Noncancer Deaths in White Adult Cancer Patients

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Background: **The cancer-specific death rate is a commonly used indicator in the assessment of progress against cancer. However, since the cause of death is often not substantiated and complete medical information is lacking, the validity of cancer-specific mortality rates is being questioned.** ***Purpose:*** **We investigated the validity of the cancer-specific death rate by examining noncancer deaths of cancer patients in a large patient population.** ***Methods:*** **Data were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program on cancer patients diagnosed between 1973 and 1987, with follow-up complete through December 1987. The SEER database consists of 1.2 million records from nine population-based registries covering nine geographic regions of the United States. Rates of noncancer deaths in the U.S. population were obtained from the National Center for Health Statistics. Cancer mortality rates were subtracted from overall mortality rates to obtain noncancer death rates by sex and the 5-year age group for each calendar year. Excluded from the study were patients of races other than White and those diagnosed at age 85 years or more due to absence of noncancer death rate comparisons. Also excluded were cancer cases discovered at autopsy and in persons less than 20 years of age. The statistical analysis employed a log-linear model.** ***Results:*** **The ratio of patient-to-general-population noncancer death rates, as calculated by dividing the number of patient noncancer deaths per year by the number found in the matched U.S. population data and referred to as the noncancer relative hazard, is considered significant with values greater than 1 for those with all cancers combined and for the common solid tumors examined. Of the 12 leading causes of death other than cancer in the patient population, the most common causes were circulatory and respiratory failures. The noncancer relative risk of death decreased rapidly after diagnosis and also decreased with the patient's age at diagnosis. It increased slightly with the calendar year of diagnosis.** ***Conclusions:*** **Because more noncancer deaths occurred shortly after diagnosis, it appears that this excess was caused by treatment of the cancer. Generally, cancer-specific death rates underestimate the mortality associated with a diagnosis of cancer. Therefore, because the degree of underestimation changes with time, an examination solely of cancer-caused mortality in assessing progress against the disease is incomplete. [J Natl Cancer Inst 85:979–987, 1993]**

The cancer-specific death rate is commonly used to assess progress in the struggle against this disease; examples of such use have been published (*1-3*), and a discussion appeared in this Journal in 1990 (*4*).

We are skeptical of the value of attributed cause of death in assessing progress because causes and their relative importance are unobservable. Those diagnosed with cancer are in many cases older persons who have multiple medical problems, and death is frequently the culmination of these problems. To ascribe primary causality to any one condition may be an unwarranted oversimplification. Compounding the difficulty of attribution is the fact that many who have been diagnosed with cancer live for a considerable time and may not receive medical scrutiny immediately before they die. Because the cause of death in such cases is not observable, proving the correctness of cancer-specific mortality rates appears impossible. It is feasible to compare the rates of noncancer death in those diagnosed with cancer with those in the overall population. If all excess mortality associated with cancer is recorded as being due to cancer, then noncancer death rates in the patients and in the overall population should be the same, on the assumption that the patient and the general population do not differ. Compared with the overall population, the patient population, however, may have an increased susceptibility to disease in general. This susceptibility may be caused by factors such as unhealthy lifestyles or genetic vulnerabilities. Consequently, a higher death rate from causes other than cancer might be expected in the cancer patient population. However, a generalized lack of resistance to disease would not explain systematic changes in relative noncancer mortality rates with time after the diagnosis of cancer.

In this article, we examine the rates of noncancer deaths in cancer patients; where these rates differ from those of the general population, we examine the effects of sex, age, time since cancer diagnosis, and calendar year of diagnosis on the difference.

Methods

Mortality data were obtained on case patients diagnosed with cancer between 1973 and 1987 from the Surveillance, Epidemiology, and End Results (SEER) Program. Follow-up on these cases was complete through December 1987 (*5*). The SEER Program[1] consists of nine population-based registries covering nine geographic regions of the United States (*6,7*). Rates

*See "Notes" section following "References."

of noncancer deaths in the U.S. population were obtained from the National Center for Health Statistics (*8*) for each calendar year 1973-1987. Patients of races other than White were excluded from the study, as were those diagnosed at age 85 years or more because comparison of noncancer death rates in these groups with that of the United States was not feasible: Because the mix of non-White races in SEER differs from that in the United States as a whole, the overall U.S. non-White mortality experience may not apply when restricted to areas monitored by SEER. Patients diagnosed at age 85 years or more were excluded because official mortality tables (*8*) report the experience of these people at these ages in a single category (85+) even though the death rate increases steeply with age. For the same reason, neither years of life nor deaths at or after age 85 were included in this analysis, even for patients diagnosed before age 85. Death certificate-only cases and cases discovered at autopsy were also eliminated from consideration, as were cancer cases diagnosed in persons less than 20 years of age.

Cancer mortality rates were subtracted from overall mortality rates to obtain noncancer death rates by sex and 5-year age groupings for each calendar year. Frey et al. (*7*) found some differences in both trends and absolute values of cancer mortality rates between the SEER population and the U.S. population as a whole; these differences would imply differential noncancer mortality rates. Obtaining noncancer death rates for the SEER population would be a large undertaking, involving the examination of individual records of abstracted death certificates. Because the magnitude of the differences found by Frey et al. was generally modest, we do not believe that substantial damage to our conclusions results from the use of U.S. mortality data.

The SEER database consists of about 1.2 million records. Data were examined separately for each type of cancer by the patient sex, year of diagnosis (1973 through 1987), and age at diagnosis grouped in the 5-year intervals 20-24, 25-29, . . . 80-84. These groupings were those of the U.S. mortality tables. The number of person-years and the number of noncancer deaths were counted for each year following a diagnosis of cancer within the sex and age categories. The expected number of noncancer deaths was obtained for each category by multiplying the number of patient-years in the category by the U.S. noncancer death rate of the relevant sex and age group for the particular calendar year. The current examination of the data relied heavily on combining these categories in various ways. For example, to examine the influence of age on experience during the 1st year after diagnosis, we combined the data on 1st-year experience at various ages for the several calendar years of diagnosis. When categories were combined, the patient-years, numbers of noncancer deaths, and expected numbers of deaths add to yield the corresponding values for the combination.

