Pergamon

J Clin Epidemiol Vol. 47, No. 12, pp. 1451–1461, 1994
Elsevier Science Ltd. Printed in Great Britain

0895-4356(94)E0041-M

A METHOD FOR PARTITIONING CANCER MORTALITY TRENDS BY FACTORS ASSOCIATED WITH DIAGNOSIS: AN APPLICATION TO FEMALE BREAT CANCER

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(Received 7 July 1993; received for publication 25 February 1994)

Abstract—U.S. cancer mortality data derived from information recorded on death certificates are frequently relied upon as an indicator of progress against cancer. A limitation of this measure is the lack of information pertaining to the onset of disease, such as year-of-diagnosis, age-at-diagnosis, stage of disease at diagnosis and histology of lesions. However, population-based cancer registries collect these types of data and allow the calculation of an incidence-file based mortality rate. This incidence-based mortality rate allows a partitioning of mortality by variables associated with the cancer onset. Breast cancer incidence-based mortality measures are created and compared to mortality rates based on death certificates over a comparable time period. Novel mortality measures, such as mortality rates by stage-at-diagnosis, age-at-diagnosis and year-of-diagnosis, are used to illustrate the value of this approach.

Incidence-based mortality Breast cancer mortality rates Stage-at-diagnosis
Age-at-diagnosis Year-of-diagnosis Lead time bias

INTRODUCTION

A number of different measures of the progress against cancer, such as cancer incidence, survival and mortality rates, have been studied. Each has its own limitations [1]. Incidence and survival rates can be affected by biases caused by screening, such as lead time and length biases. Mortality rates may be insensitive to recent changes in early detection or advances in treatment if they are largely composed of deaths due to cancers that were diagnosed prior to the recent activities, so that there has been insufficient time for the reductions to be reflected in the mortality rates. These limitations notwithstanding, mortality data are often viewed as the best measure of progress against cancer [1].

U.S. cancer mortality data are derived from information recorded on death certificates. As a consequence, information pertaining to the onset of disease, such as year-of-diagnosis, age-at-diagnosis, stage of disease at diagnosis and histology of lesions is not generally available from the mortality data. This hampers efforts to detect improvements in cancer mortality that may be linked to recent treatment advances for specific stages of disease or increases in early detection since current mortality rates reflect the previous experiences of many different years-of-diagnosis cohorts. To obtain onset of disease information, incidence data need to be collected. There is also the need for active follow-up of these cases. Typically, population-based cancer registries collect these types of data. For example, the Surveillance, Epidemiology, and End Results (SEER) Program of the National

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Cancer Institute (NCI) collects incidence information on approximately 10% of the cancers occurring in the U.S. [2]. Once a cancer has been reported to the SEER Program, the case is followed to monitor vital status. As a result, it is possible to calculate a cause-specific mortality rate among those persons diagnosed with cancer and reported to the SEER Program. The numerator for the "incidence-file-based mortality rate" consists of the number of breast cancer deaths among those persons with a breast cancer diagnosis reported to the cancer registry. The denominator for this rate is the population at risk at the time of the deaths. This mortality rate can be partitioned by variables associated with the cancer diagnosis.

For this paper, incidence-based (IB) mortality measures for breast cancer are created and compared to mortality rates based on death certificates over a comparable time period. The main purpose of these analyses is to validate the IB mortality rates relative to the death certificate based rates. If these measures can be shown to be comparable (using female breast cancer, in this example), it is hoped that this methodology can be applied to the further study of mortality patterns for other cancer sites. Breast cancer is chosen for study for two major reasons. First, it is an important cancer, being one of the leading causes of deaths in women. The median survival from breast cancer is greater than 10 years so that there are a number of different year-of-diagnosis cohorts contributing to the annual mortality rates. Secondly, there have been recent increases in the use of mammography and improvements in adjuvant therapy that could cause a decrease in mortality. Thus, it is important to attempt to discern improvements in mortality that may be masked in the overall breast cancer mortality rates [3].

Novel mortality measures, such as mortality rates by stage-at-diagnosis, age-at-diagnosis, and year-of-diagnosis, are used to illustrate the utility of this methodology. Stage-specific mortality rates may provide insight as to whether recent increases in early detection activities or improved treatment are beginning to have a beneficial impact on mortality. Early detection (e.g., screening mammography) may affect the stage-at-diagnosis if the cancer is screened-detected at an earlier stage than in the absence of screening. This shift may not imply a benefit from screening if the screen-detected case (with the earlier stage at diagnosis) has the same lifespan as he/she would have in the absence of screening. This "no benefit" stage shift would be reflected in increased mortality for the earlier stages and an equal decrease in mortality for the later stages with no change in overall mortality. However, if the stage shift truly reflects increased benefit, then there should be a mortality decline for later stages without a compensating increase in mortality for the earlier stages. Finally, the strengths and limitations of this method are outlined.

MATERIALS AND METHODS

Since annual breast cancer mortality rates are composed of deaths from prevalent breast cancers diagnosed as many as 15–20 years earlier (median survival from breast cancer can exceed 10 years), many years of follow-up are needed for IB mortality rates to be comparable to mortality rates based on death certificates. The breast cancer data from the Connecticut Tumor Registry (one of the participants in the SEER Program) were selected for these analyses since data are available from 1935. This allows cases diagnosed at least 33 years ago to contribute to the IB mortality measures beginning in 1969.

