we consider two extreme cases: a) the extra rate is proportional to the background rate: $e(x,t) = a(t)b(x)$; b) the extra rate is independent of age and depends only on time: $e(x,t) = e(t)$. As shown in Appendix C, the ratio $\frac{E_x^2}{B_x}$ is proportional to the background rate $b(x)$ in case (a), while in case (b) it is proportional to $1/b(x)$. Thus for populations with fairly uniform age distributions over the period of observation, the ratio $\frac{E_x^2}{B_x}$ will be largest in case (a) at oldest ages $x$ when the background rate $b(x)$ is highest, and largest in case (b) at young ages $x$ when $b(x)$ is lowest. This complete reversal shows that we must specify how the carcinogen acts before we can predict its effect on different age groups.

Cases (a) and (b) are not unreasonable; each might occur as the consequence of certain assumptions about the cancer mechanism. Case (a) (with $a(t)$ constant) occurs according to the $k$-stage theory when the concentration of additional carcinogen is constant [see (A.12) and (A.9)]. Case (a) (with $a(t) = c(t)$) also occurs if the carcinogen affects the last of $k$ stages [see (A.9) and (A.14)]. Case (b) (with $e(t)$ equal to $c(t)$) occurs when the agent induces cancer in one stage [see (A.14)].
We have assumed that the background rates increase with age. This is consistent with a k-stage mechanism for background cancers only if k is greater than one (see (A.9). Thus both assumptions (b) and that of increasing background rates occur when the background cancers are induced in two or more stages, while the carcinogen related cancers are induced by a completely independent one-stage mechanism.

The dramatically different consequences of (a) and (b) show that limitation of study to subgroups of the population on the basis of age should be based upon additional evidence about the way the carcinogen acts. For example, the bronchial carcinomas found among workers exposed to chloromethyl methyl ether (CMME) were small cell in type and appeared after as little as ten years after exposure [14]. The carcinomas linked to cigarette smoking in the general population, however, are most often squamos cell in type and tend to occur late in life. This is evidence that CMME acts independently of and in fewer stages than cigarette smoking and other background exposures. Such evidence, either from experimental or epidemiological data, would suggest restriction of study to the young.

The next two examples illustrate further how altering the assumptions of an analysis reverses its conclusions about cancer detection. Pochin [15] compares cancer mortality rates among a population exposed to specified constant levels of natural radiation to those of a control population exposed to lower levels. He concludes that confining study to malignancies fatal by age 35 would substantially reduce the time necessary to detect the excess mortality. His analysis includes assumption (b), as well as the assumption that the background rates increase with age. Assumption (b) seems highly intenable for this situation. It means that the additional radiation induces all cancers in one stage independently of the background radiation, the latter doing so in more than one stage. Since he assumes constant exposure for both populations, case (a) seems much more appropriate. As shown above, this implies that study should be restricted to the elderly.
Cutchis [6] estimates the increase in non-melanoma skin cancer incidence in the U.S. as a function of time following an increase of ultraviolet radiation due to alterations in stratospheric ozone. He assumes that the skin cancer incidence rate among individuals aged $x$ is proportional to accumulated lifetime UV dose, with the proportionality factor dependent upon age $x$. This implies (Appendix C) that the extra rate among those aged $x$ at any time after the increase depends on whether they were born before or after the increase. The situation is illustrated in Figure 7. In 7.A those born subsequent to the increase have received extra radiation exposure all of their lives, while in 7B those born prior to it have received additional exposure for only $T$ years of their lives. Thus the age-standardized extra rate for the entire population would not stabilize at its maximum value until about a century after the increase, when everyone has received additional exposure for his entire lifetime. For this reason Cutchis argued that surveillance of skin cancer rates is infeasible as a method for monitoring UV levels. Figure 8 shows the slow increase with time of the ratio of the age-standardized extra rate to its maximum value, as well as the sluggish response of this ratio following reduction of UV levels.