We calculated the noncancer mortality rates by dividing the total number of noncancer deaths by the total patient-years. This calculation treated deaths due to cancer as if they were censoring events, i.e., as if the patient were lost to follow-up at that time. For the purpose of knowing the time of death due to causes other than cancer, the patient *was* lost to follow-up then. The examination of mortality rates for noncancer causes by treating cancer deaths as censoring events is intuitively appealing; a technical justification is found in chapter 7 of Kalbfleisch and Prentice (*9*).

The statistical term "hazard" is the probability of death within 1 year for persons alive at the beginning of the year. The noncancer hazard is the probability of dying of something other than cancer in the year for persons at risk at the beginning of the year. The noncancer relative hazard of a patient population is its noncancer hazard divided by the noncancer hazard for the subset of the U.S. population matched by sex, age, and calendar year. In practice, the noncancer relative hazard is calculated by dividing the number of patient noncancer deaths by the number expected in matched U.S. population data.

Statistical modeling was used to determine whether a main-effects model for age, years since diagnosis, and calendar year of diagnosis could adequately summarize the effects of these factors. It could not, indicating that the effect of any one factor changes with the values of the other factors. Statistical methods were also used to examine the reality of evidence for changes in the noncancer relative hazard and to provide a concise summary of the magnitude of such changes.

The statistical analysis employed the log-linear model described in chapter 6 of McCullagh and Nelder (*10*). This model posits that the logarithm of the mean of a Poisson process varies linearly with the covariates considered. In modeling the noncancer relative hazard, the dependent variable is the number of noncancer deaths in the patient population; the model always includes as an independent variable the expected number of noncancer deaths calculated from U.S. figures. The coefficient of the expected number of deaths is forced to be 1 so that the noncancer relative hazard is the logical dependent variable, but a reasonable variability structure of the model is preserved. Factors whose effects are being investigated, e.g., age at diagnosis, also appear as independent variables in the model. The number of person-years and the expected number of noncancer deaths for the SEER population were considered fixed in the modeling. The assumption of Poisson variability in outcome in the modeling is troublesome because it ignores heterogeneity in susceptibility to noncancer causes of death. Patient-to-patient variation could cause the distribution of differences from the mean to be greater than that modeled by the Poisson process. Ignored overdispersion could cause chance effects to appear statistically significant, including a noncancer relative hazard value greater than 1. Consequently, an overdispersion factor that multiplies the variance of the Poisson distribution was assumed using methods described by McCullagh and Nelder (*10*). To estimate overdispersion, we used the linear effect of calendar year of diagnosis on the noncancer relative hazard for three age groups. This estimate was chosen because the change in the noncancer relative hazard with calendar year was small, so there was little danger of lack of fit of a linear model. Lack of fit of a model is not easily distinguished from overdispersion.

Results

Overview

Table 1 shows the outcomes for all the SEER patients. The column "Noncancer relative hazard" shows the ratio of noncancer deaths in the patient population to those expected based on U.S. experience. Deaths from causes other than cancer were not a negligible risk for cancer patients: Noncancer deaths constituted 21% of all deaths, with a range over the types of cancer studied from 10.3% in lung cancer to 44.7% in prostate cancer.

Table 2 shows the 12 leading causes of death other than cancer in the patient population. These 12 causes accounted for about 60% of the deaths. The most common causes were circulatory and respiratory malfunction.

Fig. 1 shows the population hazard rates plotted by age on a logarithmic axis; hazard rates are expressed as the number of deaths per 100000 person-years at risk. The overall hazard, the hazard due to cancer, and the hazard not due to cancer are shown for three calendar years. For both sexes, the overall hazard decreased with calendar year. The risk of death from cancer changed little with calendar year for men. For women under age 40, the cancer risk decreased with calendar year; for women over 60 years of age, the risk increased. Cancer mortality was about 5% of the total mortality for men 20-25 years old; the proportion rose to a

Table 1. Status of the patients in the SEER population

Diagnosis	No. alive	No. died of cancer	No. died of other causes (%)	Noncancer relative hazard
All cancers	442554	369763	100844 (21.4)	1.37
Lung cancer	19778	92514	10651 (10.3)	2.73
Colon cancer	41420	35019	11759 (25.1)	1.09
Prostate cancer	40510	20781	16814 (44.7)	1.14
Breast cancer	94747	31988	12217 (27.6)	1.09

Table 2. Leading noncancer causes of death of SEER patients

Noncancer cause of death	No.	%
Acute myocardial infarction	20015	19.8
Other chronic ischemic heart disease	13857	13.7
Cerebrovascular disease	4942	4.9
Chronic airway obstruction (lung disease)	3932	3.9
Pneumonia	3789	3.8
Cardiovascular disease	3615	3.6
Cardiac arrest	2583	2.6
Congestive heart failure	1590	1.5
Atherosclerosis	1538	1.5
Emphysema	1427	1.4
Diabetes mellitus	1320	1.3
Septicemia	955	0.9
Other causes	41281	40.9

peak of 28% at ages 60-64 and then declined to 17% at ages 80-85. For women, cancer accounted for about 10% of the deaths at ages 20-24; the proportion of cancer deaths peaked at 44% at ages 50-54 and then declined to 14% at ages 80-84. The noncancer hazard paralleled overall mortality in decreasing with calendar year.