The incidence-based data in these analyses include all women diagnosed with breast cancer from 1935 to 1988 regardless of whether they were ever diagnosed with another type of cancer. Since the incidence file maintained by the registry is based on cancer cases rather than persons with cancer, an incidence-based mortality file is created based on the cancer subject. The earliest diagnosis of invasive breast cancer for a given individual was selected as the time of diagnosis for the incidence-based mortality data set. This diagnosis is chosen because, on the basis of hospital records, it is often difficult to differentiate between recurrence of a primary and a second primary cancer and it is nearly impossible, in some cases, to determine the primary cancer that caused the death. However, if the only recorded diagnosis for an individual was an *in situ* breast lesion, then this information was included in our incidence-based mortality data set. From the incidence-based file, women who were reported to have died of breast cancer between 1969 and 1988 were selected for inclusion in the final analysis file. The year 1969 was chosen to allow sufficient minimum follow-up and coincided with the advent of the ninth revision of **International Classification of Disease** (ICD) coding schemes. The Connecticut death certificate mortality data

Table 1. Comparison of sources of cases for IB mortality and DC mortality

	Included in CT breast cancer DC mortality rates	Not included in CT breast cancer DC mortality rates
Included in CT breast cancer IB mortality rates	1. Diagnosed and died in CT. 2. Death recorded as due to breast cancer in CT, but registry is unable to find a prior cancer diagnosis, so diagnosis is based only on death certificate.	1. Diagnosed in CT but died while residing in another state (*Out-migration*).
Not Included in CT breast cancer IB mortality rates	1. Not a resident of CT at the time of diagnosis but was a resident of CT at the time of death (*In-migration*). 2. Death recorded as due to breast cancer in CT, but subject is only in cancer registry file because of a different cancer diagnosis (*Unresolved cases*). 3. Breast cancers diagnosed prior to start of registry coverage. (Not a problem since mortality rates restricted to 1969 and later and registry coverage began in 1935).	

DC = death certificate; CT = Connecticut.

(DC mortality) were provided by the National Center for Health Statistics [4]. A comparison of the data sources for breast cancer deaths included in the IB and DC mortality rates appears in Table 1.

Age-adjusted rates were standardized to the 1970 U.S. population by 5-year age groups up to the age of 84 and then an age group of 85 or more [5]. The formula for age-adjusted rates is given in equation (1), where x_{ijk} is the number of breast cancer deaths in age group i for calendar year j and group k (e.g. stage-at-diagnosis), n_{ij} is the population from which the deaths occurred for age group i for calendar year j, and N_i is the standard population for age group i.

$$\mathrm{IB}_{jk} = \frac{\sum_i N_i \frac{x_{ijk}}{n_{ij}}}{\sum_i N_i} \tag{1}$$

$$\mathrm{IB}_{j,\mathrm{Total}} = \frac{\sum_i N_i \frac{\sum_k x_{ijk}}{n_{ij}}}{\sum_i N_i} = \sum_k \mathrm{IB}_{jk} \tag{2}$$

It can be seen that the group-specific IB age-adjusted mortality rates sum to the total IB age-adjusted rate, as given in equation (2). This property is valuable when it is important to determine the contributions of specific groups (e.g. localized cancers) to total mortality.

An exception to this property is when the groupings consist of ages-at-diagnosis. In this case

$$\mathrm{IB}_{jd} = \frac{\sum_{i \geq d} N_i \frac{x_{ij}}{n_{ij}}}{\sum_{i \geq d} N_i} \tag{3}$$

and therefore

$$\mathrm{IB}_{j,\mathrm{Total}} \neq \sum_d \mathrm{IB}_{jd}$$

where d = interval corresponding to age-at-diagnosis.

The number of breast cancer deaths that occurred without a previous diagnosis of breast cancer but with a diagnosis of another type of cancer was also determined from the incidence data. These represent unresolved cases in Table 1.

It is important to consider the potential effect of lead time associated with increased early detection when interpreting incidence-based measures for breast cancer. The age-adjusted incidence rates for invasive breast cancer in Connecticut were increasing by 1% per year between 1940 and 1982 [3]. From 1982 to 1986, however, the incidence rates increased by 4% annually [3]. The more recent increase was almost entirely due to tumors that were localized and under 2 cm in diameter at diagnosis, thereby suggesting that increased early detection

through the use of mammography may have been responsible for driving the incidence rates upward [3]. Sales of dedicated mammography machines grew rapidly in the 1980s and the annual rate of increase in sales for 1982–88 was seven times the rate of increase for 1974–82 [6]. Furthermore, results from several surveys of patients or physicians indicate that mammography usage has increased in recent years [7–12]. Age-specific analyses of incidence rates also show that observed increases in mammography utilization are generally concordant with increases in incidence when differential lead time by age is taken into account [13]. For the analyses in this paper we, therefore, assume that the lead time associated with increased use of mammography became important beginning in 1982 in CT. To examine the effects of lead time bias, assume a subject would be clinically symptomatic with breast cancer in 1984 and then die in 1987. If the subject were screened with mammography in 1982 and the mammogram were positive, then the cancer would be diagnosed in 1982. If mammography had no benefit, the subject would still die of the disease in 1987. The year of diagnosis would have changed from 1984 to 1982, but the year of death is still the same, 1987. Thus, the early detection did not prolong the life of the subject, although survival, the time from diagnosis to death, was increased. The net result of this lead time bias is to change the year of diagnosis of the cancer but not the year of death.