This conclusion remains valid whenever extra rates increase with accumulated lifetime dose. According to (A.13), this holds if the agent affects the first of at least two events necessary for malignant transformation. However if the agent affects the last of one or more changes, then the extra rates do not increase with total dose, and Cutchis' conclusion does not hold. In this case, according to (A.14), the extra rates following increased exposure immediately rise to their maximum value, and depend upon the $(k-1)^{st}$ power of age.
The consequent sensitivity of incidence rates to increased exposure levels, with highest extra incidence among the elderly, implies that restriction of study to the elderly would provide an effective check on increased levels. Thus here as in the previous example, the conclusions about detection of increased incidence depend strongly on assumptions about the interaction of additional and background exposures. Evidence whether or not incidence rates respond quickly to increases in UV exposures, and thus indirect evidence about which stage is UV related, would be provided by comparison of the skin cancer rates among migrants to the "sun belt" states with suitably matched controls both in place of origin and place of destination.

5. Discussion

The preceding analysis has neglected the time required for the clone of a transformed cell to grow to clinical detectability. It has also assumed that the exposed population is genetically homogeneous in susceptibility to cancer induction. Both of these factors can modify the age distribution of cancer. If there is evidence that cancers induced by the suspected carcinogen grow more rapidly than those caused by background mechanisms, or grow more rapidly in young tissue, then excess risk may be detected more easily among the young. Similarly, if the low incidence at large exposure durations reflects the earlier removal of a subgroup of the population highly susceptible to the induction of the particular cancer, then this would also be justification for the restriction of study to the young. A third factor that mitigates against searching for carcinogenic effects among the elderly is the possibility of greater diagnostic inaccuracy in this age group.
In the preceding theory the rates at which cells progress from one
tage to the next vary with the level of exogenous carcinogenic exposure.
However given constant exposure, they are assumed to be independent of
the host's age. This assumption is supported by the experiment of Peto
et al [16]. They administered the same repeated benzpyrene skin painting
treatment to mice starting at 10, 25, 40 and 55 weeks of age and found
tumor incidence after a given treatment duration to be independent of age.

Evidence against this assumption is provided by the studies [9, 10],
discussion in Section 3 i), indicating decreased cancer incidence with
increasing age at onset of exposure. These studies suggest that the
transition rates corresponding to a given exposure pattern are higher
among young invididuals. Transition rates that vary with age according
to internal hormone levels have been used by delisi [17] to fit a three-
stage theory to a wide variety of human breast cancer data.

Another possibility that is not included in the preceding theory is
that exposure accelerates the proliferation rates of partially or completely
transformed cells. If so, vulnerability to such promoting effects may vary
with age.
6. Summary

We have calculated the time and age dependence of extra incidence rates resulting from several types of exposure patterns. The calculations assume that additional exposure affects one of several stages of malignant cell transformation. The results, summarized in Table 3 of Appendix B, have been compared with observed human cancer incidence rates. Some phenomena predicted by the theory are as follows:

i) **Constant exposures.** The extra rate is proportional to the background rate, and the relative risk is a constant, independent of age and time.

ii) **Exposures of varying intensity that begin at a particular time.** If the dose-dependent stage is the first, then the extra rate is independent of age at exposure onset. The relative risk is either decreasing with age or independent of age, depending on whether or not the cancer occurs in more than one stage. If the agent affects a later stage in a two or more stage process, then the excess rate increases with age at onset.

iii) **Exposures of varying intensity that end at a particular time.** If the dose dependent stage is the last, then the extra rate at subsequent times after a tumor growth period is zero for all age groups. If the penultimate stage is dose-dependent, then the extra rate at any age is independent of the amount of time elapsed since termination.

iv) **Single exposures.** The extra rate varies as the first power of exposure intensity; as the (j-1)\(^{st}\) power of exposure age, and as the (k-j-1)\(^{st}\) power of time since exposure. Here \(k\) is the number of changes required for transformation, and \(j < k\) is the stage affected by exposure. An agent affecting the last stage induces a single pulse response within a tumor growth period after exposure.
v) **Exposures of constant intensity starting at age** \( x_0 \) **and ending at age** \( x_1 \). Here the relative risk increases with age for those with age in the range \( x_0 \) to \( x_1 \), and decreases with age for ages sufficiently greater than \( x_1 \).

We have examined the implications of these predictions for the detection of increased cancer incidence when background rates are high. We conclude that unless there is histological evidence that the agent in question produces malignancies by a mechanism that is independent of the background mechanisms, there is no justification for restricting epidemiological study to the young. Indeed, if the agent affects the last of several stages, or if exposure is fairly constant, then the most significant number of excess cancers should occur among the elderly.