Magnitude of Effect of Possible Overattribution of Deaths to Causes Other Than Cancer

For both sexes combined, there were 100844 deaths ascribed to causes other than cancer; the expectation using population rates was 73347. Assuming Poisson variability, the observed rate was thus more than 100 standard deviations above the expectation. The probability of this large an increase over the expectation by chance is small; the P value would have more than 2000 leading zeros. Estimates of overdispersion were obtained by fitting a linear model of the noncancer relative hazard for 11 sex/age/year-since-diagnosis groups to calendar year. The 11 groups were a subset of those formed from two sexes, three age groupings chosen to provide approximately equal numbers of patients, and 1st and 5th years following cancer diagnosis; the youngest men were excluded because the change in the hazard with calendar year was large and nonlinear. The estimates of overdispersion ranged from 0.697 to 2.764, with a mean of 1.79; only two of the estimates were less than 1.0. Even if the overdispersion were assumed to be 4, the number of standard deviations would be divided only by 2 (the square root of 4), and the P value would still contain 500 leading zeros. Such extreme P values must be viewed with some skepticism, but the evidence that cancer patients die of noncancer causes at a higher rate than persons in the general population is overwhelming.

The overall noncancer death rate was 1.37 times that expected from U.S. age- and sex-specific mortality figures (1.42 for men and 1.31 for women). The magnitude of the effect on cancer mortality can be estimated by treating the excess noncancer mortality as due to cancer and recalculating the cancer mortality.

If the 27497 excess noncancer deaths were considered to be due to cancer, then the cancer death count would increase

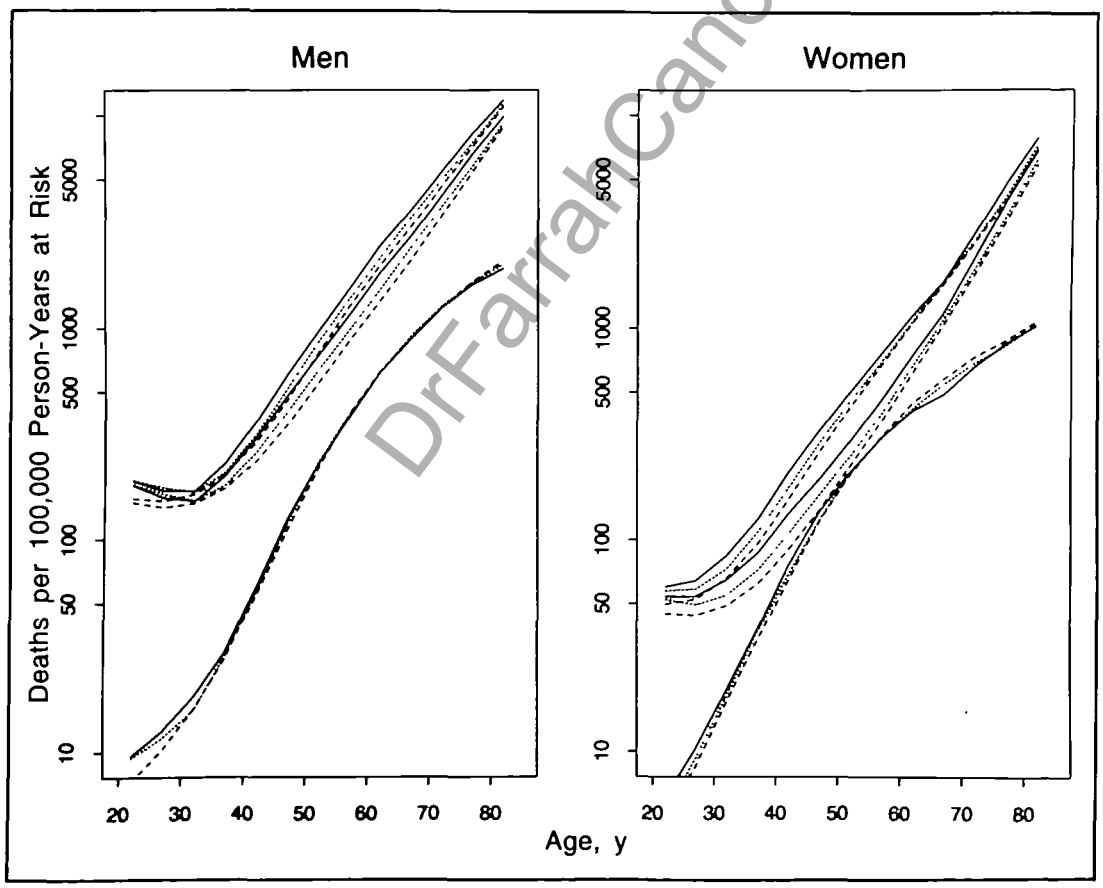

Fig. 1. Population hazard rates expressed as number of deaths per 100000 person-years at risk by age. Top set of three lines is the overall risk of death; bottom set is the risk of death due to cancer. Middle set is the hazard of death from causes other than cancer. This rate is obtained by subtracting the cancer hazard rate from the overall rate. Solid line represents the population experience in 1975, dotted line represents the population experience in 1980, and dashed line represents the population experience in 1985. Note that the ordinate is a logarithmic axis; consequently, a fixed vertical distance represents a constant ratio of rates, not a constant difference.

by 7.4%. The cancer-specific mortality rate would increase by the same proportion, since this measure is the cancer death count divided by the population size.

Another view of the magnitude of the effect of the excess noncancer deaths is provided by Fig. 2, which plots the increase in the probability of a patient's surviving various numbers of years following diagnosis, were the noncancer death rate reduced to that of the overall population. Fig. 2 shows this change for three age groups; the increases in survival ranged from less than 0.01 to almost 0.04.

