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# CONVERTING RELATIVE RISKS TO ABSOLUTE RISKS: A GRAPHICAL APPROACH

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## SUMMARY

This paper presents a graphical method for converting relative risks to absolute risks. These absolute risk estimates are a function of the patient's current age, the patient's risk of developing cancer relative to some baseline population, the age specific cancer hazard in the baseline population, and the patient's competing mortal risk from all other causes. Graphs for breast cancer morbidity in women, cardiovascular mortality in men, and lung cancer morbidity in men illustrate the method. These graphs provide the probability of developing cancer in the next twenty years given the patient's current age and relative risk. They are derived under the proportional hazards model. A graph for lung cancer in men that uses a plausible exponential hazards model is also provided. The paper illustrates the importance of competing mortal hazard from other causes on absolute cancer risk. The strengths and weaknesses of this method are discussed. The graphs presented in this paper may be used as an aid in clinical decision making and in patient counselling.

KEY WORDS Relative risk Absolute risk Breast cancer Cardiovascular disease Lung cancer

## INTRODUCTION

Relative risks are the most ubiquitous measures of morbid or mortal risk in current use in the medical literature. The powerful methodologies of case-control studies,[1] logistic regression analysis,[1] and survival analysis[2] all permit the derivation of relative risk statistics. For both clinicians and patients, however, a far more relevant statistic is absolute risk. For example, consider a man who smokes 40 cigarettes a day and who faces a decision as to whether his risk of lung cancer outweighs his discomfort due to tobacco withdrawal. He will find it far more useful to know that he has a 25 per cent chance of developing lung cancer within 20 years than to know that during the next year he is 19 times more likely to develop lung cancer than a non-smoker. Unfortunately, however, it is often impossible to obtain direct estimates of absolute risks. Such estimates require lengthy follow-up on a reasonably large cohort of subjects who are at similar risk. Since these data are often unavailable, we must infer absolute risk estimates indirectly.

The absolute risk of suffering some morbid event is affected by the patient's relative risk with respect to members of a control population, the age specific incidence of this event in this control population, and the age specific competing mortality due to other causes. Chiang[3] provides the derivation of a patient's absolute risk as a function of the preceding information. In this paper, I will illustrate the relationship between these variables with graphs for breast cancer morbidity in American women and cardiovascular mortality in American men. I illustrate the effect of time dependent relative risks on absolute risk with graphs generated from two plausible models of lung cancer hazard in men. The figures given in this paper demonstrate that one can find profound

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differences in absolute risk associated with the same relative risk for different diseases, and that the relationship between age, relative risk and subsequent absolute risk can differ substantially for different illnesses. The reasons for these differences are explained.

The approach used in this paper is similar to one being used by Dr Mitchell H. Gail and colleagues at the National Cancer Institute. These investigators are preparing a detailed evaluation of absolute breast cancer risk among women who participated in the Breast Cancer Detection Demonstration Project.[4] They have also studied the statistical properties of absolute risk estimates from cohort studies.[5]

## CONVERTING RELATIVE RISKS TO ABSOLUTE RISKS

Consider a patient's risk of developing some disease within a given period of time. To take a specific example, suppose that Ms Doe has been told that she has increased risk of developing breast cancer. Ms Doe is presently age $a$ and has not had breast cancer. We wish to determine her risk of developing breast cancer by age $a+s$. Let $\lambda(a, t)$ denote her breast cancer hazard at age $t$, let $\lambda_0(t)$ be the breast cancer hazard for $t$-year-old women from the general population, and let $\mu_0(t)$ be the mortal hazard for a $t$-year-old woman from the general population for all causes other than breast cancer. Note that $\lambda_0(t)$ is the hazard of a $t$-year-old woman randomly selected from the general population, while $\lambda(a, t)$ is the specific hazard of Ms Doe. $\lambda(a, t)$ will be affected both by known covariables such as her age at first pregnancy or family history of breast cancer, and by other unknown factors. Let $r(a, t)=\lambda(a, t)/\lambda_0(t)$ denote Ms Doe's relative risk of developing breast cancer at age $t$, and let $p(a, s)$ denote the probability that she develops breast cancer by age $a+s$. Then, we can determine $p(a, s)$ as a function of $a$, $s$, $\lambda_0(t)$, $\mu_0(t)$ and $r(a, t)$ (see Appendix I).

In the graphs given in this paper, $p(a, s)$ is plotted as a function of $a$ for different relative risk functions $r$ and hazard functions $\lambda_0$ and $\mu_0$. Often some entry event occurs at age $a$ which identifies the patient as having increased risk. For example, she may present with a benign but proliferative breast lesion. In this case the patient's relative risk may vary as a function of the time since the entry event in addition to the patient's age. For this reason, $r$ is a function of both entry age $a$ as well as current age $t$. The probability $p(a, s)$ increases with increasing relative risk $r$ and baseline hazard $\lambda_0$ but decreases as the competing hazard $\mu_0$ increases. This reflects the fact that patients may not survive long enough to develop a given disease when there is sufficiently strong competing mortality from other causes. Lifetime risks are estimated by $p(a, 105-a)$. These estimates are reasonable since only a trivial proportion of women live beyond age 105.