Finally, estimates that the full effects of increased exposure do not become evident until about a century after exposure onset assume that the extra rates increase with accumulated lifetime dose. This assumption is consistent with the above theory if the agent affects the first of several changes necessary for malignant transformation. However it does not hold if the agent affects the last of such changes. In this case the extra cancers would be detectable after a relatively short tumor growth period. Moreover the greatest excess would occur among the elderly.
References


Appendices

Appendix A: The k-stage theory

A cell is assumed to be capable of generating a malignant neoplasm when it has suffered \( k \) changes occurring in a certain order. A cell in stage \( i \) is one that has suffered \( i \) changes, \( 0 \leq i \leq k \). Denote by \( \lambda_i \) the rate at which the \( i \)th change occurs, \( 1 \leq i \leq k \). Let \( n_i(x) \) be the number of cells in stage \( i \) in the tissue of an individual of age \( x \), \( i = 0, 1, \ldots, k \). The equations for \( n_i(x) \) are

\[
\frac{d}{dx} n_i(x) = \lambda_i(x) n_{i-1}(x) - \lambda_{i+1}(x) n_i(x), \quad i = 0, 1, \ldots, k,
\]

where \( n_{-1}(x) = \lambda_{k+1}(x) = 0 \).

At birth the tissue of an individual is assumed to contain some number \( N \) of normal cells at risk of transformation. Thus the initial conditions at age \( x=0 \) are

\[
n_0(0) = N, \quad n_i(0) = 0, \quad i = 1, \ldots, k.
\]

When \( \int_0^x \lambda_i(y)dy \) is small for all \( i \) and for all ages \( x \) under consideration, the solution to (A.1, 2) is approximately (see [18])

\[
n_0(0) = N,
\]

\[
n_i(x) = N \int_0^x \cdots \int_0^{y_3} \int_0^{y_2} \lambda_1(y_1) \cdots \lambda_2(y_2) \lambda_1(y_1) dy_1 \cdots dy_i.
\]

If the time between cell transformation and tumor detection is neglected, the rate \( h(x) \) of tumor appearance in the tissue of an individual aged \( x \) is the rate of cell transformation. This is the rate at which cells enter stage \( k \), which by (A.1) with \( i=k \) is \( \lambda_k(x)n_{k-1}(x) \). Using (A.4) to determine \( n_{k-1}(x) \) yields
\[ h(x) = N \prod_{i=1}^{k} \int_0^x \int_0^{y_2} \int_0^{y_1} \lambda_{k-1}(y_{k-1}) \cdots \lambda_2(y_2) \lambda_1(y_1) \, dy_1 \, dy_2 \cdots \, dy_{k-1}. \]

Suppose now that a population of individuals of various ages is exposed to a carcinogenic agent at concentration \( c(t) \), where \( t \) represents calendar time. We assume that the transition rates for the cells of exposed individuals depend on time through the following dependence on carcinogenic concentration:

\[ \tilde{\lambda}_i(t) = s_i + p_i c(t), \quad i = 1, \ldots, k. \]

An individual of age \( x \) at time \( t \) was aged \( y < x \) at time \( t - x + y \); thus the transition rates \( \lambda_i \) and \( \tilde{\lambda}_i \) are related by

\[ \lambda_i(y) = \tilde{\lambda}_i(t - x + y), \quad 0 \leq y \leq x, \quad i = 1, \ldots, k. \]

Use of (A.7) in (A.5) yields the incidence rate \( h(x,t) \) for individuals in the population who are aged \( x \) at time \( t \):

\[ h(x,t) = N \prod_{i=1}^{k} \int_0^x \int_0^{y_2} \int_0^{y_1} \tilde{\lambda}_{k-1}(t - x + y_{k-1}) \cdots \tilde{\lambda}_2(t - x + y_2) \tilde{\lambda}_1(t - x + y_1) \, dy_1 \, dy_2 \cdots \, dy_{k-1}. \]

The background of spontaneous rate corresponding to \( c(t) = 0 \) is obtained from (A.8) and (A.6) as

\[ b(x,t) \equiv b(x) = N s_1 \cdots s_k x^{k-1}/(k-1)! \]