All Cancers Combined

We investigated the influence on the noncancer relative hazard of age at diagnosis of cancer, calendar year of diagnosis, and the number of years since diagnosis. Initially, we sought to determine whether there was a simple relationship between these factors and the noncancer relative hazard. The predicting variables were divided into three categories each, and a log-linear model was then fit. For age at diagnosis, we used categories of 20-59, 60-69, and 70-84 years for men and categories of 20-54, 55-69, and 70-84 years for women. The division points were chosen to include approximately equal numbers in each group. Calendar year was categorized into equal intervals (i.e., 1973-1977, 1978-1982, and 1983-1987); the number of years since diagnosis was categorized likewise (i.e., 1-5, 6-10, and 11-15 years). These variables were subdivided to enable us to use standard methods for testing the statistical significance of main effects and interactions. The log-linear models showed all to be highly significant; thus, the effect of any one factor changed with the level of the other two. A simple description of the effect of age, calendar year of diagnosis, and number of years since diagnosis on excess noncancer mortality is not possible even with the subdivided data.

The problems of interpretation posed by these interactions are exemplified in a graph (not shown) of the noncancer relative hazard against year of diagnosis, the data being summed over all other factors. There was a sharp upward trend in the noncancer relative hazard in the later calendar years, a totally unexpected result. This anomaly was caused by the decrease in the noncancer relative hazard with time since diagnosis, a result shown below. Cancer patients diagnosed in the later calendar years covered by the data had only a limited follow-up time, so year of diagnosis was confounded with follow-up time. When only the noncancer relative hazard for the 1st year after diagnosis was graphed against calendar year, the increase disappeared.

Fig. 3 is a graph of the noncancer hazards by age for patients diagnosed during three different time periods. The hazard increased sharply with age for both men and women. Fig. 4 shows the corresponding noncancer relative hazards, which are the noncancer hazards adjusted for the overall population experience. The noncancer relative hazard declined with age; i.e., the hazard from causes other than cancer became a lower proportion of the population noncancer hazard as the patient aged. Although not shown, the observed excess hazard, i.e., the patient noncancer hazard

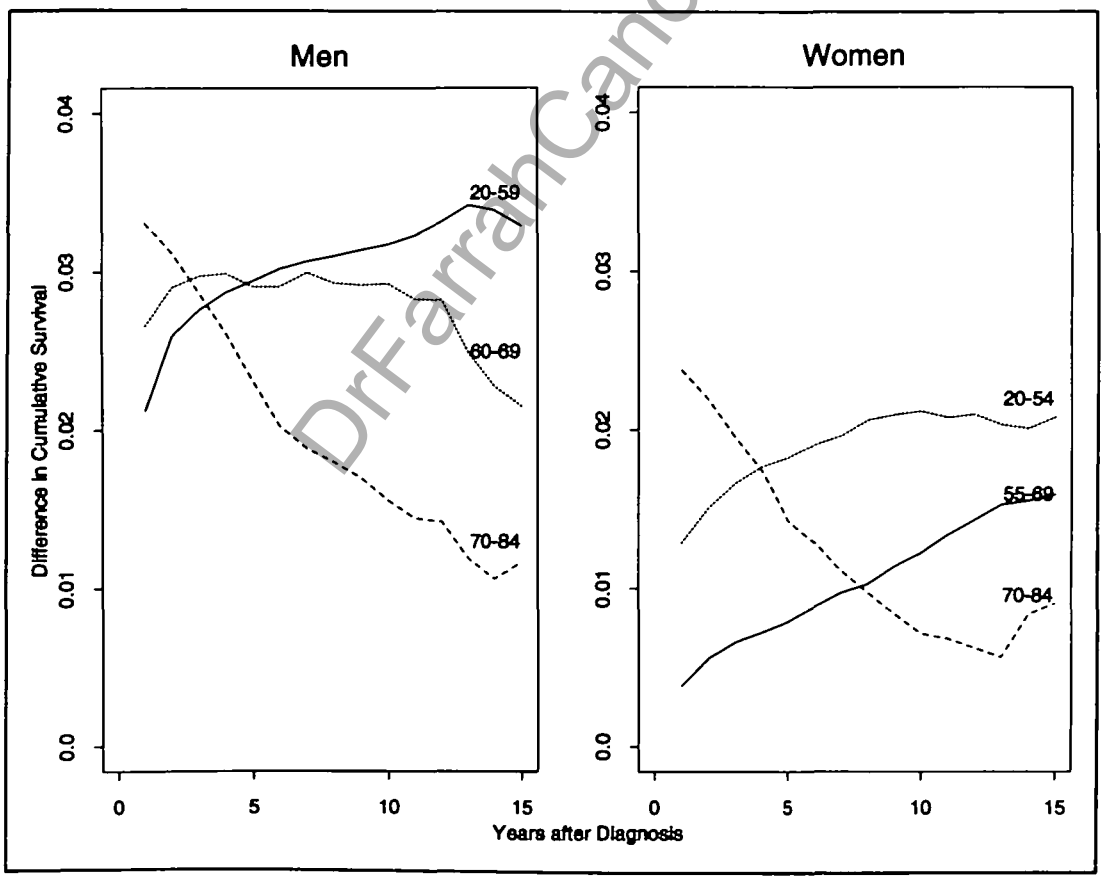

Fig. 2. Difference in cumulative probability of survival at various years following diagnosis, were excess deaths from causes other than cancer eliminated. Three lines in each graph show the experience of different age groups; results for men and women are shown on separate plots.

