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The increasing incidence of breast cancer since 1982: relevance of early detection

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Breast cancer incidence in the United States has been rising dramatically since 1982, as shown in data collected by the Surveillance, Epidemiology, and End Results (SEER) Program. In women aged 50 and older, incidence rates for *in situ* and localized invasive tumors have increased over the period 1982 – 86, while rates for regional and distant tumors have remained stable. The incidence of localized tumors <1.0 cm, 1.0 – 1.9 cm, and 2.0 – 2.9 cm in size has increased more rapidly than that of tumors 3.0 cm or more in size among women over age 50. Survival rates also have improved among cases diagnosed over this time period. These data suggest that early detection may be playing a role in the recent increase in female breast cancer incidence, though other factors cannot be ruled out. Conclusions regarding improved cancer control await confirmation by reduced breast cancer mortality.

Key words: breast cancer, early detection, incidence, mammography, mortality, SEER, survival, United States.

Introduction

The incidence of female breast cancer has been changing in the United States over the time period 1973 – 86, based on data collected by the Surveillance, Epidemiology, and End Results Program (SEER).[1,2] Breast cancer incidence increased in 1974 and then declined through 1977. Devesa *et al*[3] noted that several events occurred in the early 1970s to heighten public awareness of cancer. Of particular relevance to breast cancer was the initiation of the Breast Cancer Detection Demonstration Projects[4] and the diagnosis of breast cancer in prominent public figures.[5] An increased public awareness of breast cancer may have resulted in a short-term increase in the number of visits to doctors for breast cancer screening or in response to symptomatology.[3] Subsequent to 1977, incidence rates increased slowly through 1981 and then rose dramatically between 1982 and 1986.[1,2]

Of particular interest is the role that early detection may be playing in this recent increase. Early detection of breast cancer may include diagnoses among asymptomatic women who are screened by physical examination and mammography as part of a routine medical exam, and additional diagnoses among symptomatic women resulting from increased use of mammography by physicians. In the latter case, women also may be seeking medical care earlier than in the past because they are better informed concerning early symptoms of breast disease and may be practicing breast self-examination. In this report, we have examined the magnitude of the recent increase in female breast cancer incidence in relation to the secular trend based on long-term incidence data for the state of Connecticut. We have also investigated incidence by stage of disease and tumor size to determine whether patterns are suggestive of an effect due to an increased early detection. Moreover, we analyzed the recent trend in survival to determine whether increases in observed survival rates are consistent with predicted improvement due to early detection.

Materials and methods

Breast cancer cases diagnosed between 1973 – 86 were identified through the SEER Program. Additional cases, diagnosed between 1940 – 72, were available from the Connecticut Tumor Registry (CTR), which is also a SEER

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Program participant. The SEER Program is based at the National Cancer Institute (NCI) and has supported, since 1973, the collection of data on all cancers diagnosed among residents in nine geographic areas of the US: the metropolitan areas of San Francisco, California; Detroit, Michigan; Atlanta, Georgia; and Seattle, Washington; as well as the states of Connecticut, Utah, New Mexico, Iowa, and Hawaii. Patient follow-up for survival status and cause-of-death information also are collected. Population data from the Census Bureau and mortality data from the National Center for Health Statistics (NCHS) are obtained and enable the calculation of cancer incidence, mortality, and patient survival rates.

Age-specific breast-cancer incidence trends were modeled using Poisson regression techniques (Appendix).[6] The models were fitted using GLIM,[7] a widely available statistical package. Since the age-specific incidence rates were approximately parallel, overall age-adjusted incidence rates were calculated from the model using direct standardization to the 1970 US population. Using models with no interaction between age group and year, produced age-standardized rates whose relative values are invariant to the choice of the standard.[8] The models also allowed the identification of a 'join point'[9]—a point in time when there is a significant change in the log-linear incidence trend. Models were fit fixing the join point over a series of calendar years to identify the best-fitting model.[10] The 95 percent confidence interval (CI) for the join point was calculated by the profile likelihood method.[11] All CIs shown are 95 percent intervals. Results of the fitted models were plotted on a log scale since the Poisson regression model assumes that the rates change over time in a multiplicative manner (*i.e.*, they change linearly on a log scale).