Death certificate mortality rates are independent of lead time bias. To obtain a new IB mortality measure independent of this lead time bias, we cross-classify calendar year IB mortality rates by the year of diagnosis. For the IB mortality measures that reflect the impact of increased early detection, we calculate a new IB mortality measure that is the sum of the IB mortality rates for each year of diagnosis after the beginning of increased screening, i.e. from 1982 forward. This measure is independent of lead time bias because the bias does not affect the year of death (only the years of diagnosis are affected). The measure is the sum of the IB mortality rates for all years of diagnosis influenced by increased early detection.

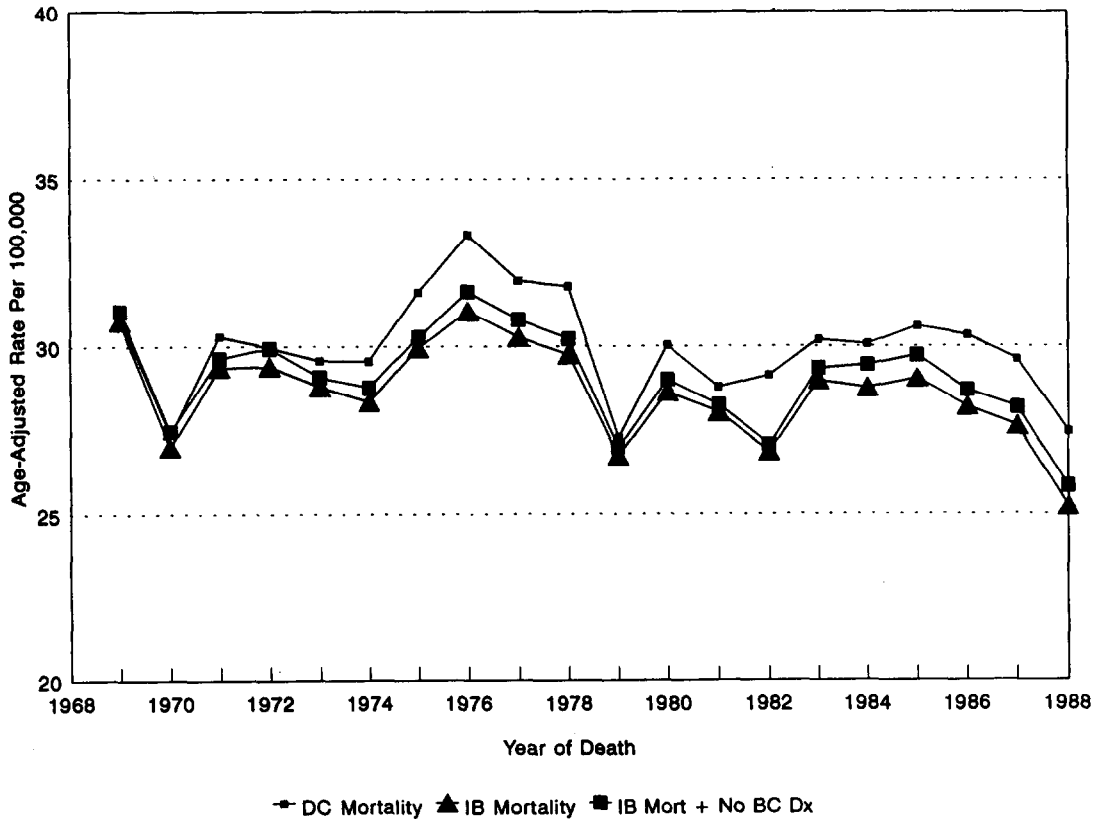

Fig. 1. Comparison of age-adjusted breast cancer mortality rates. Death certificate mortality (DC mortality), incidence-based mortality (IB mortality), and incidence-based mortality (IB mort) and breast cancer deaths with no breast cancer diagnosis (No BC Dx).