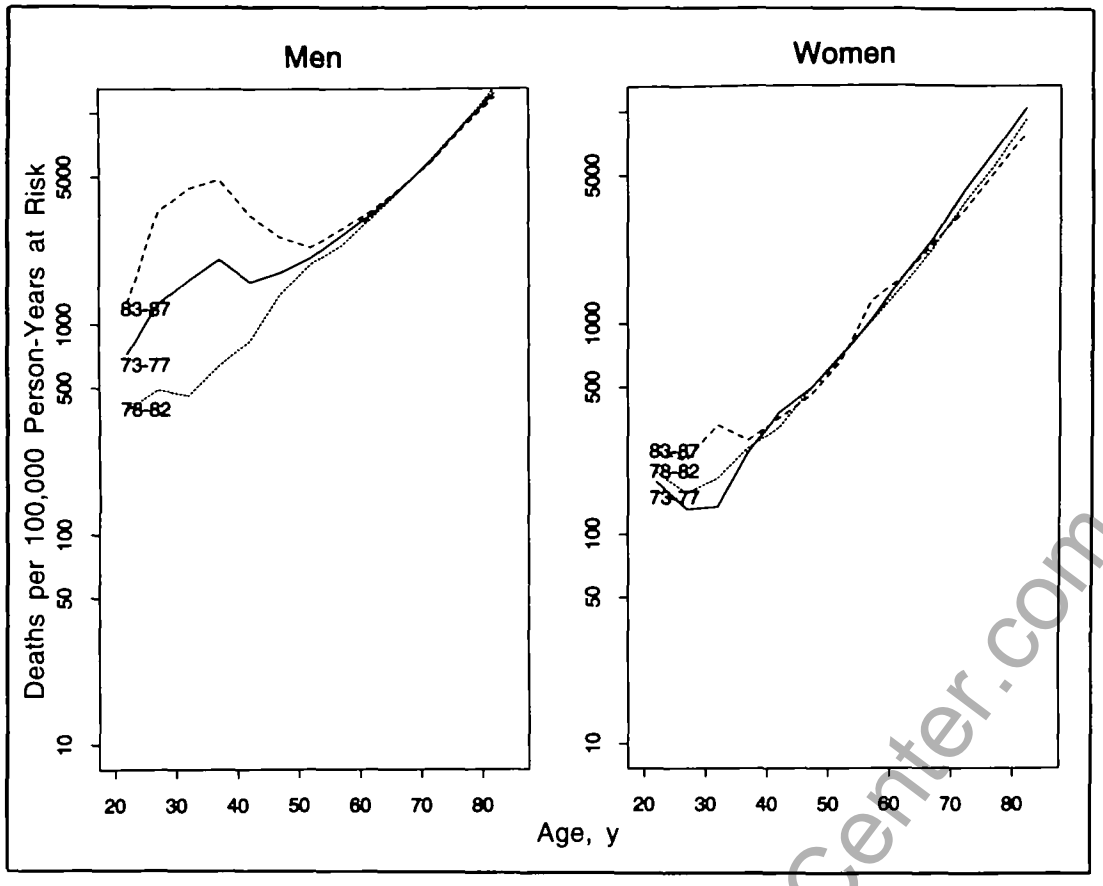

Fig. 3. Noncancer hazard by age for patients diagnosed during three different periods. Scale is the same as that for Fig. 1.

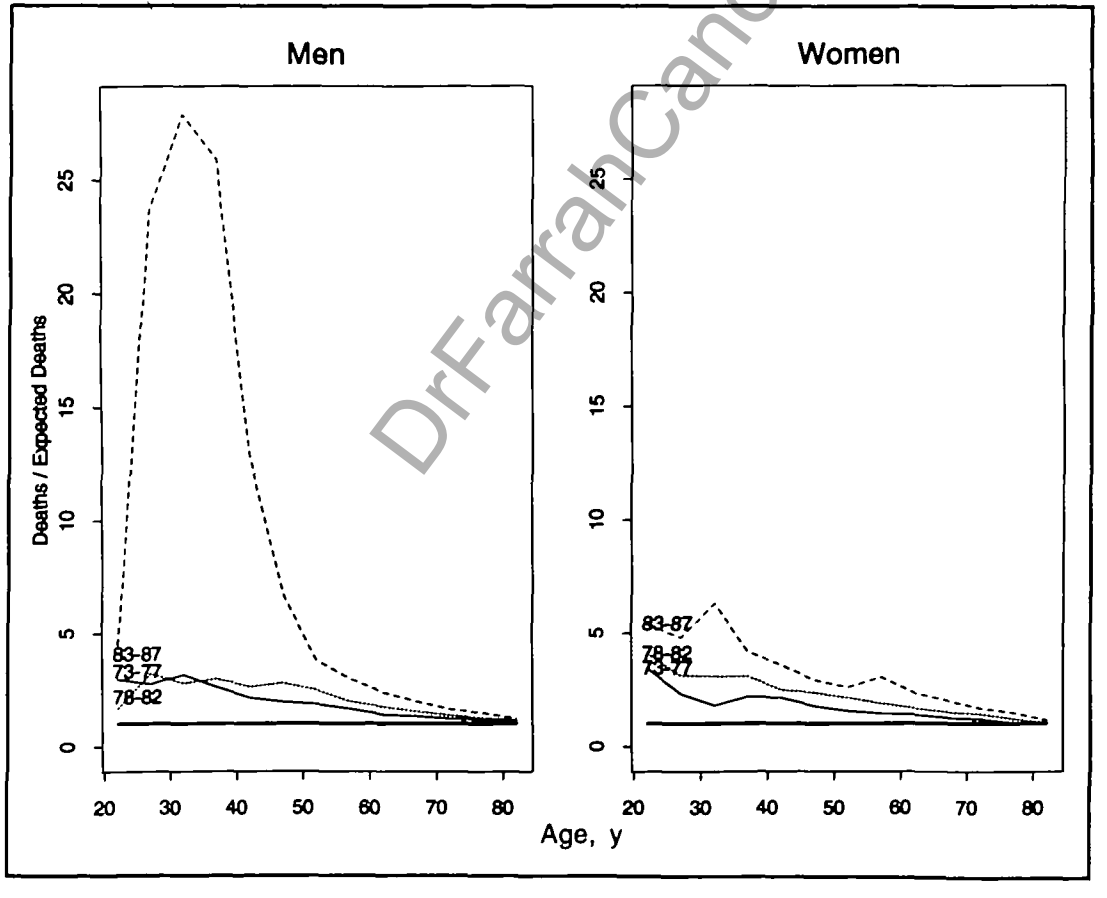

Fig. 4. Noncancer relative hazard by age for patients diagnosed during three different periods. The relative hazard is the hazard from Fig. 3 divided by the population hazard.

minus the population noncancer hazard, increased with age, although not as rapidly as the population noncancer hazard did. The reversal of the effect of calendar year of diagnosis in women over age 65 between Fig. 3, in which hazard increased, and Fig. 4, in which relative hazard decreased, was due to the decrease in the U.S. noncancer mortality in older women.