The regression models were used principally to generate the best-fitting lines for graphical comparisons of incidence trends. Results of statistical testing are not included since the large population sizes virtually assured that even small differences in slopes were statistically significant. Separate analyses were conducted for women aged 49 or less and for those 50 years and older. These age groups serve as a surrogate for pre- and post-menopausal status, respectively, and menopausal status has been suggested as having etiologic and biologic importance for breast cancer.[12]

Incidence trends were compared by stage of disease since studies of the efficacy of breast cancer screening with mammography and physical examination have demonstrated that cancers detected at screening tend to be *in situ* or, if invasive, tend to be localized to the area of the breast.[13] Incidence also was plotted by categories of tumor size to identify trends suggestive of increased early detection.

A Cox regression model[14] was used to test for differences between the survival experience of SEER patients diagnosed with invasive breast cancer in 1982 – 85 and those diagnosed prior to 1982 (Appendix). Significance testing was deemed appropriate, in this case, to detect changes in short-term survival trends which were too subtle to discern from graphical data alone. To obtain consistent data for purposes of modeling over the individual diagnosis years 1973 – 84, follow-up was restricted to three years after diagnosis. For 1985 cases, only two years of follow-up were available.

Results

Female breast cancer incidence for the nine SEER areas has been rising since 1977, although the increase has been most notable since 1982 (Figure 1). Survival rates have improved somewhat over the period, while the mortality trend has remained relatively stable. Breast cancer mortality rates for the SEER areas were similar to those for all US women (not shown).

The SEER data, alone, were not suitable to evaluate the importance of the recent increasing incidence of breast cancer because of the large perturbation in the incidence trend in 1974 – 76. It was desirable to estimate

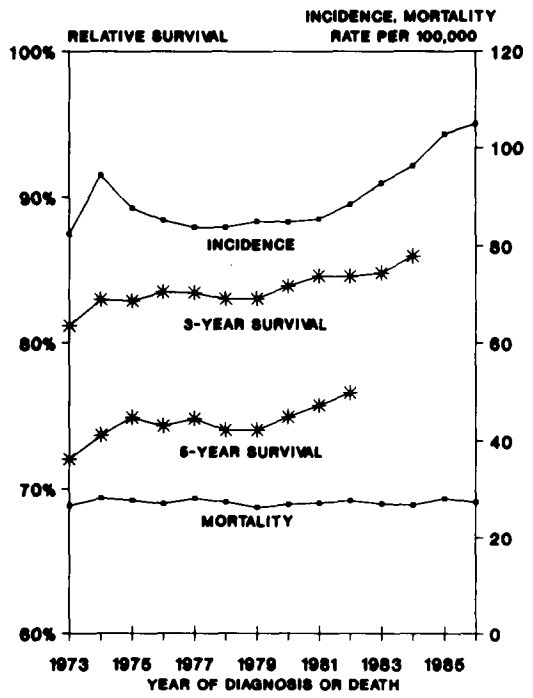

Figure 1. Invasive breast cancer incidence, relative survival, and mortality among women of all races and ages in the nine SEER areas. Incidence and mortality rates are age-adjusted by the direct method to the 1970 US standard population.

the breast cancer incidence trend that might have occurred in the absence of the dramatic effect in 1974 – 76 attributed to increased public awareness concerning breast cancer. If the years 1974 – 76 are removed from the analysis, very few data points remain for characterizing the breast cancer trend prior to the recent increase in incidence. Therefore, data from the CTR spanning the period 1940 – 86 were analyzed in conjunction with those from other SEER registries available for 1973 – 86.