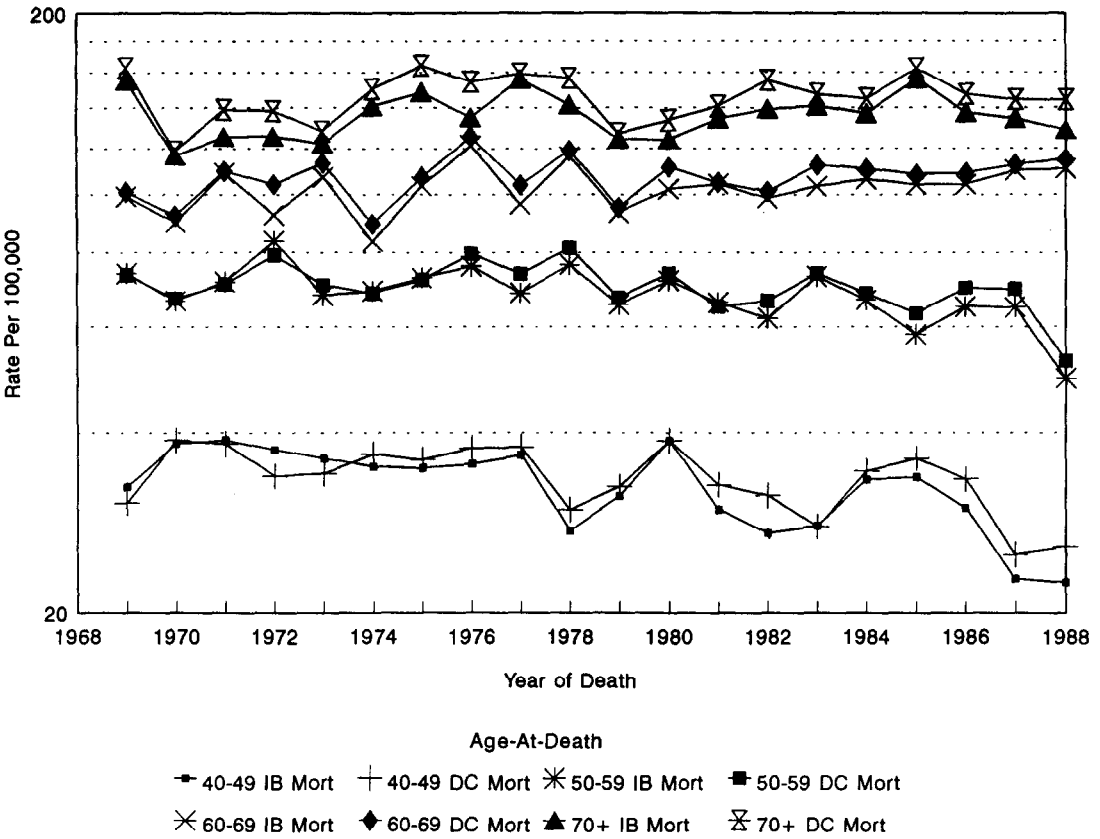

Fig. 2. Comparison of age-specific breast cancer mortality rates. Incidence-based mortality (IB mort) and death certificate mortality (DC mort).

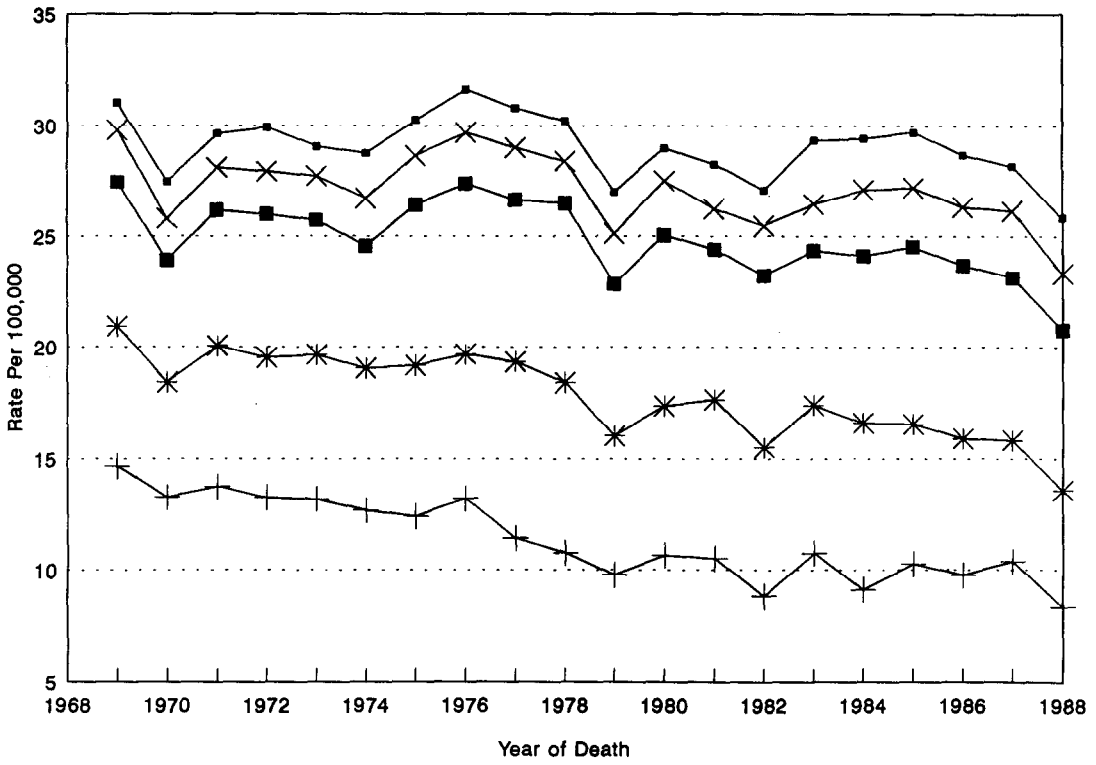

Fig. 3. Incidence-based breast cancer mortality by time since diagnosis. Total incidence-based mortality (IB mortality), cumulative incidence-based mortality (cum IB mort).

RESULTS

To validate the IB mortality rates relative to the DC mortality rates for breast cancer, several comparisons are reported. In Fig. 1 the age-adjusted breast cancer mortality rates based on death certificates (DC mortality), the mortality rates derived from the incidence file (IB mortality), and the combination of IB mortality and mortality rates among those diagnosed with a different type of cancer are displayed. The DC mortality rates generally are the largest, followed by the combination of rates, described above, and then the IB rates. Increases and decreases in the three mortality curves appear to mirror each other over the time period. The greatest percentage difference between the IB mortality rates and DC mortality rates was −8% for 2 years, 1976 and 1988, with an average percentage difference of −4.5%. The greatest percentage difference between the IB mortality rates including those diagnosed with other types of cancers and with mortality rates based on death certificates was −7% in 1982 with an average of difference of −3%.

Figure 2 reports the DC mortality rates and the corresponding IB mortality rates for selected age at death groups (40–49, 50–59, 60–69, 70 +) on a log scale so that similar proportional changes in age-specific curves are equivalent. We found that the IB mortality rates again mirror the rates from death certificates in each age-at-death group. The 40–49, 50–59, 60–69 and 70 + age-at-death groups had average percentage differences of −3.5%, −3.1, −4.2% and −6.6%, respectively. The rates for 40–49 and 50–59 year olds have been declining over recent years while the 60–69 year old rates have increased slightly, and the 70 + year old rates show little change.