The noncancer mortality hazard for men 20-59 years old diagnosed in 1983-1987 was clearly much higher than that for men diagnosed earlier. This increase was even more obvious when the data were adjusted for population experience and the relative hazard was displayed. The increase appeared to be due primarily to human immunodeficiency virus (HIV) infections in those diagnosed during those years. The noncancer hazards for men aged 20-59 at diagnosis for the three calendar year groups were 0.017, 0.016, and 0.030 (earliest to latest). An examination of the ninth revision of the International Classification of Diseases[2] (ICD)-coded causes of death in the SEER data showed that code 042 (HIV infection) and code 279 (deficiency of cell-mediated immunity) made up eight cases in 1973-1977, 22 cases in 1978-1982, and 596 cases in 1983-1987. Eliminating patients dying of these causes did not change the noncancer hazard for the first two periods, but the noncancer hazard for 1983-1987 dropped to 0.022. The frequency of ICD code 136 (other unspecified infectious and parasitic diseases) also increased over time: There were 10, 24, and 114 deaths from these causes in the three periods (earliest to latest). If patients dying of these causes were also eliminated from the calculation, the noncancer mortality hazard for the last period would drop to 0.020, a figure not greatly different from the figures for the other two periods. The increase in the hazard due to any other ICD-coded cause of death was at most one-third the amount of these three causes.

Fig. 5 is a graph of the noncancer relative hazard by the number of years following diagnosis. The hazard decreased sharply with increasing time after diagnosis for both men and women. The hazard started lower at advanced ages and decreased less with time. The risk of death from causes other than cancer for patients in the younger age groups has remained well above that for the population at large as long as these patients have been monitored.

Fig. 6 is a graph of the noncancer relative hazard by year of diagnosis. By the consideration of only the experience during particular years after diagnosis, the bias resulting from the confounding of calendar year of diagnosis and follow-up time was almost eliminated. Unfortunately, restricting attention to single years also reduced the sample size and so increased the variability. Visual inspection alone could not be used to determine whether there was a real increase in the relative hazards with year of diagnosis except for the youngest men. To address this issue, log-linear models containing constant, linear, and quadratic terms were successively fit to the data corresponding to each line on the graph. For young men, the quadratic model was clearly superior to the linear model ($P<.0001$), confirming the reality of the increase.

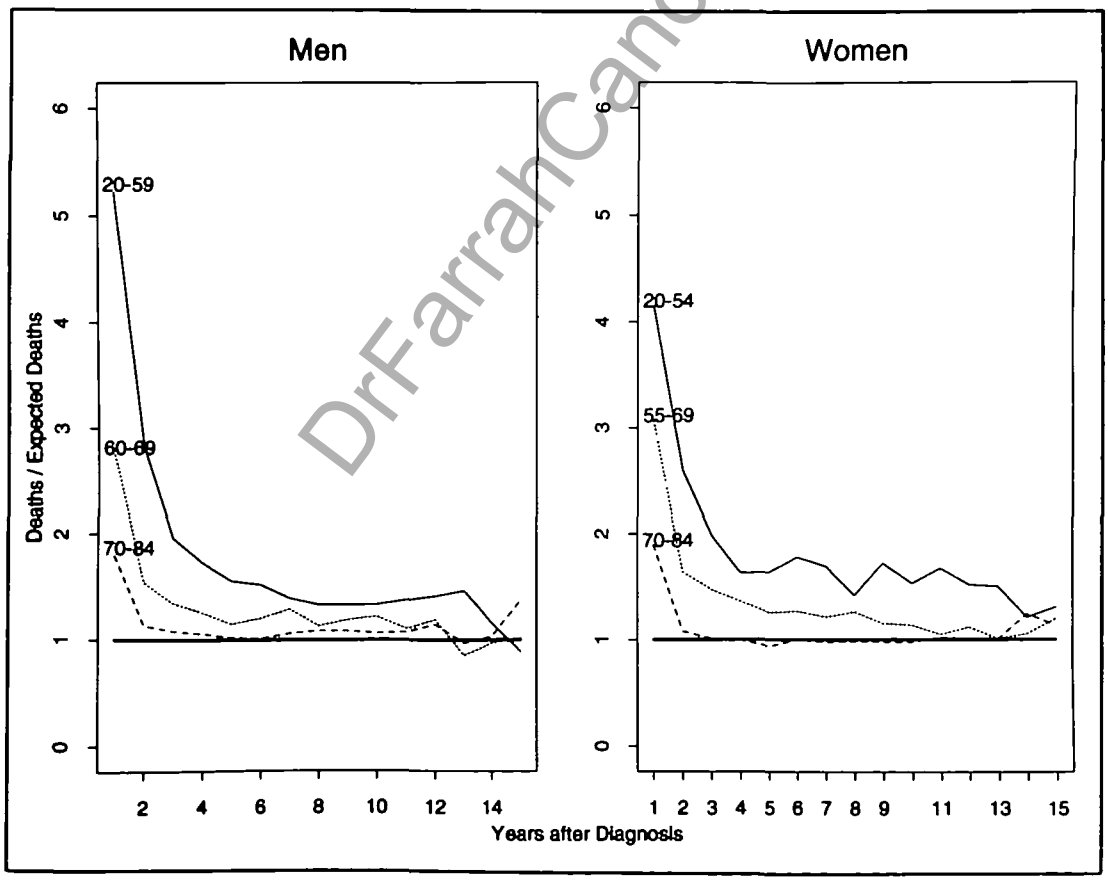

Fig. 5. Noncancer relative hazard by the number of years following diagnosis. Three lines show patients diagnosed at three age groups.