Since the breast cancer incidence trend in the CTR was similar to the remaining areas during 1973 – 86, the trends were assumed to be parallel in the overall model. A difference in the magnitude of the incidence rates was allowed since CTR rates were generally higher than those in other SEER areas (Figure 2). Although a temporary increase in incidence can be seen in the CTR data during 1974 – 76, including historical data back to 1940 in the model served to smooth out the effect of this perturbation and provided a basis for estimating the long-term historical trend. The best-fitting model indicated a change in the incidence trend after 1982 (CI = 1982, 1983). The slope (which represents the yearly change in the log of the incidence rate) is 0.0115 (CI = 0.0108, 0.0122) prior to 1982 and is 0.0394 (CI = 0.0355, 0.0433) after 1982. This translates to an annual rate of change in incidence of 1.16 percent prior to 1982 and 4.02 percent after 1982 (Appendix).

Among women 50 years of age and older, incidence rates for *in situ* and localized invasive tumors have increased over the period 1982 – 86, while rates for regional and distant tumors have remained stable (Figure 3). The incidence of *in situ* tumors also increased among women under 50 years of age (not shown), while little change has occurred in the rates for localized, regional and distant disease in this group.

For cases of localized cancer of the breast, incidence trends by tumor size at diagnosis were consistent with an effect from increasing numbers of screening diagnoses (Figure 4). Incidence rates increased more rapidly for the smaller tumor sizes (<1.0 cm, 1.0 – 1.9 cm, 2.0 – 2.9 cm) than for tumors 3 cm or greater in size, in women aged 50 and older. In women under age 50 (not shown), only tumors 1.0 – 1.9 cm in size showed an increasing trend.

In order to identify changes in survival associated with the recent increase in early stage disease and smaller size tumors, two-year observed survival rates were examined among patients aged 50 and older (Figure 5). This is the age group in the general population most frequently screened by mammography. Survival rates generally improved among cases diagnosed over the period 1973 – 85, but it is difficult to discern whether the survival trend for cases diagnosed after 1982 represents an improvement over that for previous diagnosis years. Results from the Cox regression model indicated a significant improvement in survival across the diagnosis years 1973 to 1982 (regression coefficient of the diagnosis-year variable for 1973 – 82 associated with the change in the hazard function $\hat{\alpha}$ = – 0.0116, CI = – 0.0169, – 0.0063). For cases diagnosed after 1982, however, survival improved at a greater rate. The additional

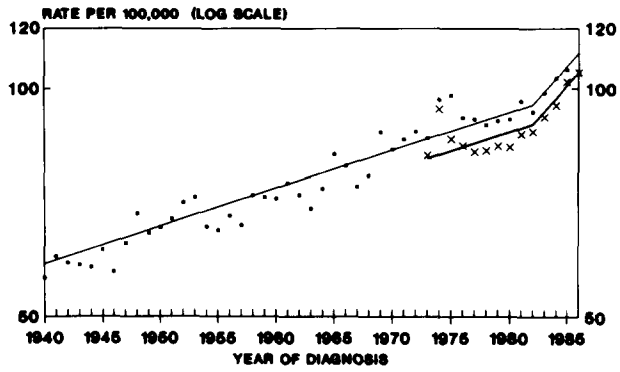

Figure 2. Observed and predicted age-adjusted incidence of invasive breast cancer among women of all races and ages in the state of Connecticut (CTR) and in the eight remaining SEER areas (Connecticut excluded). Incidence rates are age-adjusted by the direct method to the 1970 US standard population. A join point is located at diagnosis year 1982 indicating a significant change in the log-linear incidence trend. (•) CTR (observed); (—) CTR (predicted). (×) SEER (observed); (—) SEER (predicted).