The extra incidence rate \( e(x,t) \) due to additional exposure at concentration \( c(t) \) is the difference between the exposed rate \( h(x,t) \) of (A.8) and the background rate, (A.9):

\[ e(x,t) = h(x,t) - b(x,t). \]
\[ e(x,t) = N \hat{\lambda}_k(t) \int_0^x \cdots \int_0^{y_2} \hat{\lambda}_{k-1}(t-x+y_{k-1}) \cdots \hat{\lambda}_1(t-x+y_1) \, dy_1 \cdots dy_{k-1} \]

\[ - N s_1 \cdots s_k x^{k-1}/(k-1)! . \]

When the concentration \( c(t) \) of additional carcinogen is a constant \( c \), then (A.8) and (A.10) simplify to

\[ h(x,t) \equiv h(x) = N \hat{\lambda}_1 \cdots \hat{\lambda}_k x^{k-1}/(k-1)! , \]

\[ e(x,t) \equiv e(x) = N(\hat{\lambda}_1 \cdots \hat{\lambda}_k - s_1 \cdots s_k) x^{k-1}/(k-1)! . \]

Appendix B: The \( k \)-stage theory with one carcinogen affected stage

Assume that exactly one transition rate \( \hat{\lambda}_j \) is affected by the carcinogen, so that in (A.6) \( p_i = 0 \) for \( i \neq j \). Then with the symbol \( \ast \) indicating proportionality, use of (A.6) in (A.10) yields

\[ e(x,t) \ast \int_0^x \cdots \int_0^{y_{j+2}} \int_0^{y_{j+1}} c(t-x+y_j)y_{j-1}^{y_{j-1}} dy_{j-1} dy_{j+1} \cdots dy_{k-1}, \ j < k \]

\[ \ast = c(t)x^{k-1} , \ j = k . \]

In particular, dose dependence of transition to the first stage of a sequence of at least two stages implies that the extra incidence rate is proportional to the \( (k-2)^{\text{nd}} \) fold integral of total lifetime dose.

It is convenient to use an alternative expression for \( e(x,t) \) obtained from (A.13) by integrating over the variables \( 0 < y_j < y_{j+1} < \cdots < y_{k-1} < x \) in the order \( y_{k-1}, y_{k-2}, \ldots, y_{j+1} \):

\[ e(x,t) \ast \int_0^x (x-y)^{k-1-j} c(t-x+y)y_{j-1}^{y_{j-1}} dy , \ j < k \]

\[ \ast = c(t)x^{k-1} , \ j = k . \]
We now examine some special cases of the relations (A.13) and (A.14) corresponding to various patterns \( c(t) \) of exposure.

i) **Constant concentrations** for \( c(t) = c \), (A.13) reduces to

\[
e(x, t) = cx^{k-1},
\]

i.e., the extra rate at age \( x \) is proportional to carcinogen concentration \( c \) and to the \((k-1)\)th power of age.

ii) **Exposure starting at time** \( t_0 \). If \( c(t) = 0 \) for \( t < t_0 \), then the extra incidence rate \( e(x_0 + \tau, t_0 + \tau) \) at any age \( x_0 + \tau \) after the age \( x_0 \) of onset of additional exposure can be obtained from (A.14).

Using the change of variables \( z = y - x_0 \), we have

\[
e(x_0 + \tau, t_0 + \tau) = \int_0^\tau (\tau - z)^{k-1} (x_0 + z)^{j-1} c(t_0 + z) dz, \quad j < k
\]

\[
= c(t_0 + \tau)(x_0 + \tau)^{k-1}, \quad j = k.
\]

Thus \( e(x_0 + \tau, t_0 + \tau) \) is increasing in \( x_0 \) for \( j > 1 \) and independent of \( x_0 \) for \( j = 1 \).

iii) **Exposure ending at time** \( t_1 \). Suppose that \( c(t) = 0 \) for \( t > t_1 \).