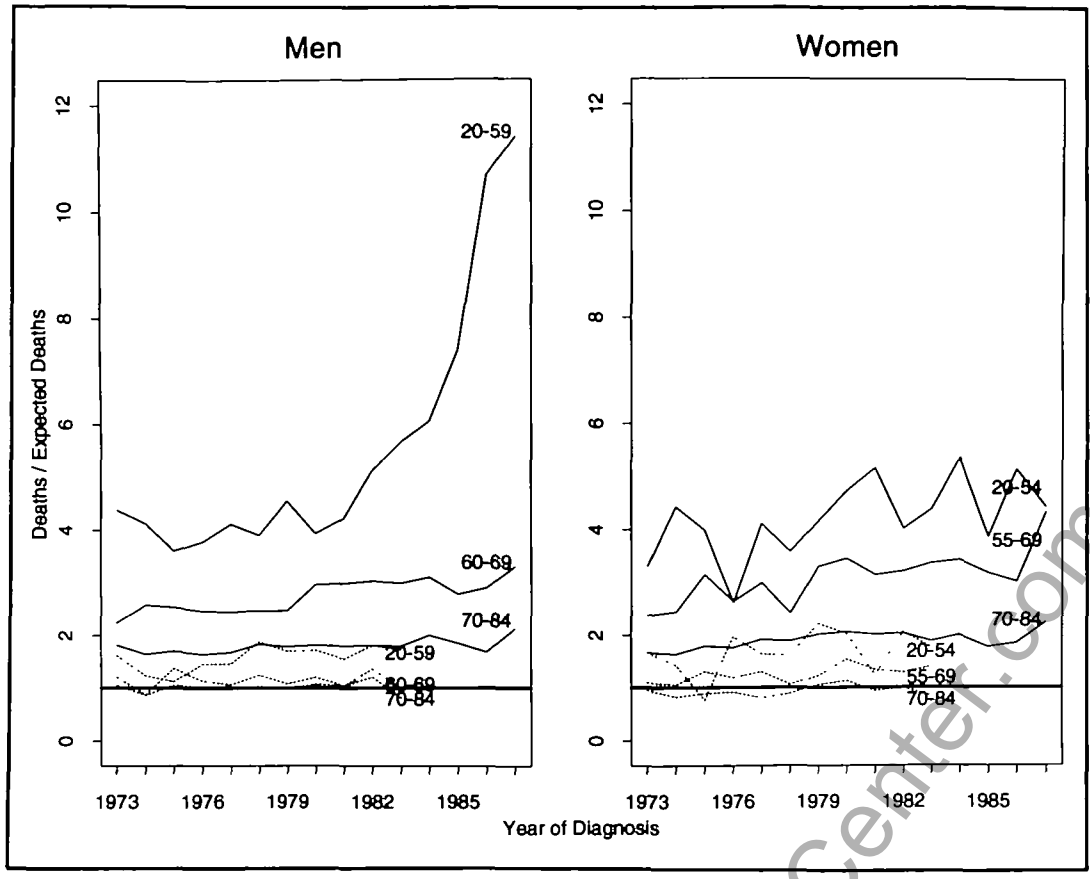

Fig. 6. Noncancer relative hazard by the year of diagnosis. Three solid lines show the relative hazard during the 1st year following diagnosis for different age groups; dashed lines show the relative hazard for the 5th year following diagnosis.

For men 60-69 years old, there was evidence of a linear trend of a 2%-per-year increase in the noncancer relative hazard for the 1st year following diagnosis. The fit relative hazard increased from 2.37 in 1973 to 3.16 in 1987. (Note that the log-linear model implies that increases are *compounded* over time, e.g., $3.16/2.37 \approx 1.02^{15}$.) For men whose cancer was diagnosed after the age of 69, the increase in the 1st-year noncancer relative hazard was small but statistically significant ($P = .02$). The yearly increase was 0.9%, and the fit values increased from 1.68 (1973) to 1.90 (1987). The noncancer relative hazard during the 5th year after diagnosis had evidence of an increase of 3.2% per year in the youngest age group; no such change was evident in the two older age groups.

The women's data showed evidence of an increasing noncancer relative hazard during the 1st year following diagnosis for all three age groups. Among those aged 20-54, the increase was 2.2% per year, with values rising from 3.58 (1973) to 4.93 (1987). For women 55-69 years old at diagnosis, the increase was 2.3% per year, with values rising from 2.59 (1973) to 3.58 (1987). For women over 69, the increase was 0.96%, with values rising from 1.76 (1973) to 2.02 (1987). For the 5th year following diagnosis, there was little evidence of a change in the noncancer relative hazard with calendar year of diagnosis for women in any age group.

For both men and women patients, a statistically significant excess compared with overall population rates of the noncancer hazard was evident in all age groups and for all years after diagnosis, except in the oldest men 5 years after diagnosis.

Lung Cancer

The overall noncancer relative hazard for lung cancer was 2.73. For men, it was 2.61; for women, it was 3.17. Overdispersion from Poisson variation was estimated from the changes in the noncancer relative hazard with year of diagnosis for 12 sex/age/year-since-diagnosis groups. Estimates ranged from 0.76 to 2.69.

The observed hazard rate was 108 standard deviations above the overall population rate. The evidence for excess noncancer hazard in the patients is overwhelming using any reasonable assumptions about overdispersion.

The noncancer relative hazard decreased dramatically with age and with the number of years after diagnosis. For men, it increased significantly with the calendar year of diagnosis. The increase was approximately 3% per year for all age groups for the 1st year after diagnosis, and all increases were highly significant; the largest P value was .0004. For the 5th year following diagnosis, the annual increases were estimated to be 11.4% for patients diagnosed at ages 20-59, 5.9% for those diagnosed at ages 60-69, and 7.9% for those diagnosed at or after the age of 70. The P values for these groups were well below .05, except for the middle age range which had a P value of .29.