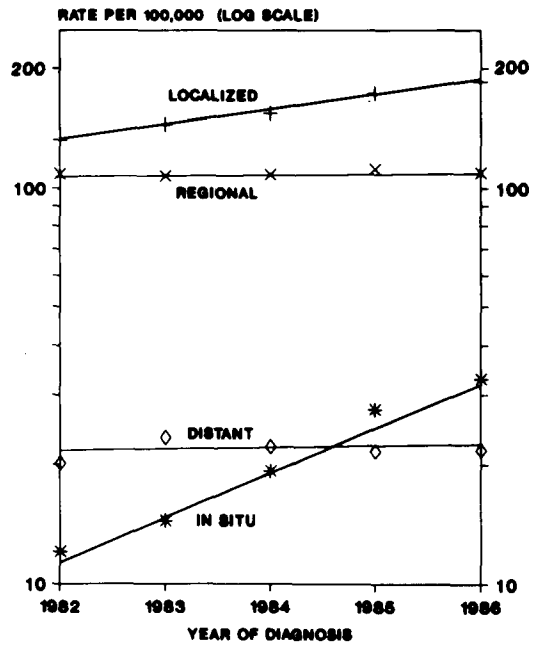

Figure 3. Age-adjusted breast cancer incidence by stage of disease among women age 50 and over, all races, in the nine SEER areas. Incidence rates are age-adjusted by the direct method to the 1970 US standard population.

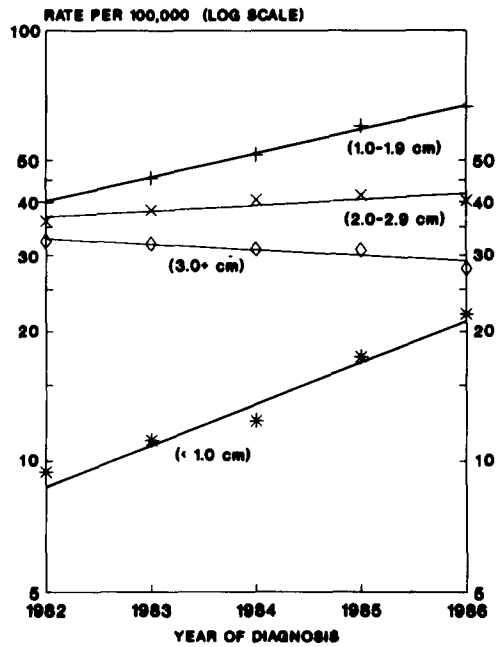

Figure 4. Age-adjusted incidence of localized cancer of the breast by tumor size at diagnosis among women age 50 and over, all races, in the nine SEER areas. Incidence rates are age-adjusted by the direct method to the 1970 US standard population.

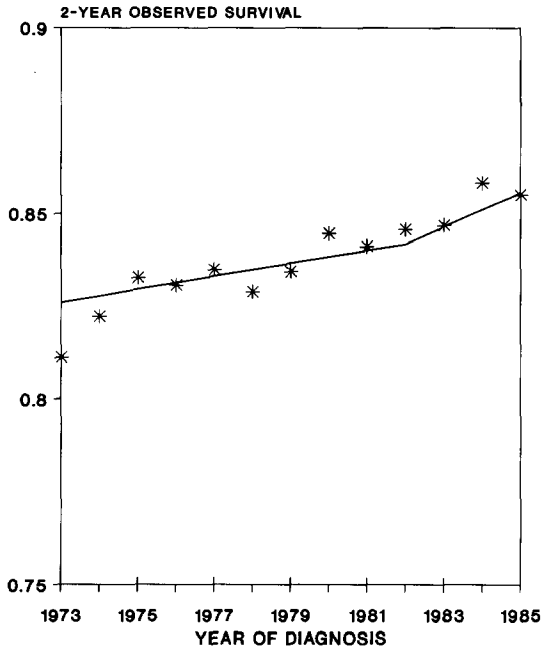

Figure 5. Observed and predicted two-year survival for invasive breast cancer among women aged 50 + , all races, in the nine SEER areas.

improvement in survival, above the 1973 – 82 trend, was statistically significant (regression coefficient associated with the incremental change in the trend = $\hat{\gamma}$ = – 0.0220, CI = – 0.0436, – 0.0004).

The survival model was used next in conjunction with survival data among screen-detected cases from the Breast Cancer Detection Demonstration Project (BCDDP) to determine whether survival improvements were consistent with expected increases in survival associated with early detection. For each year after 1982, cases were apportioned into those comprising the historical incidence trend and those in excess of the historical trend. Cases associated with the historical trend were assumed to have survival rates projected from the pre-1982 survival trend (*i.e.*, before the survival trend was influenced by the influx of new cases with improved survival due to early detection). The remaining cases in excess of the historical trend were assumed to have the survival experience of screen-detected invasive cases from the BCDDP trial, which was reported to be 0.97 at two years.[15] A two-year survival rate for all SEER cases diagnosed from 1982 through 1986 then was derived by calculating a weighted average of the survival experience of these two groups (Table 1). The 'derived' survival rates correspond closely with the survival rates from the model fit to the observed data, indicating that improvements in survival are consistent with expected increases due to early detection.