I calculated the relative risks given in the figures in this paper with respect to women or men from the general population. In the literature, however, the calculation of relative risks is usually with respect to people who lack the risk factor of interest. If the prevalence of the risk factor is high, then people who lack the risk factor may have substantially lower risk than members of the general population. For example, the risk of lung cancer in the general population is substantially greater than that of non-smokers since a large proportion of the general population smoke. Before using the graphs in this paper for such common risk factors, one must convert risks relative to unexposed people to risks relative to the general population. Let $R$ denote the morbid risk for exposed people relative to unexposed people, let $R_0$ denote the morbid risk for unexposed people relative to the general population, and let $p$ denote the prevalence of the risk factor. Then we can easily show (see Appendix II) that

$$R_0=1/[1+p(R-1)]. \tag{1}$$

If $R^*$ is the risk associated with a given level of exposure relative to unexposed people and $R_1^*$ is the corresponding risk relative to the general population, then $R_1^*=R^*R_0$.

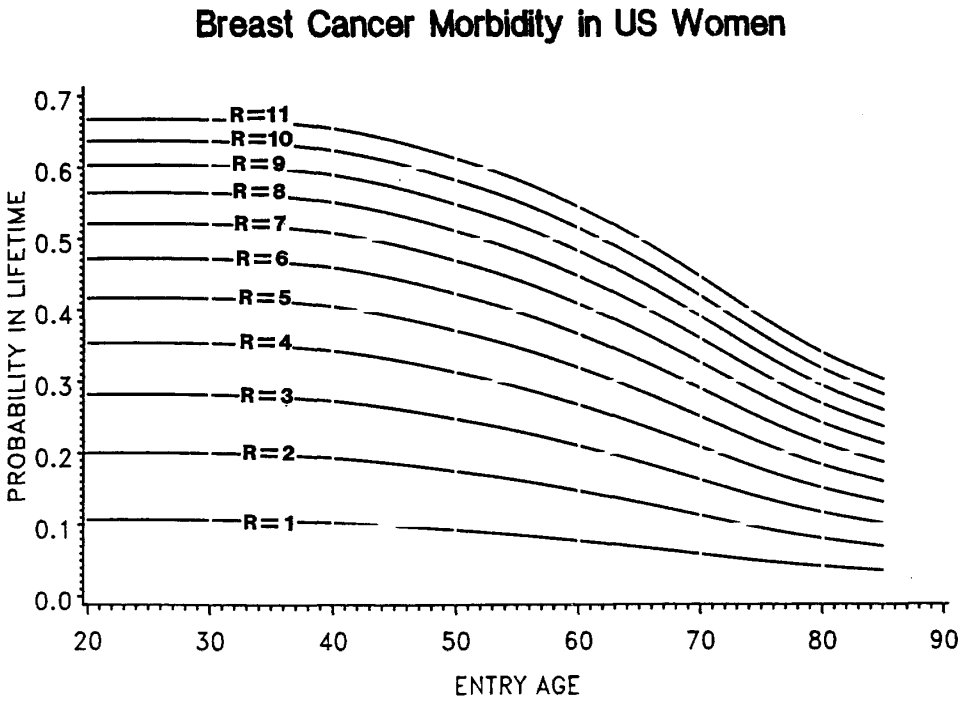


Figure 1. Lifetime risk of developing breast cancer (ICD-9 code 174). The abscissa denotes the patient's age when she is first known to have increased risk of developing breast cancer; she has not developed breast cancer prior to this age. The ordinate gives her lifetime probability of developing breast cancer after her entry age. The lines labelled $R = 1, 2, \ldots, 11$ denote her relative risk of breast cancer at her entry age. These curves were derived under the proportional hazards assumption and use morbidity and mortality data from the SEER and NCHS databases for American women in 1983

In the graphs given in this paper, I derived $\lambda_0(t)$ and $\mu_0(t)$ from age specific morbidity and mortality rates obtained for American men and women from the Surveillance Epidemiology End Results (SEER) and National Center for Health Statistics (NCHS) databases. Details on the computational methods appear in Appendix III.

## BREAST CANCER

Figure 1 shows the lifetime probability of developing breast cancer given the patient's relative risk $r(a, t) = R$ and the age at which the patient is first identified as being at increased cancer risk (entry age $a$). For example, a woman first identified at age 52 as having an eightfold increase in breast cancer risk will have a 50 per cent chance of developing breast cancer in the remainder of her lifetime. This lifetime probability is conditioned on the fact that she has survived to age 52 without developing breast cancer.

A feature of Figure 1, which is perhaps surprising, is that lifetime risk decreases with increasing entry age. To understand this relationship we must look at the age specific morbidity rates for breast cancer, and mortality rates for all causes except breast cancer. Figure 2 shows that breast cancer morbidity rises rapidly with increasing age. This increase, however, is small in comparison to the increase in mortality from all causes (Figure 3). Thus, an 80-year-old woman is less likely to develop breast cancer than a comparable 40-year-old woman because the 80-year-old is unlikely to survive long enough to develop this disease. That is, for the older woman, in comparison with a younger woman who has the same relative risk, the decrease in future life expectancy more than compensates for the increased cancer hazard.