To examine the effect of length of follow-up since diagnosis on the IB mortality rates, mortality rates associated with deaths that occurred within 3, 5, 10, and 15 years of diagnosis are displayed in Fig. 3. Deaths from cancers diagnosed within 10–15 years of diagnosis appear to yield rates that are close to the total IB mortality rates (and thus are closest to the death certificate based mortality rates which serve as our standard). In addition, deaths from breast cancers diagnosed within 3–5 years yield curves that have shapes similar to the total mortality and that begin to show a decline prior to the total IB rates. In general, the rates in the 1980s are lower than the rates in the 1970s.

In Table 2, IB mortality rates are stratified by calendar year of death and year of diagnosis in order to remove the influence of a lead time effect. IB mortality rates in the lower right-hand portion of the table are derived only from cases diagnosed from 1982 forward, during the period of increasing breast cancer screening by mammography, whereas IB mortality rates in the upper left-hand portion of the Table are derived from cases diagnosed prior to the rapid rise in screening activities. To compute a new IB mortality measure for deaths in 1988, for example, we sum the IB mortality components in 1988 for diagnosis years 1982–1988. The resulting rate, 17.79 per 100,000, appears at the bottom of the last column of rates shown in Table 3.

Now one needs to compare this new mortality measure to a comparable measure calculated for a time period prior to the presumed influence of increased early detection. We use the data from 1970 to 1981 to calculate comparable cumulative IB mortality measures in the absence of mammography screening. (Data from 1969 were excluded as this was the first year of the 9th revision and the 1969 rates are somewhat out of line with the rates in the 1970s). Table 3 reports cumulative IB mortality rates for 1–7 years since diagnosis for 1970–1981 data and since 1982 for 1982–1988 data. If there is a benefit from mammography screening, the new IB mortality measures after 1981 should be lower than the measures prior to screening. To account for downward trends in mortality prior to the extensive use of mammography, perhaps due to breast cancer awareness, breast self-examination, and extensive use of clinical breast examinations, regression lines were generated for cumulative IB mortality rates by number of years since diagnosis for the time period 1970–1981. The line was then extended to the point of the new mortality measure, after the impact of increased early detection. The 95% confidence intervals for the predicted new point were calculated [14]. These data are reported in Table 3. Although several of the new mortality measures were smaller than predicted values, all fell within 95% confidence intervals. For example, the 7-year IB mortality measure of 17.79 for 1988 is below the trend line (Fig. 4) but lies within the 95% confidence interval.

Figure 5 presents the IB mortality rates by stage-at-diagnosis, representing one of the first presentations of mortality in this way. The stage with greatest contribution to IB mortality

Table 2. IB mortality rates by year of diagnosis (Year DX) and year of death.

	Year of Death																		
	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988
Total rate:	26.99	29.36	29.4	28.79	28.34	29.95	31.05	30.27	29.75	26.7	28.62	28.03	26.83	28.96	28.74	29.02	28.24	27.63	25.22
Year DX																			
1964	1.31																		
1965	2.01	1.68																	
1966	2.71	1.66	1.37																
1967	2.43	1.97	2.51	1.75															
1968	4.48	4.32	2.22	1.9	1.02														
1969	4.92	4.97	4.05	3.55	2.25	2.06													
1970	3.88	5.11	4.41	2.92	3.04	2.36	1.96												
1971	0	3.68	5.83	4.97	3.33	2.14	2.63	1.87											
1972	0	0	3.01	5.76	4.28	4.63	2.74	2.35	1.97										
1973	0	0	0	2.45	4.79	4.2	3.73	3.28	2.64	1.39									
1974	0	0	0	0	3.6	4.91	5.43	4.63	3.75	3.2	1.78								
1975	0	0	0	0	0	3.29	5.03	4.57	3.89	2.9	2.2	1.89							
1976	0	0	0	0	0	0	2.75	4.13	4.3	3.34	2.77	1.95							
1977	0	0	0	0	0	0	0	2.72	3.6	4.08	3.94	2.77							
1978	0	0	0	0	0	0	0	0	2.86	3.98	4.47	4.36							
1979	0	0	0	0	0	0	0	0	0	1.72	4.26	4.03							
1980	0	0	0	0	0	0	0	0	0	0	1.93	3.8							
1981	0	0	0	0	0	0	0	0	0	0	0	2.69							
1982													1.56	3.86	4.02	3.27	2.51	2.49	1.86
1983													0	2.61	2.86	4.84	3.62	2.01	2.35
1984													0	0	2.25	2.93	3.67	3.43	2.18
1985													0	0	0	2.51	3.59	4.35	3.03
1986													0	0	0	0	2.52	3.36	3.45
1987													0	0	0	0	0	2.68	2.92
1988													0	0	0	0	0	0	2.00

Table 3. Cumulative IB mortality rates by number of years since diagnosis of breast cancer and by year of death