Then the extra rate \( e(x_1 + \tau, t_1 + \tau) \) at date \( \tau \) time units after termination for an individual aged \( x_1 \) at time of termination is by (A.14)

\[
e(x_1 + \tau, t_1 + \tau) = \int_0^{x_1} (x_1 + \tau - y)^{k-1} c(t_1 - x_1 + y)^{j-1} dy, \quad j < k
\]

\[
= 0, \quad j = k.
\]

It follows from (A.17) that when \( j = k-1 \), the extra rate is independent of the time \( \tau \) elapsed since termination of exposure.

iv
iv) Single exposures at time $t_0$. For $c(t) = c_0(t-t_0)$, (A.14) yields

$$e(x + \tau, t + \tau) = c_0^k \frac{(x-t_0)^{j-1}}{x_0^{j-1}}, \quad j < k,$$

$$= c_0^k (x-t_0)^{k-1} \quad j = k.$$

Thus the extra rate is proportional to exposure intensity $c$, and varies as the $(j-1)^{st}$ power of exposure age $x_0$. For $j < k$ the extra rate varies as the $(k-j-1)^{st}$ power of time $\tau$ since exposure, while for $j = k$ the extra response is a single pulse at time $t_0$.

v) Constant exposure beginning at age $x_0$ and ending at age $x_1$. It follows from (A.14) that $e(x,t) = e(x)$ depends only on age and not on time. When $j = k$, the excess-to-background ratio $e(x)/b(x)$ is by (A.9) and (A.14) constant in the age range from $x_0$ to $x_1$ and zero elsewhere. When $j < k$ (A.9) and (A.14) yield

(A.18) $e(x)/b(x) = 0, \quad x < x_0$

$$= \int_{x_0}^{x} (x-y)^{k-1-j} x^{-k} y^{j-1} \, dy, \quad x_0 < x < x_1$$

$$= \int_{x_0}^{x_1} (x-y)^{k-1-j} x^{-k} y^{j-1} \, dy, \quad x_1 < x.$$

The formulae (A.18) can be used to analyze the ratio $e(x)/b(x)$ when $j < k$. One can verify by expanding $(x-y)^{k-1-j}$ and differentiating that

(A.19) $\frac{d}{dx} \left[ \int_{x_0}^{x} (x-y)^{k-1-j} x^{-k} y^{j-1} \, dy \right] = \frac{x_j}{x^{k-1}} (x-x_0)^{k-j-1}$,
and

\[(A.20) \quad \frac{d}{dx} \left[ \int_{x^1}^{x^1} (x-y)^{k-1-j} x^{1-k} y^{j-1} dy \right] = \frac{1}{x^k} (x_0^j (x-x_0)^{k-1-j} - x_1^j (x-x_1)^{k-1-j}) \, . \]

Comparison of (A.18) with (A.19) shows that \(e(x)/b(x)\) increases with age \(x\) in the range \(x_0 < x < x_1\). (A.18) and (A.20) indicate that \(e(x)/b(x)\) decreases in \(x\) for values of \(x\) greater than \(x_1\) in case \(j = k-1\), and greater than \(x_1 + (x_1-x_0) \sum_{r=1}^{\infty} (x_0/x_1)^r/(k-1-j)\) in case \(j < k-1\).

The predicted forms for the extra rate and relative risk for each of the preceding five exposure patterns are shown in Table 3.

Appendix C: Implications for cancer detection

Let \(b(x)\) and \(e(x,t)\) denote the background and extra incidence rates of a particular cancer for individuals of age \(x\) at time \(t\) in a population subjected to increased exposure at concentration \(c(t)\) and observed for a time period from \(t_0\) to \(t_0 + \tau\). Let \(\ell(x,t)\) denote the number of individuals of age \(x\) at time \(t\) in the population. The expected number of additional cancers occurring at age \(x\) and observed in the period is

\[(A.21) \quad E_x = \int_{t_0}^{t_0 + \tau} e(x,t)\ell(x,t)dt \, . \]

The expected number of background or spontaneous cases is

\[(A.22) \quad B_x = b(x)\ell(x) \, , \]

where \(\ell(x) = \int_{t_0}^{t_0 + \tau} \ell(x,t)dt\) is the total number of person-years at risk in the period. Let a significant excess of cancers be characterized by

\(E_x \geq 2\sqrt{B_x} \, , \)

vi
that is by

\[ \frac{E_x^2}{B_x} \geq 4. \]