Since these results are based on observed survival rather than relative survival, it was important to consider the extent to which reduced non-breast cancer mortality associated with the younger age distribution of screened cases may explain survival improvements since 1982. Calculations based on US life tables[16] indicated that only a negligible portion of the survival improvement since 1982 can be attributed to reduced non-breast cancer mortality associated with a younger age distribution. Thus, the bias from using the observed survival rates as opposed to relative survival was minor.

Table 1. Comparison of 'derived' and 'modeled' two-year survival rates for invasive breast cancer among women aged 50 years and over, all races

	Historical trend			Screening				
Diagnosis year	Survival[a]		Percent cases	BCDDP survival[b]		Percent cases	Derived survival[c]	Modeled survival[d]
1982	0.842	×	100.0	+ 0.97	×	0	= 0.842	0.842
1983	0.843	×	97.3	+ 0.97	×	2.7	= 0.847	0.847
1984	0.845	×	94.6	+ 0.97	×	5.4	= 0.852	0.851
1985	0.847	×	92.0	+ 0.97	×	8.0	= 0.857	0.856

[a]Survival rates projected from regression model fit to the 1973 – 81 survival trend.
[b]Survival rate of screen-detected cases from the Breast Cancer Detection Demonstration Project (Ref. 15).
[c]Survival rates obtained as a weighted average of the survival experience of groups 1 and 2 above.
[d]Survival rates from the regression model fit to the observed survival data for cases diagnosed between 1973 – 85.

Discussion

Female breast cancer incidence has increased dramatically since 1982 based on data from the nine reporting areas of the SEER Program. This increase has occurred mainly in early stage disease and in tumors diagnosed at a smaller size. Survival rates also have improved for cases diagnosed over this time period. These data suggest that earlier detection of breast cancer cases is likely to be playing a role in the recent overall increase in female breast cancer incidence.

Increased breast cancer incidence associated with local stage disease and with tumors detected at a smaller size also has been reported by White[17] for the Seattle-Puget Sound SEER registry—one of the cancer-reporting areas included in our analyses. White's analyses differed from ours in that they did not take into account the long-term trend of rising incidence suggested by the historical data from Connecticut.[18] Rather, 1986 – 87 incidence rates in the Seattle-Puget Sound area were compared with the somewhat erratic incidence rates for 1974 – 78, which have been linked to increased public awareness of breast cancer.[1,3,5]

The reason for the long-term historical increase in breast cancer incidence in Connecticut is not known, although others have suggested the influence of changes in several possible risk factors such as the age at menarche, age at menopause, oral contraceptive use, oophorectomy rates, and diet.[18,19] Cancer registry data from upstate New York also has shown an average annual increase in breast cancer incidence of about one percent over the period 1940 – 75.[20] In contrast to the historical trends in Connecticut and upstate New York, Devesa and Silverman[21] noted little change in breast cancer incidence between the Second and Third National Cancer Surveys when analyses were restricted to the seven geographic areas common to both surveys. If the national secular trend for breast cancer incidence is smaller than that which we estimated for Connecticut, the change in the trend after 1982 then would be even larger.

Several surveys suggest that mammography usage has increased over recent years.[22 – 26] Between 1984 and 1989 there has been a two-fold increase in the percentage of physicians who order mammograms for asymptomatic patients, according to a national survey sponsored by the American Cancer Society.[22] In the Atlanta, Georgia metropolitan area,[23] the number of mammograms performed annually has risen from 19,800 in 1983 to 30,200 in 1984, 53,500 in 1985, and 70,500 in 1986. The number of mammographic units newly installed in the US also has increased. There were 132 units in 1982; 326 in 1983; 645 in 1984; 1,621 in 1985; and 2,186 in 1986.[24] Although this demonstrates a substantial increase in the resources to perform mammography, the latter two surveys do not indicate to what extent mammography may have been used for screening *vs* aiding the diagnosis of symptomatic patients.