	Year of Death												Regression estimates:		Observed
Number of years since DX:	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	⩾ 1982	(95% CI)	⩾ 1982
1	3.88	3.68	3.01	2.45	3.60	3.29	2.75	2.72	2.86	1.72	1.93	2.69	2.00	(0.77,3.22)	1.56
2	8.80	8.79	8.84	8.21	8.39	8.20	7.78	6.85	6.46	5.70	6.19	6.49	5.34	(4.15,6.54)	6.47
3	13.28	13.76	13.25	13.18	12.67	12.40	13.21	11.42	10.76	9.78	10.66	10.52	9.17	(7.43,10.91)	9.13
4	15.71	18.08	17.30	16.10	16.00	17.03	16.94	16.05	14.65	13.12	14.60	14.88	13.32	(10.28,16.36)	13.55
5	18.42	20.05	19.52	19.65	19.04	19.17	19.68	19.33	18.40	16.02	17.37	17.65	16.42	(13.60,19.23)	15.91
6	20.43	21.71	22.03	21.55	21.29	21.53	22.31	21.68	21.04	19.22	19.57	19.60	19.04	(16.26,21.82)	18.32
7	21.74	23.39	23.40	23.30	22.31	23.59	24.27	23.55	23.01	20.61	21.35	21.49	21.02	(17.48,24.57)	17.79

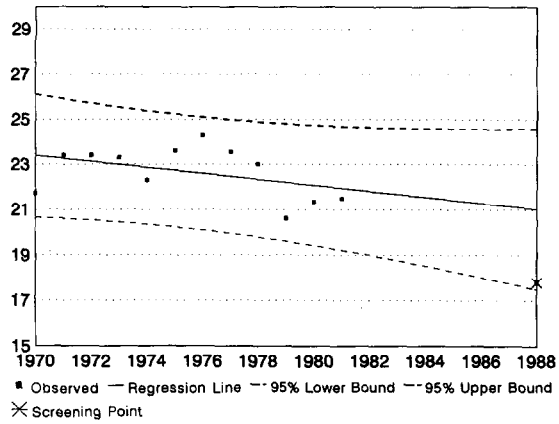

Fig. 4. Regression analysis of incidence-based mortality for 7 years since diagnosis comparing data from 1971–1981 to 1988 data. 95% confidence intervals were reported.

is regional disease with localized and distant disease making similar, smaller contributions to the IB mortality rates. Recent mortality among women diagnosed with regional disease has declined compared to mortality rates in the 1970s. Mortality among women diagnosed with distant disease may also be declining though additional years of data are needed to confirm this trend. In contrast, mortality among localized disease cases has increased in the mid-1970s and then leveled off. The patterns of declining mortality rates for late stage disease correlate with the declines in the overall mortality rates.

Figure 6 reports IB mortality rates by age-at-diagnosis, again the first report of this type of mortality rate. There is a decreasing mortality trend in the 40–49 age-at-diagnosis group. This decreasing trend correlates with the decline in the total IB mortality rates.

DISCUSSION

Differences in DC and IB mortality rates

The major sources of deaths for the death certificate-based and IB mortality rates are outlined in Table 1. Although a vast majority of the deaths are included in both rates, there are some differences. The death certificate-based mortality rates are generally greater than the IB rates although the trends for the two rates mirror one another over time.

A potential problem when comparing an incidence-based mortality file with a state death certificate file is the inclusion, in the incidence-based file, of breast cancer deaths among persons who have moved out of the state

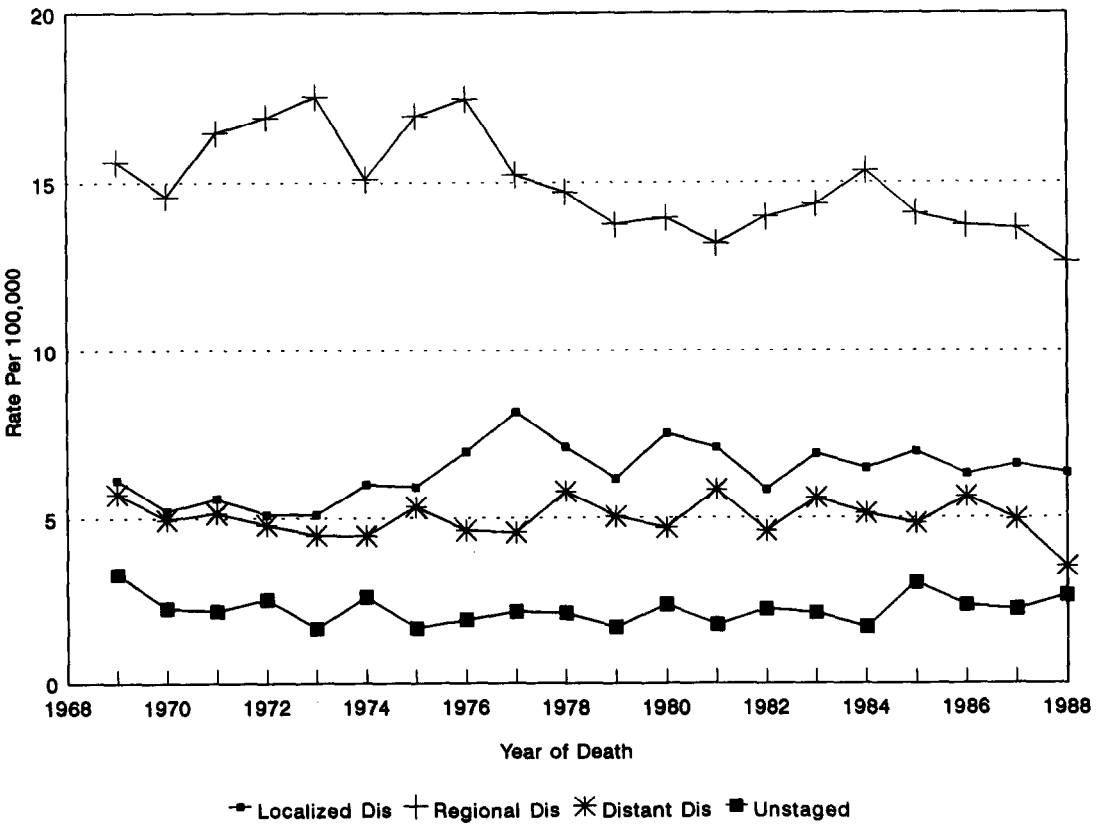

Fig. 5. Incidence-based breast cancer mortality by stage-at-diagnosis. Disease (Dis).