Determination of the age \( x \) that maximizes the ratio \( \frac{E_x^2}{B_x} \) requires specification of the form of \( e(x,t) \). Consider two cases: (a) \( e(x,t) = a(t)b(x) \); (b) \( e(x,t) = e(t) \). Substitution of each of these two forms for \( e(x,t) \) in (A.21) yields in case (a)

\[ (A.23) \quad \frac{E_x^2}{B_x} = b(x) \cdot \frac{(\int a(t)\ell(x,t)dt)^2}{L(x)}, \]

and in case (b)

\[ (A.24) \quad \frac{E_x^2}{B_x} = \frac{1}{b(x)} \cdot \frac{(\int e(t)\ell(x,t)dt)^2}{L(x)}. \]

Note that the right-hand factor in (A.23) and (A.24) depends on age \( x \) only through the function \( \ell(x,t) \). If the factor does not vary appreciably with \( x \) and if \( b(x) \) increases with \( x \), then \( \frac{E_x^2}{B_x} \) is maximized at low ages in case (a) and at high ages in case (b).

We next calculate the age-standardized excess incidence rate

\[ \overline{e}(t) = \frac{\int e(x,t)\ell(x,t)dx}{\int \ell(x,t)dx}. \]

We assume, as did Cuchis [15], the following:

(i) \( \ell(x,t) = \ell(x) \) for \( t_0 < t < t_0 + \tau \);

(ii) \( c(t) = 0, \ t < t_0 \)

\[ = c \quad t > t_0; \]

(iii) \( e(x,t) = g(x) \int_0^x c(t-x+y)dy \).

vii
Assumptions (ii) and (iii) imply that

\[ e(x, t_0 + \tau) = \begin{cases} cxg(x) & \text{if } x < \tau \\ ctg(x) & \text{if } x > \tau \end{cases} \]

If incidence rates are calculated for ages up to say, 80 years, then

\[ \bar{e}(t_0 + \tau) = c \left( \int_0^\tau x g(x) \lambda(x) dx + \tau \int_\tau^{80} g(x) \lambda(x) dx \right) / \int_0^{80} \lambda(x) dx , \quad \tau < 80 \]

\[ = c \int_0^{80} x g(x) \lambda(x) dx / \int_0^{80} \lambda(x) dx , \quad \tau > 80 . \]

Thus the age standardized excess rate does not stabilize at its maximum value \( \bar{e}(t_0 + 80) \) until 80 years after the time of exposure increase.
TABLE 1
Incidence Rate of Bladder Cancers by Occupational Category:
Cancers/10^5 Man-Years

(Cole, Hoover, Friedell, 1972)

<table>
<thead>
<tr>
<th>Occupational Category</th>
<th>Age</th>
<th>h^+</th>
<th>b^^</th>
<th>e/b^*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-59</td>
<td>22.5</td>
<td>11.4</td>
<td>.97</td>
</tr>
<tr>
<td></td>
<td>60-74</td>
<td>188.5</td>
<td>87.7</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>75-89</td>
<td>284.5</td>
<td>217.5</td>
<td>.31</td>
</tr>
</tbody>
</table>

^Men ever employed in dyestuffs, rubber, leather, paint, organic, chemical industries
^^All others in study
* e = h-b

TABLE 2
Cancer Mortality Rate Experienced 1945-54 by Physician Societies:
Deaths/10^5 Man-Years

(Seltser and Sartwell, 1965)

<table>
<thead>
<tr>
<th>Society</th>
<th>Age</th>
<th>h^+</th>
<th>b^^</th>
<th>e/b^*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiological Society of North America</td>
<td>35-49</td>
<td>36.4</td>
<td>68.2</td>
<td>-</td>
</tr>
<tr>
<td>American Academy of Ophthalmology and Otolaryngology</td>
<td>50-64</td>
<td>409.1</td>
<td>163.6</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>65-79</td>
<td>1000.0</td>
<td>672.7</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td>35-79</td>
<td>306.8</td>
<td>193.2</td>
<td>.59</td>
</tr>
</tbody>
</table>

^Radiological Society of North America
^^American Academy of Ophthalmology and Otolaryngology
* e = h-b
### Table 3