Women had less evidence of an increase in the noncancer

relative hazard with calendar year of diagnosis. The estimates of change were smaller for women than for the men, and only women 60-69 years old for the 1st year after diagnosis had a P value less than .05 (i.e., .002), and the estimate of change for women was 2.8% per year.

Colon Cancer

The overall and sex-specific noncancer relative hazards for colon cancer were 1.09. Estimates of overdispersion from Poisson variation in the 12 groups ranged from 0.31 to 1.78.

The observed hazard rate was about 10 standard deviations above that expected from the overall population experience. Even with an assumed overdispersion of 4, the observed rate would have been significantly higher.

The noncancer relative hazard decreased with age and with the number of years after diagnosis. Analyses by year of diagnosis showed little evidence of a change in the noncancer relative hazard; only one of the 12 tests of statistical significance of a linear effect of year had a P value less than .05 (i.e., .016). The next smallest P value was .19.

Prostate Cancer

The noncancer relative hazard for men with prostate cancer was 1.14. The estimates of overdispersion ranged from 0.78 to 2.08. The observed hazard rate was 17.1 standard deviations above the expectation assuming Poisson variability. The probability of this great an excess occurring by chance is very small.

The only appreciable change in the noncancer relative hazard with year of diagnosis was a decrease of 1.6% per year for patients diagnosed at or over 70 years of age (P = .0001).

Female Breast Cancer

The overall noncancer relative hazard for women with breast cancer was 1.09. The estimates of overdispersion ranged from 0.49 to 1.36. The observed hazard rate was 9.6 standard deviations above the expectation assuming Poisson variability. The probability of this great an excess occurring by chance is very small.

There was no evidence of a systematic change in the noncancer relative hazard with year of diagnosis for the 1st year after diagnosis for women under age 55. For women aged 55-69, the noncancer relative hazard for the 1st year after diagnosis increased 2.7% per year (P = .001). For women 70 years or older, the noncancer relative hazard increased from about 1.0 in 1973 to about 1.2 in 1980 and then decreased again to near 1.0 in 1987. The quadratic model of change fit the data significantly better than the linear model (P = .0001). For the 5th year following diagnosis, no evidence of a change in the noncancer relative hazard with year was evident.

Discussion

The data from all cancers combined, as well as those from solid tumors, leave no doubt that there was a greater rate of noncancer deaths in cancer patients than in the population at large. Variability in mortality rates greater than that of a Poisson process did not account for this difference between patients and the population at large.

The excess of noncancer deaths in cancer patients occurred shortly after diagnosis, suggesting that a large portion of the excess is attributable to treatment. The excess of noncancer deaths does not imply a misattribution of primary cause of death. For example, assume that a particular treatment, used only for cancer, increased deaths due to an unambiguously identifiable cause. Coding this cause instead of the cancer as primary would not be wrong. However, ignoring deaths from this cause in studying the outcome of treatment of the cancer would be totally unjustified.

Optimal medical treatment of a deadly disease may itself cause deaths. Deaths due to treatment may well increase with treatment severity, while deaths due to disease decrease. The optimal policy for minimizing the overall death rate is to increase treatment intensity until any additional increase causes as many deaths from treatment as it prevents from the disease.

The argument that we make is not that treatment-related deaths are either unexpected or evidence of poor treatment; rather it is that, in the assessment of outcome, deaths due to causes other than cancer cannot be ignored. If this exhortation is followed for all diseases, it becomes very difficult to attribute the cause of death in those people with more than one serious medical problem. A timely example is provided by the recent increase in noncancer deaths among cancer patients infected with HIV. We believe that this indeterminacy of the cause of death is real and cannot be avoided. What can be done is to study those who do or do not have particular combinations of conditions.

The acknowledgment of an excess of noncancer deaths in cancer patients does not immediately suggest improvements for the monitoring of cancer mortality. Those who die of cancer in any year were diagnosed in unknown numbers during previous years. Without knowledge of the proportions of diagnoses at particular times, corrections for excess noncancer mortality cannot be made.

The admission that cause of death is indeterminate might, however, be used to improve cohort studies. Consider randomized trials of screening programs. One expected benefit of screening is the less intense treatment of early disease as compared with that of advanced disease. The decrease in mortality due to conservative treatment might not be detected in an examination of deaths due to cancer, but it would cause an overall increase in time from initial screening to death from any cause. The restriction of attention to deaths in those diagnosed with cancer eliminates the lessening of the probability of showing an effect that would result if all deaths were considered.

Patterns other than a large excess of noncancer deaths shortly after diagnosis were evident in the data. The relative hazard (noncancer death rates in cancer patients divided by

noncancer death rates in the overall population) decreased with increasing age, while the excess hazard (noncancer death rates in cancer patients minus those in the overall population) increased with increasing age. This is so because the excess hazard does not increase with age nearly as rapidly as does the noncancer death rate in the overall population.

Overall, the rate of excess noncancer death increased with the year of diagnosis. The most likely explanation for this observation is the increasing intensity of treatment with time as new regimens are demonstrated to be effective.

For some patterns in the data, we can offer no explanations. One such pattern is the differential effect on survival for the two sexes at differing ages, were the excess noncancer mortality eliminated. Another pattern is the difference by sex in the noncancer relative hazard—it is greater in men than in women overall, but it is greater in women than in men with colon and lung cancers.

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Notes

[1]Ed. note: SEER is operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

[2]U.S. Department of Health and Human Services: International Classification of Diseases, 9th Revision. Clinical Modification, 4th ed., vol. 1. DHHS Publ. No. (PHS)91-1260. Washington, D.C.: DHHS, 1991.

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