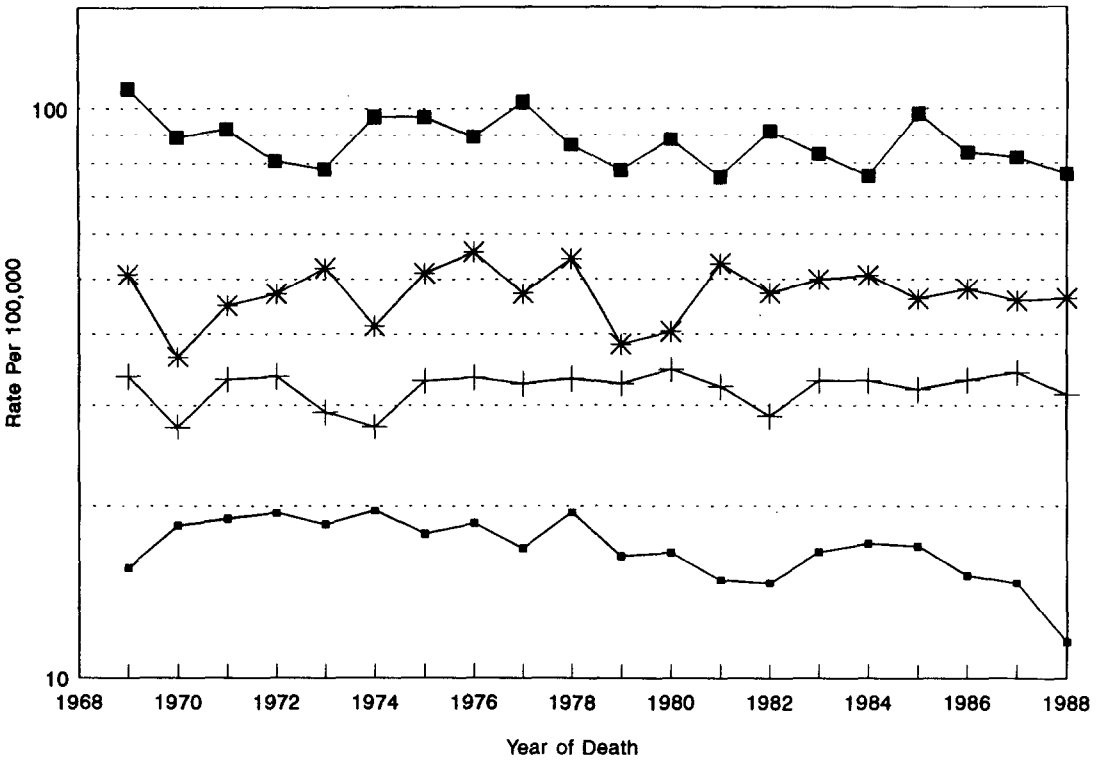

Fig. 6. Incidence-based breast cancer mortality by age-at-diagnosis (Age Dx).

subsequent to their initial breast cancer diagnosis and taken up residence in another state (Table 1, *Out-migration*). Such deaths would not be included in the state death certificate file. The CT registry has reciprocal agreements with the states of FL, NY, NH, MA and RI and regularly obtains death certificates for persons who were diagnosed with cancer in CT and later died in one of these states. Even after obtaining these death certificates, however, a group remains of 8–9% of all known deaths among women diagnosed with breast cancer for whom death certificates are not obtained because they occur in other states. Thus, out-migration, which would tend to inflate IB mortality rates relative to the state mortality rates, is incompletely ascertained while the ascertainment of in-migration (Table 1, *In-migration*) is likely more complete and would tend to increase state mortality rates relative to IB mortality rates. The fact that the state death certificate mortality rates for breast cancer are consistently higher than the IB mortality rates further suggests that in-migration rather than out-migration is having a greater influence on the IB mortality rates. Another potential source for the discrepancy is misclassification of the cause of death (Table 1, *Unresolved cases*). Work by Percy *et al.* [15] shows that the misclassification of microscopically-confirmed breast cancers on death certificates is relatively small; which suggests that in-migration is the more important of these two factors.

Given the above discussion and the extensive follow-up period available from the Connecticut Tumor Registry, with information on cases diagnosed as early as 1935, the likely explanation for the DC rates being greater than the IB rates is in-migration. That is, cancer patients, diagnosed while residing outside of Connecticut, are dying inside the state of Connecticut. As a consequence, the deaths appear in the Connecticut death certificate-based mortality rates but not in the IB mortality rates because the original cancer diagnoses were not reported to the Connecticut Cancer Registry (since these people were not residing in the state of Connecticut at the time of diagnosis). A likely scenario is that a couple raise a family in Connecticut but retire to Florida. One of the couple is diagnosed with cancer in Florida but returns to Connecticut for care by their family and eventually dies in Connecticut.