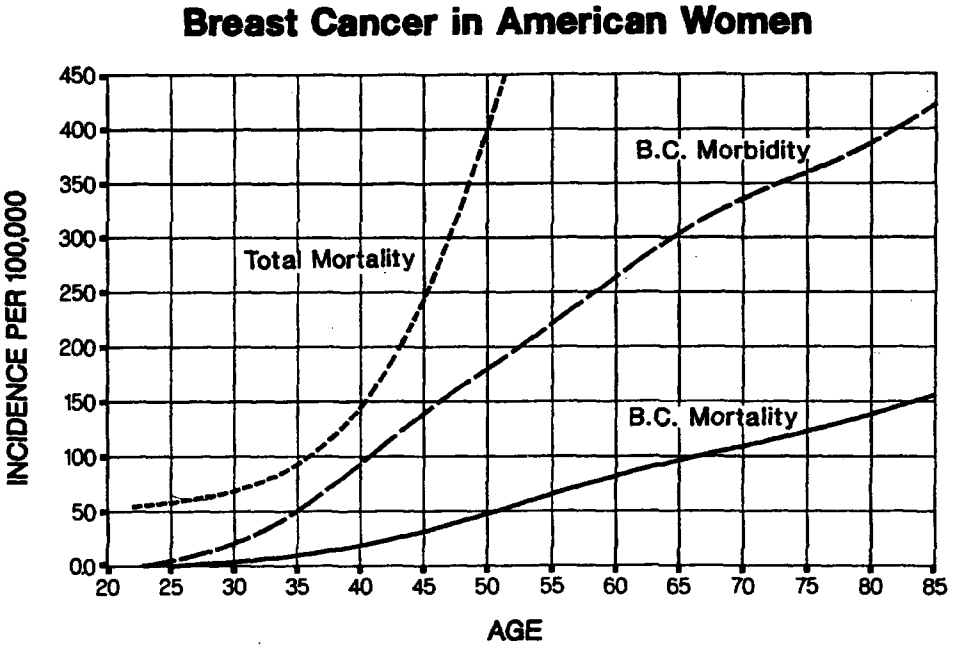


Figure 2. Age specific mortality from all causes and from breast cancer, and age specific breast cancer morbidity in American women in 1983. The morbidity and mortality data are obtained from the SEER and NCHS databases respectively

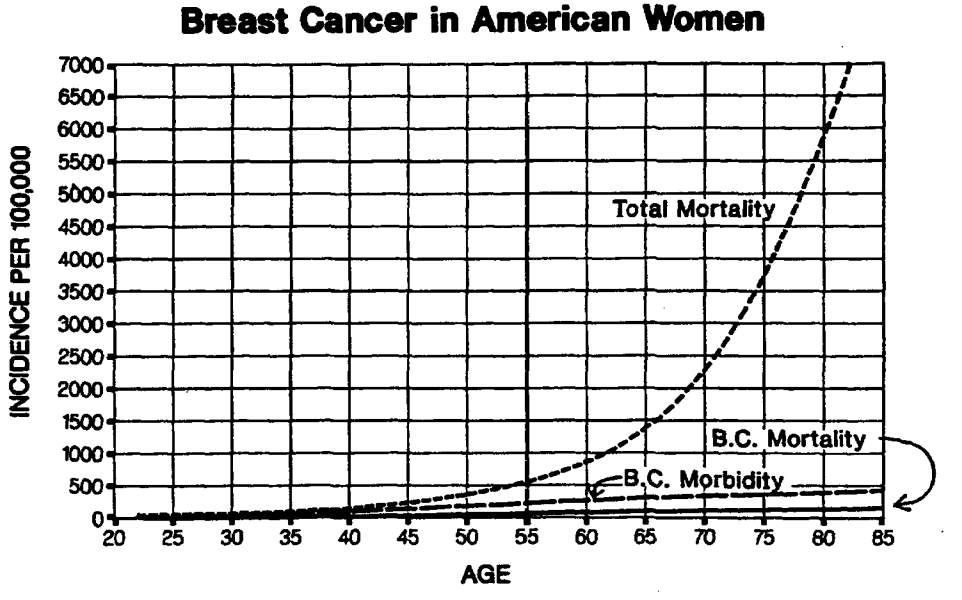


Figure 3. This is Figure 2 redrawn on a different scale. Note that breast cancer morbidity is small in comparison to total mortality for older women. The large competing mortality from other causes explains the drop in absolute breast cancer risk for older women observed in Figures 1 and 4

Figure 1 shows that 20-year-old women from the general population ($R = 1$) have an 11 per cent lifetime risk of developing breast cancer. This agrees reasonably closely with estimates reported by others.[6]

Figure 1 was derived under the proportional hazards assumption of constant relative risk from entry age until the age at which the woman either develops breast cancer or dies of other causes.