Information on trends in the prevalence of mammographic screening in the general population are limited. Prior to 1984, the proportion of women aged 50 and older who had a mammogram within the past year may have been as low as five percent.[25] A 1987 national survey[26] reported that 15 percent of women aged 40 and older had a mammogram within the past year. This suggests a substantial relative increase in the use of mammography in recent years.

If the increased incidence of female breast cancer is due primarily to early detection associated with screening by mammography, improved survival and a reduction in mortality are the expected outcome, since the efficacy of mammographic screening has been demonstrated in a number of studies.[4,27 – 31] However, if a large portion of diagnoses associated with the increased use of mammography occurs among patients who are already symptomatic, the effect on mortality would be less predictable. Further, if increased diagnoses occur for large numbers of cancers that are not biologically significant, little or no effect on mortality would be expected. The lack of a notable improvement in recent breast cancer mortality rates does not preclude an effect related to early detection, since deaths in each calendar year occur among cases initially diagnosed over a wide range of prior years. Thus, many of the recent breast cancer deaths will have occurred among cases diagnosed several years prior to the increase in the use of mammography.

Future breast-cancer incidence patterns may be projected under the assumptions that early detection is the major cause of the recent increase and that a large proportion of the early detected cases otherwise would have been identified at a later time. Mammography utilization is currently increasing in the US. At some point after the pattern of mammography use stabilizes, breast cancer incidence might be expected to return to the pre-1982 incidence trend as projected forward in time. It would not necessarily return precisely to the background trend since some of the tumors identified early by mammography might not ever have become clinically apparent.

Kessler, Feuer, and Brown[32] have projected future breast cancer incidence rates using the background trend estimated in this paper. They used the installation of new mammography machines as a proxy for mammography utilization, assumed that two percent of the cases found through early detection would never become clinically evident, and allowed for a two- or three-year time lag between early detection by mammography and clinical detection. Based on these assumptions, they projected that screening patterns would stabilize around 1990 and that incidence rates would start to decline in 1989 and

would approach the background secular trend by 1992.

The evidence supporting early detection as a major factor in the recent increase in breast cancer incidence rates is not conclusive. White has suggested that the predicted increase in incidence due to mammography utilization in the Seattle-Puget Sound area may not account entirely for the observed increases among women in the youngest and oldest age groups.[17] A similar conclusion was reached by investigators who conducted a survey of the method of breast cancer discovery for patients diagnosed during a four-month period in the state of Utah.[33] Other factors also may be influencing breast cancer trends. Many epidemiologic studies have shown that women who have their first child at a later age or who remain nulliparous are at increased risk for breast cancer.[12] Blot *et al*[24] reported that changes in age-specific breast cancer mortality rates among US white women during 1950 – 80 were correlated generally with changes in patterns of childbearing in early adulthood. However, the authors also found evidence of reduced breast cancer mortality in the most recent five-year period among younger women, raising the possibility that recent changes in the detection and management of this cancer now may be influencing the mortality rates. Hahn and Moolgavkar[19] investigated the association between the total childbearing history of cohorts of Connecticut women born between 1855 and 1945 and concluded that changes in decade of first birth and nulliparity do not explain observed changes in breast cancer incidence. Further evidence that the trend toward delayed childbearing does not explain fully the recent increase in the incidence of breast cancer can be gleaned from breast cancer incidence projections developed by White.[35] The projections were based on the estimated effect on breast cancer risk of the changing distribution of age at first birth for cohorts of US women between 1910 and 1954 and assumed no future incidence trends other than the age at first birth effect. White's projections for breast cancer incidence in 1985 were about 20 percent lower than observed rates[1] in each group for age 40 years and above. These studies suggest that changing population fertility patterns may play a role, but are unlikely to account for the recent increase in breast cancer incidence.