Administrative errors, such as incorrect linkages for individuals in the incidence and mortality files, are another source of possible discrepancies between IB and DC mortality; however, they are not included in Table 1.

Strengths and limitations of IB mortality rates

There are a number of advantages in using the IB mortality rates. IB mortality rates allow cross-classifying mortality data by variables related to the cancer diagnosis, such as age-at-diagnosis, stage-at-diagnosis, time-since-diagnosis, calendar year of diagnosis, histology, grade, diagnosis procedure, and type of therapy. As indicated earlier, this new type of mortality data is not available from usual mortality sources.

Some limitations of IB mortality rates must be considered. Since the IB mortality rates are composed of deaths among cases diagnosed in previous years, the follow-up of cases diagnosed a number of years in the past may be required. The number of years required is a function of the lethality of the site-specific cancer, the higher the lethality, the fewer the number of years required for an accurate index. It appears that at least 10 years of follow-up are required to obtain measures of the incidence-based breast cancer mortality that mirror the death certificate mortality rates. This suggests that total IB mortality rates might be calculated for the entire nine registry SEER Program, which started in 1973, for the period 1983–88. The number of years required to allow a computational version of the IB mortality measure to be within 10% of the DC mortality are given in Table 4 [16]. Second, IB mortality rates can only be computed when population-based incidence data are available and may not mirror the national mortality trends. Of course, trends in the IB mortality rates can also be compared to the national mortality trends, as when SEER-area mortality rates from death certificates were compared to national mortality rates [17].

Another limitation of IB mortality or any mortality rate partitioned by variables associated with stage-at-diagnosis is the impact of changing technology on the staging of disease. New diagnostic technology, such as CT scanning, enables more sensitive staging of disease. One consequence of this is that mortality for localized disease cases could decrease since new technology can detect advanced disease that in the past would have been classified as early stage disease. In addition, the advanced disease cases detected by new technology may have a better prognosis than cases with frank signs of advanced disease. If the prognosis for the advanced cases is the same, there would be no change in overall mortality but there would be a decrease in mortality for both localized and advanced stage diseases, due to more sensitive reclassification of disease, rather than better treatment. This has been called the Will Rogers phenomenon [18]. Thus, decreases in several stage-specific mortality rates without a decrease in overall mortality may need to be examined more carefully to determine the causes for the changes. In our analysis of female breast cancer, no such pattern is seen.

Table 4. Number of years required for IB cancer mortality data to be within 10% of DC cancer mortality data [16]

Organ	Years
Brain and central nervous system	3
Breast (female)	8
Colon, rectum	5
Kidney	4
Lung (males or females)	3
Melanoma	10
Ovary	5
Prostate	8
Stomach	2
Thyroid	11
Uterus, corpus	6

Effects of screening and lead time on IB mortality rates

In general, mortality rates have been viewed as being independent of screening biases while incidence data are affected by these biases. Thus IB mortality would be expected to be affected by screening biases in some way. Since screening causes an earlier detection of cancers than would have occurred without screening (due to lead time), the screen-detected cases would have an earlier age-at-diagnosis and earlier year-of-diagnosis, even if the screening is not beneficial, i.e. does not increase lifespan. Thus, lead time bias is a potential problem in IB mortality measures.

Since annual breast cancer mortality is composed of deaths from many different year-of-diagnosis cohorts it is difficult to observe mortality reductions due to recent changes in early detection and treatments. It has been suggested that breast cancer mortality be examined among cancers diagnosed in the recent past (say the past 5 years) to evaluate the effects of recent changes [1]. However, this mortality measure

would be affected by lead time bias if lead time is greater or if the time since screening had begun is greater than the fixed number of years being examined. In the special case where incidence is increased due to the introduction of new early detection methodology, as assumed in 1982 with mammography, it is possible to construct IB mortality measures that are independent of lead time associated with the increased early detection. This is accomplished by creating annual cumulative IB mortality measures based on all deaths in cases diagnosed after the introduction of the new screening test. If there is lead-time bias, the cancer will be diagnosed at an early time but die in the same year as an unscreened equivalent case. Since the new IB mortality measure accumulates mortality due to each year of diagnosis it is not affected by changes in year of diagnosis. By assuming lead time began in 1982, annual IB mortality due to all cases diagnosed from 1982 to the present would not be affected by whether the case was diagnosed earlier due to screening. Thus, this new IB mortality measure is independent of lead time bias associated with increased early diagnosis since 1982.

An important finding from the IB mortality analyses was that very recent declines in mortality among cases originally diagnosed at regional or distant stage are not being compensated by increases in mortality for localized breast cancer (Fig. 5). This could mean that we are beginning to see mortality benefits associated with increased efforts aimed at early detection and treatment of breast cancer.

Although this analysis was restricted to breast cancer, it is the hope that this method will be useful for other sites, allowing greater insight into the causes of changes in mortality rates. The incidence-based mortality rates by diagnostic variables are illustrative of the types of analyses that can be created. In our examples, the mortality rates were classified by single diagnostic variables (either stage-at-diagnosis or age-at-diagnosis). However, meaningful interpretations of temporal trends may require the cross classification of multiple diagnostic variables to account for age–period–cohort effects. Work is underway to study the types of cross classification needed to make valid inferences using this new measure of mortality.

Acknowledgement—The authors wish to thank Valerie Van Holten for thoughtful discussions about the database for the SEER Program. The authors wish to thank Sam Shapiro for his innovative thoughts on the need for careful investigation of more recent mortality data.

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