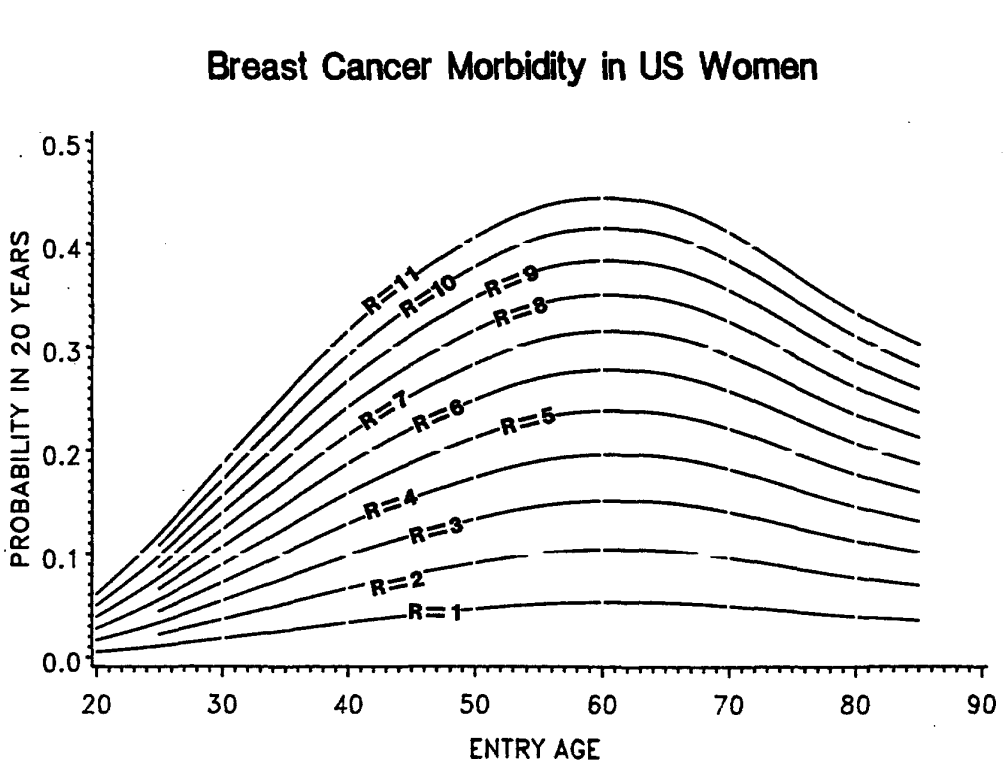


Figure 4. The ordinate of this graph gives the risk of developing breast cancer within 20 years of entry age. See Figure 1 for further explanations

A less stringent, and hence possibly more reasonable, assumption is that the relative risk remains constant for, say, 20 years after entry age. This permits the construction of graphs such as Figure 4, which shows, for given relative risk, the probability that a woman develops breast cancer within 20 years of her entry age. For example, a 47-year-old woman with an eightfold increase in breast cancer risk has a 30 per cent chance of developing this disease by age 67. It is interesting to note that the absolute risk curves in Figure 4 reach a maximum at an entry age near 60. Prior to this age the 20 year cancer risk rises in response to the increasing age specific cancer incidence. Thereafter, the competing mortality causes the 20 year risk to decline. Note also that Figures 1 and 4 agree closely for entry ages greater than 75. This is because few women survive past their 95th birthday.

## CARDIOVASCULAR DISEASE

Figure 5 gives 20 year absolute risk for cardiovascular mortality in American men (ICD-9 codes 390–448). The contrast in the shape of the curves in Figures 4 and 5 is remarkable. The latter curves increase continuously with increasing entry age and approach one for large relative risks. An explanation of the differences between Figures 4 and 5 is given by the age specific mortality rates for cardiovascular and all causes of death in Figure 6. Note that cardiovascular mortality represents a major fraction of total mortality for all ages. For this reason, competing mortality from other causes never overcomes the increases in cardiovascular mortality that are associated with increasing age.

## LUNG CANCER

Figures 1, 4, and 5 were derived under the proportional hazards assumption which appears reasonable when information on time dependent relative risks is unavailable. Doll[7] has provided