Recent reports have linked the use of oral contraceptives (OCs) to increased breast cancer risk in younger women,[36-43] although conflicting findings from other studies leave this issue unresolved.[44-46] Data on OC use are not collected routinely on the SEER population. However, in a case-control study[43] of breast cancer cases diagnosed during 1980 – 82 in eight of the nine SEER areas, information about OC use and other reproductive risk factors was collected through personal interviews. Breast cancer risk was found to increase with duration of OC use among nulliparous women, 20 – 44 years of age, who experienced menarche before age 13. Although the relative risk reached 11.8 among women in this group who used OCs for 12 years or longer, the authors concluded that the increased risk associated with such a small group of susceptible women would have little impact on overall breast cancer risk.

Descriptive data from the nine population-based cancer-reporting areas in the SEER Program suggest that the recent increase in female breast cancer incidence is consistent with an increase due to early detection. Similarly, increases in observed survival rates are comparable to predicted rates based on the improved survival associated with early detected cases. The influence of other risk factors on the breast cancer trend cannot be ruled out and should be investigated further. If the recent observed patterns of breast cancer incidence and patient survival are indicative of improved cancer control efforts, then breast cancer mortality rates would be expected eventually to decline.

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Appendix

Incidence model

The Poisson regression model for invasive breast cancer incidence trends using data from the CTR since 1940 and SEER since 1973 is:

$$LN(\textit{incident cases}_{ray}) = LN(\textit{population}_{ray}) + \alpha_r + \beta_a + (\gamma \times y) + [\omega \times \{(y - \delta) \times I_\delta\}] + \epsilon_{ray}$$

with the constraint $\sum_r \alpha_r = 0$, $\sum_a \beta_a = 0$,

where

r = registry (1 = CTR, 2 = SEER [with CTR removed])

a = age group (1 = 0 – 29, 2 = 30 – 39, 3 = 40 – 49, 4 = 50 – 59, 5 = 60 – 69, 6 = 70 +)
y = diagnosis year (40, . . .,86)
δ = 'join point' where the incidence trend changes slope
$I_\delta = \begin{cases} 1 \text{ if } y \geq \delta \\ 0 \text{ if } y < \delta \end{cases}$
γ = the common slope of the age-specific incidence trends prior to δ
ω = the change in the slope of age-specific incidence trends after δ (*i.e.* the slope after time δ is $\gamma + \omega$)
ϵ_{ray} is a Poisson random variable with mean = $\text{LN}(\text{population}_{ray}) + \alpha_r + \beta_a + (\gamma \times y) + [\omega \times \{(y - \delta) \times I_\delta\}]$.

The annual percentage rate of change in the incidence rates is calculated as $e^\gamma - 1$ prior to 1982 and $e^{\gamma + \omega} - 1$ after 1982.

Cox proportional hazards model

The general form of the Cox model

$$\lambda(t|\underset{\sim}{X}) = \lambda_0(t)\, g(\underset{\sim}{X}) \text{ with } \lambda_0(t),\ g(\underset{\sim}{X}) \geq 0$$

was used, where $\lambda_0(t)$ is the underlying hazard (*i.e.*, when all covariates are zero) which is modeled non-parametrically, and $g(\underset{\sim}{x}) = \exp(\underset{\sim}{X}\underset{\sim}{\beta})$ in order to ensure that $\lambda(t|x) > 0$ for all $\underset{\sim}{\beta}$. In our model,

$$\underset{\sim}{X}\underset{\sim}{\beta} = [\alpha \times (y - 82)] + [\gamma \times \{(y - 82) \times I_{82}\}]$$

where:

y = diagnosis year (y = 73, . . .,85)
$I_{82} = \begin{cases} 1 \text{ if } y \geq 82 \\ 0 \text{ if } y < 82 \end{cases}$
α = the coefficient associated with the hazard trend prior to 1982
γ = the coefficient associated with the change in the hazard trend after 1982.

From this form of the hazard function, the survival function is

$$S(t|\underset{\sim}{x}) = S_0(t)^{\exp(\underset{\sim}{X}\underset{\sim}{\beta})}$$

where

$$S_0(t) = \exp\left[-\int_0^t \lambda_0(u)\, du\right].$$