**Expected Incidence Rates** and Relative Risk According to k-Stage Theory with One-Stage Affected by Additional Exposure

<table>
<thead>
<tr>
<th>Exposure Pattern</th>
<th>constant exposure from age $x_0$ to age $x_1$</th>
<th>single exposure at $t_o$: $c(t) = c(t-o)$</th>
<th>variable exposure ending at $t_o$: $c(t) = 0, t &gt; t_o$</th>
<th>variable exposure starting at $t_o$: $c(t) = 0, t &lt; t_o$</th>
<th>constant exposure: $c(t) = c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$b(x,t)$ background incidence rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$x^{-1}$ proportional to $(k-1)^{st}$ power of age, independent of time</td>
</tr>
<tr>
<td>$e(x,t)$ extra incidence rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>independent of exposure age, increases with time since exposure onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$f(x,t,t_o)$ $g(x,t,y)dy$ $x^{-1}$ if $j=k-1$ independent of time since exposure termination</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$c(t-x_t)^{k-1}$ proportional to $c$, to $(j-1)^{st}$ power of exposure age, and to $(k-j)^{st}$ power of time since exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$c(t-x_t)^{k-1}$ if $j=k-1$, increases with age until $x_0 + (x_1 - x_0) \cdot \left(\frac{t}{t-o}\right)^{k-1}$, then decreases; if $j \neq k$, increases with age until $x_1$, then decreases</td>
</tr>
<tr>
<td>$r(x,t) = \frac{e(x,t)}{b(x,t)}$ relative risk minus one</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>constant proportional to $c$ when $x = t_o$, 0 otherwise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>constant proportional to $c$, to $(k-2)^{nd}$ power of time since exposure, for $0 &lt; t-t_o &lt; x$; 0 otherwise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>constant proportional to $c$, to $(k-j)^{th}$ power of age, for $0 &lt; t-t_o &lt; x$; 0 otherwise</td>
</tr>
</tbody>
</table>

(1) up to a proportionality constant

(2) $z^+ = \max(z,0)$; $f(x,t,t_o) = \left[\max(x-(t-t_o)^+,0)\right]^{-1}$

(3) $g(x,t,y) = (x-y)^{k-1}y^{k-1} c(t-x+y)$
Fig. 1. Incidence rate of bronchial carcinoma versus rate of cigarette smoking. Incidence rates are standardized for age in men who started to smoke at ages 15 to 24 years and were not known to have changed their smoking habits. Reprinted with permission from Doll [7].
Fig. 2. Incidence rate of occupational nasal sinus cancer in nickel refiners first employed at different ages. Reprinted with permission from Doll [7].
Fig. 3. Incidence rate of bronchial carcinoma versus time since cigarette smoking was stopped, compared with rates in continuing smokers and non-smokers. Incidence rates are standardized for amount smoked in continuing smokers and for amount smoked and age at stopping in ex-smokers. All rates are shown versus age less average stopping age among ex-smokers and are expressed as percent of smokers' rate at average stopping age. Reprinted with permission from Doll [7].
Fig. 4. Extra incidence rate of bronchial carcinoma versus time since termination of cigarette smoking. Extra rate is expressed as percent of rate at time of stopping. Points represent difference between rates in ex-smokers and non-smokers as shown in Fig. 3.
Fig. 5. Extra incidence of leukemia induced by ionizing radiations at different ages: patients irradiated for ankylosing spondylitis in Britain. Reprinted with permission from Doll [7].
Fig. 6. Incidence of bladder tumors among men employed in the dyestuffs industries versus exposure duration, as measured by years of employment in the industry. Incidence is expressed as percent of duration standardized incidence for each of four chemical exposure categories. Reprinted with permission from Case et al [8].
Fig. 7. Increased exposure level versus time and versus age for constant additional exposure beginning at time \( t_0 \). Shaded area represents accumulated extra dose for individuals aged \( x \) at time \( t_0 + \tau \) (A) when \( x < \tau \), and (B) when \( x > \tau \).
Fig. 8. Percent of maximum age standardized extra rate of nonmelanoma skin cancer due to increased UV exposure at constant concentration, and recovery curves following reduction of UV levels. Reprinted with permission from Cutchis [6].