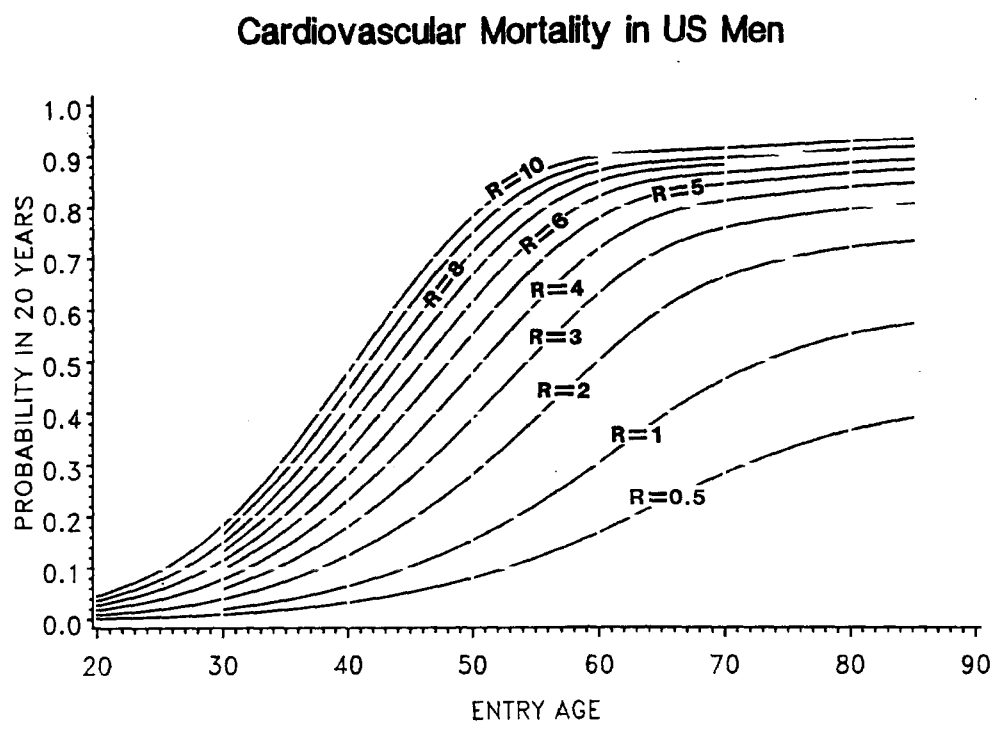


Figure 5. Twenty year risk of cardiovascular death in American men (ICD-9 codes 390–448). These curves were derived under the proportional hazards assumption and use mortality data from the NCHS database for American men in 1983

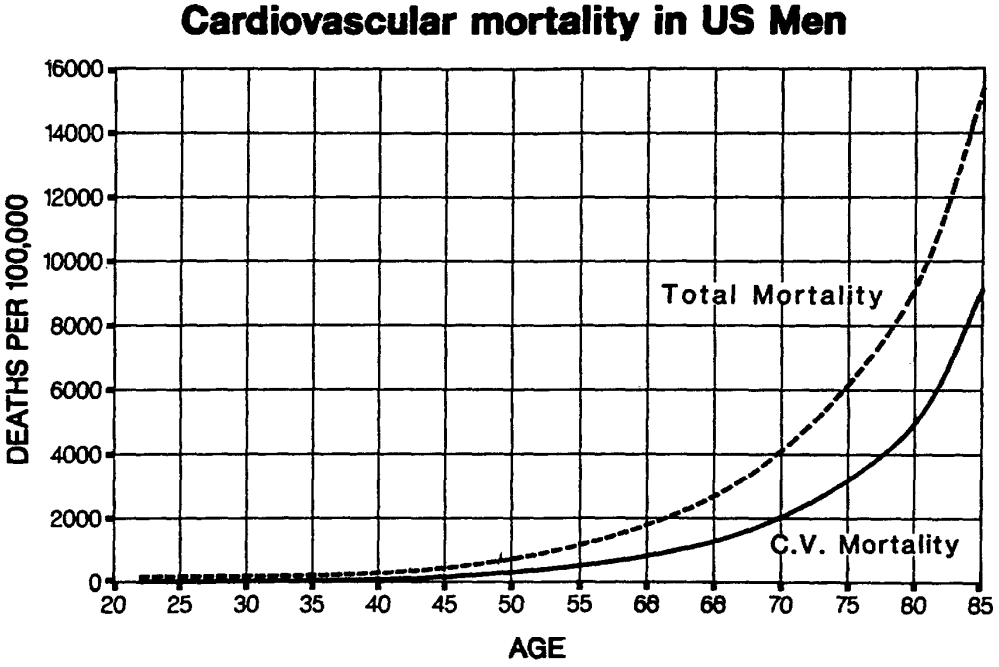


Figure 6. Age specific mortality from all causes and from cardiovascular disease in American men in 1983 (NCHS database). The increase in absolute risk associated with increasing entry age in Figure 5 results from the increasing cardiovascular mortality which constitutes a major fraction of total mortality for all age groups

evidence that the relative risk of lung cancer among smokers varies with age and duration of smoking. Specifically, he obtained an excellent fit to a model in which lung cancer incidence among smokers and non-smokers increased in proportion to $t^k$, where $t$ is age and $k$ is a constant. He found that $k$ was approximately 7·5 and 4 for smokers and non-smokers, respectively.

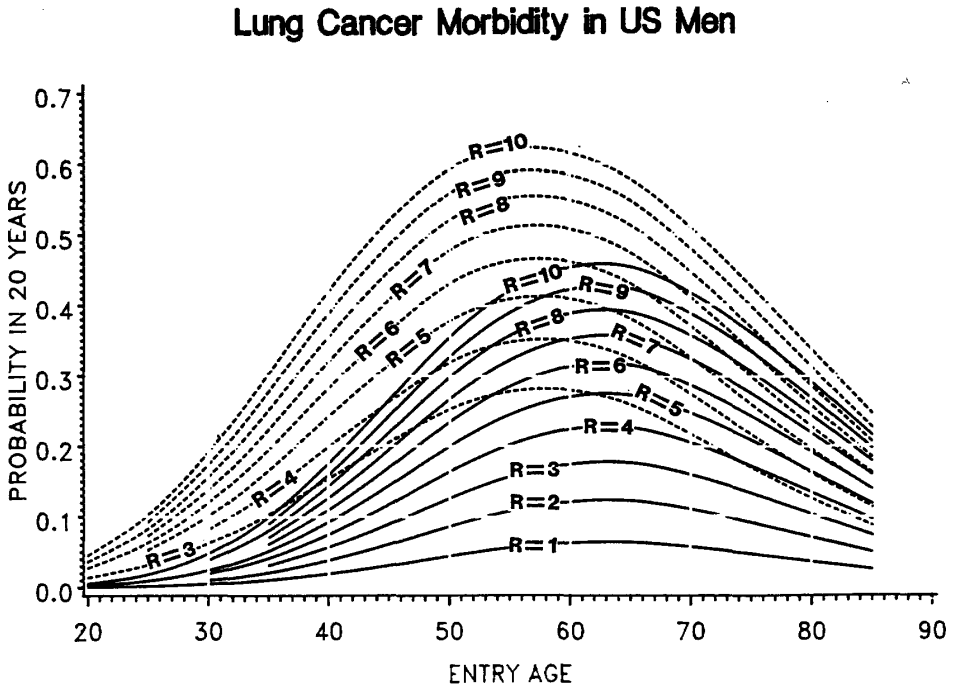


Figure 7. Twenty year risk of developing cancer of the lung or bronchus in American men (ICD-9 codes 162.2–162.9). These curves use morbidity and mortality data from the SEER and NCHS databases for American men in 1983. The solid curves were derived under the proportional hazards assumption. The dashed curves were derived under the assumption that the relative risk of lung cancer increases in proportion to the patient's age raised to the 3·5th power (see text)

This suggests that a reasonable lung cancer relative risk function for smokers has the form $r(a, t)=(b_1 t^{7\cdot5})/(b_2 t^4)=R(t/a)^{3\cdot5}$, where $a$ is the smoker's current age, $t$ is age at some time in the future, and $R$ is the relative risk at age $a$ given the smoking history. (We assume the smoker has not developed lung cancer by age $a$ and that smoking history remains unchanged.) Figure 7 gives 20 year absolute lung cancer risk figures for men using this relative risk function (dashed curves) as well as for a constant relative risk function (solid curves). This figure demonstrates that different relative risk models can have a profound effect on absolute risk. Note that the curves generated by the time dependent and constant hazard functions in Figure 7 agree reasonably closely for older men but diverge substantially at younger ages. This reflects the fact that older people have a short remaining life expectancy and that their relative risk does not increase substantially before their death.

## EXAMPLES

Table I provides published relative risks for breast cancer, heart disease, and lung cancer for use in conjunction with the graphs provided in this paper.[8–12] For example, we found[8] that the relative risk of breast cancer associated with atypical hyperplasia was 4·4 times that of the general population. Interpolation between $R=4$ and $R=5$ in Figure 4 provides the estimate that a 49-year-old woman who presents with this lesion will have a 19 per cent chance of developing breast cancer within 20 years. In contrast, a 49-year-old woman with ductal carcinoma *in situ* has a relative risk of invasive breast cancer of 11, which yields an absolute 20 year risk of 40 per cent.

Doyle *et al.*[11] present relative risks of death due to coronary heart disease among male smokers and non-smokers. In this study, the relative risks for deaths from all causes were similar to those

Table I. Some relative risks for breast cancer morbidity, cardiovascular mortality and lung cancer mortality

| Risk factor | Disease | Denominator | Relative risk | Reference no. |
|---|---|---|---|---|
| Proliferative breast disease | Breast cancer morbidity | Women | 1·9 | 8 |
| Atypical hyperplasia | | | 4·4 | 8 |
| Bilateral breast cancer in sister by age 50 | | | 5·5 | 9 |
| Non-comedo. ductal carcinoma *in situ* | | | 11 | 10 |
| Non-smoker | Coronary heart disease mortality | Men | 0·55 | 11 |
| Smoker | | | 1·3 | 11 |
| <20 per day | | | 1·1 | 11 |
| >20 per day | | | 2·0 | 11 |
| Non-smoker | Lung cancer mortality | Non-smoking men | 1·0 | 12 |
| Smoker | | | 9·2 | 12 |
| 1–9 per day | | | 4·6 | 12 |
| 10–19 per day | | | 8.6 | 12 |
| 20–39 per day | | | 15 | 12 |
| >40 per day | | | 19 | 12 |

for coronary heart disease, and allowed us to use the latter as reasonable estimates of the risk of cardiovascular mortality. Thus, men who smoke more than 20 cigarettes a day have a twofold increase in risk of cardiovascular death; from Figure 5 we see that a 60-year-old man who smokes this much will have a 50 per cent chance of dying from cardiovascular disease by age 80.

In the preceding examples on breast cancer and heart disease, the relative risks given in Table I are derived with respect to the general population of women and men respectively. Such relative risks may be applied directly to Figures 4 and 5 respectively without knowledge of the prevalence of the risk factor involved. Many studies, however, report risk relative to individuals who are free of the attribute of interest. For example, Fraumeni and Blot[12] report risks of lung cancer mortality among male smokers relative to non-smokers. Given the short survival time for lung cancer patients, we can use these relative risks for lung cancer morbidity. Before we apply these risks to Figure 7, however, we must convert from risks relative to male non-smokers to risks relative to men from the general population. Let $R$ denote the cancer risk of smokers relative to non-smokers, let $R_0$ denote the cancer risk of non-smokers relative to the general population, and let $p$ denote the proportion of the population who smoke. Bradstock *et al.*[13] found that 31·5 per cent of Americans smoke. Use of equation (1) with $p=0{\cdot}315$ and $R=9{\cdot}2$ from Table I gives $R_0=0{\cdot}28$. Hence, we must multiply the lung cancer relative risks in Table I by $R_0=0{\cdot}28$ to convert the denominator from non-smoking men to men from the general population. For example, men who smoke more than 40 cigarettes per day have a relative risk of 19 compared to male non-smokers, or of 5·3 compared to all men. Thus, Figure 7 indicates that a 60-year-old man who smokes over 40 cigarettes a day has a 20 year risk of developing lung cancer of 28 per cent, under the assumption of a constant relative risk model. Contrast this risk with the 50 per cent risk of cardiovascular death for a 60-year-old man who smokes more than 20 cigarettes a day. Clearly, cardiovascular disease poses a much greater threat to smokers than lung cancer even though the relative risk for lung cancer is much greater than that for cardiovascular disease.

## DISCUSSION

The figures presented in this paper, or similar figures for other diseases, provide useful information for physicians and patients who contemplate prophylactic treatment options or modifying personal habits and lifestyles. One must interpret these figures, however, with caution. Errors in the absolute risk estimates in this paper may result from any of the following:

1. Relative risk estimates from case-control or other studies may be in error, either due to chance or due to any of the biases that threaten epidemiologic studies. For example, some studies[7, 14] suggest that the relative risk of lung cancer for the average smoker is substantially higher than the estimate of 9·2 given by Fraumeni and Blot.[12]
2. Relative risks are derived with respect to a specific group of control patients. The morbid or mortal risk for these control subjects may vary substantially from the general population used in this paper. If the control group differs from the general population primarily through the absence of the risk factor, and if the prevalence of the risk factor in the general population is known, then one can adjust the relative risks by using equation (1).
3. Figures 1, 4, and 5 and the solid curves in Figure 7 are based on the proportional hazards assumption. Failure of this assumption may lead to inaccuracies in the risk estimates, as demonstrated in Figure 7. Of course, specific time dependent hazard models may also be in error. For example, Gaffney and Altshuler[15] present evidence that a two stage clonal growth model may provide a better fit to smoking and lung cancer data than does Doll's simple power model.[7]
4. In this paper I have assumed that the competing mortal hazard from other causes is the same for people at elevated cancer risk as for members of the general population. This may not always be true. For example, smokers have increased risk of both lung cancer and heart disease. Thus, for smokers, the competing mortal risk in the lung cancer figure is an underestimate. This implies that this figure, to some extent, overestimates lung cancer risk for smokers. (Of course, the smoker has little comfort with the knowledge that his risk of developing lung cancer is reduced by his increased risk of death due to heart disease.) One way that this problem may be avoided is to look at mortal risk from all causes.
5. The morbid and mortal incidence rates used in this paper are cross-sectional; that is, they are age specific rates in 1983. Changes in either total mortality or cancer morbidity that occur in the coming years will affect absolute risk estimates.

In spite of the preceding uncertainties, clinical decisions must be made in the light of the best available information. The superior clinical relevance of absolute risks over relative risks make the estimation of the former worthwhile in spite of the difficulties associated with this task. The graphs provided in this paper should facilitate assessment of the clinical relevance of relative risks reported for cardiovascular disease, breast cancer, and lung cancer, and should help to determine the advisability of an individual's change in lifestyle or adoption of various prophylactic treatment options.

## APPENDIX I

Let $F(a, t)$ denote the probability that Ms Doe survives until age $t$ without developing breast cancer. Then we can easily show[2] that

$$F(a, t)=\exp\left\{-\int_a^t [r(a, x)\lambda_0(x)+\mu_0(x)]\,dx\right\}.$$

The probability that she develops breast cancer in a small interval $(t, t+\Delta t)$ equals the probability of her disease free survival until age $t$ times her conditional probability of developing breast cancer by age $t+\Delta t$ given that she was free of cancer at age $t$. This probability approximately equals $F(a,t)r(a,t)\lambda_0(t)\Delta t$. Letting $\Delta t$ approach zero and integrating between $a$ and $a+s$ gives

$$p(a,s)=\int_a^{a+s} F(a,t)r(a,t)\,\lambda_0(t)\mathrm{d}t.$$

Note that $p(a,s)$ is conditioned on the fact that Ms Doe has not developed breast cancer by age $a$.

## APPENDIX II

To derive equation (1), let $D$ denote the event that a person develops cancer, let $F$ and $\tilde{F}$ denote the events that he was or was not exposed to the risk factor of interest respectively, and let $R_1$ denote the cancer risk among exposed people relative to the general population. Then

$$Pr[D]=Pr[F]Pr[D|F]+Pr[\tilde{F}]Pr[D|\tilde{F}]. \tag{2}$$

Now

$$p=Pr[F],$$

$$R_1=Pr[D|F]/Pr[D], \quad R_0=Pr[D|\tilde{F}]/Pr[D]$$

and

$$R=Pr[D|F]/Pr[D|\tilde{F}]=R_1/R_0.$$

Hence dividing equation (2) by $Pr[D]R_0$ gives $1/R_0=pR+(1-p)$. Inverting both sides of this expression gives equation (1).

## APPENDIX III

The values of $\lambda_0(t)$ and $\mu_0(t)$ used in this paper are derived from unpublished incidence rates in 1983 from the SEER and NCHS databases. These databases provide age specific incidence rates in 5 year intervals. Estimation of rates for ages between the centres of these intervals was by linear interpolation. I estimated the hazard functions $\lambda_0(t)$ and $\mu_0(t)$ by the corresponding incidence rate expressed as an annual rate per patient.

I obtained the cumulative hazard functions from age $a$ to age $t$ by exact integration of the appropriate linear spline functions. I then approximated the probability $p(a,s)$ by means of an adaptive quadrative rule based on Simpson's rule that uses fourth divided differences[16] to determine the points at which the integrand is evaluated.[17] Calculation of these integrals was to an accuracy of three decimals.

The preceding derivations are performed by a program written in FORTRAN-77. This program generates tables of values of $p(a,s)$ for given values of $a$, $s$ and $R$ and functions $r(a,t)\lambda_0(t)$ and $\mu_0(t)$. An SAS program is also available to draw graphs such as Figures 1, 4, 5 and 7 from these tables. These programs are self-documented and are available from the author on request.

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## REFERENCES

1. Breslow, N. E. and Day, N. E. *Statistical Methods in Cancer Research: Volume 1. The Analysis of Case Control Studies*, International Agency for Research on Cancer, Lyon, France, 1980.
2. Kalbfleisch, J. D. and Prentice, R. L. *The Statistical Analysis of Failure Time Data*, Wiley, New York, 1980.
3. Chiang, C. L. *Introduction to Stochastic Processes in Biostatistics*, Wiley, New York, 1968.
4. Baker, L. H. 'Breast cancer detection demonstration project: five year summary report', *CA-A Cancer Journal for Clinicians*, **32**, 194–225 (1982).
5. Benichou, J. and Gail M. H. 'Estimates of absolute cause specific risk in cohort studies', *Biometrics*, in revision.
6. Seidman, H., Mushinski, M. H., Gelb, S. K. and Silverberg, E. 'Probabilities of eventually developing or dying of cancer – United States, 1985', *CA-A Cancer Journal for Clinicians*, **35**, 36–56 (1985).
7. Doll, R. 'The age distribution of cancer: implications for models of carcinogenesis', *Journal of the Royal Statistical Society A*, **132**, 133–166 (1971).
8. Dupont, W. D. and Page, D. L. 'Risk factors for breast cancer in women with proliferative breast disease', *New England Journal of Medicine*, **312**, 146–151 (1985).
9. Ottman, R., Pike, M. C., King, M.-C., Casagrande, J. T. and Henderson, B. E. 'Familial breast cancer in a population-based series', *American Journal of Epidemiology*, **123**, 15–21 (1986).
10. Page, D. L., Dupont, W. D., Rogers, L. W. and Landenberger, M. 'Intraductal carcinoma of the breast: follow-up after biopsy only', *Cancer*, **49**, 751–758 (1982).
11. Doyle, J. T., Dawber, T. R., Kannel, W. B., Kinch, S. H. and Kahn, H. A. 'The relationship of cigarette smoking to coronary heart disease: the second report of the combined experience of the Albany, NY and Framingham, Mass., studies', *Journal of the American Medical Association*, **190**, 108–112 (1964).
12. Fraumeni, J. F. and Blot, W. J. 'Lung and pleura', in Schottenfeld, D. and Fraumeni, J. F. (eds), *Cancer Epidemiology and Prevention*, W. B. Saunders, Philadelphia, 1982, 564–582.
13. Bradstock, M. K., Marks, J. S., Forman, M., Gentry, E. M., Hogelin, G. C. and Trowbridge, F. L. 'Behavioral risk factor surveillance 1981–1983', *MMWR, Center for Disease Control Morbidity and Mortality Weekly Report*, **33**, 155–455 (1984).
14. Pathak, D. R., Samet, J. M., Humble, C. G. and Skipper, B. J. 'Determinants of lung cancer risk in cigarette smokers in New Mexico', *Journal of the National Cancer Institute*, **76**, 597–604 (1986).
15. Gaffney, M. and Altshuler, B. 'Examination of the role of cigarette smoke in lung carcinogenesis using multistage models', *Journal of the National Cancer Institute*, **80**, 925–937 (1988).
16. Ralston, A. *A First Course in Numerical Analysis*, McGraw-Hill, New York, 1965, 72.
17. Dupont, W. D. *An Adaptive Automatic Integration Algorithm Based on Simpson's Rule*, M.Sc. Thesis, Mathematics Dept., McGill University, Montreal, 1971.