Journal of Cancer Policy 5 (2015) 8–17

Journal of Cancer Policy

journal homepage: www.elsevier.com/locate/jcpo

Original Research

Why have breast cancer mortality rates declined?

Steven A. Narod[a,b,*], Javaid Iqbal[a], Anthony B. Miller[b]

[a] Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada
[b] Dalla Lana School of Public Health, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 20 January 2015
Accepted 12 March 2015
Available online 6 June 2015

Keywords:
SEER program
Breast cancer
Incidence rate
Mortality rate
Survival
Case fatality rate
Prevention and control

ABSTRACT

The recent decline in breast cancer mortality in the USA might be due to prevention or to screening mammography or to improved treatment protocols. We sought to determine which factors are likely to be responsible for the observed decline in breast cancer mortality.

We used the Surveillance, Epidemiology and End Results (SEER) database to estimate incidence rates, mortality rates, and survival from breast cancer for white women who were diagnosed with invasive breast cancer from 1975 to 2011.

From 1975 to 2010, the mortality of breast cancer declined from 32 per 100,000 per year to 21 per 100,000 per year (34%). At the same time, the incidence increased by 30%, in particular for localized breast cancers (62%) without a commensurate decline in the number of regional breast cancers. From 1975 to 2002, 10-year survival increased by 28% (from 64.9% to 82.8%). The increase in survival was greater for regional cancers (23%), than for localized (10%) or for distant cancers (3%).

The decline in breast cancer mortality in the USA from 1975 to 2010 is unlikely to be the result of advances in prevention or screening. The large increase in the incidence of localized cancers without a corresponding decrease in advanced breast cancers suggests a prominent stage shift, due to overdiagnosis. The drop in the mortality rate could be accounted for by an improvement in cancer survival, likely due to increased use of adjuvant chemotherapy over the period.

Introduction

It is widely acknowledged that deaths from breast cancer in the United States have been decreasing over the past few decades but the determinants of change are in want of explanation [1]. There are many possible factors, but two schools of thought predominate. Advocates of mammography claim that early detection is bearing fruit [2–4]. This could be through formal mammographic screening or because better awareness leads to smaller cancers, palpable or not [5]. The other school of thought attributes the decline to adjuvant systemic therapies, including cytotoxic drugs, adjuvant hormonal therapies and biologics such as Herceptin [6–8]. There may also be a small contribution from regional radiotherapy [9,10]. One might consider the possibility that the breast cancers are changing, perhaps as a consequence of evolving changing patterns of risk factors. Moreover, the current patient population may not be identical to that of the past, due to the impacts of fertility and immigration on the ethnic distribution of American women [11,12]. To provide compelling evidence in favor of one or another position would require detailed information on demographics, risk factors, screening behaviors, clinical presentation, treatments received and outcomes for a large and representative sample of American women. Given limited information, such as cancer incidence, stage, mortality and case-fatality at several points in time in a fixed population, one can venture an educated guess. In the United States, this information has been compiled through the Surveillance, Epidemiology, and End Results (SEER) registry system and is available to researchers without cost.

In the following pages, we analyze incidence, mortality and case-fatality rates for the last several decades and seek to measure and explain the decline in mortality. Cancer incidence refers to the number of new cancers diagnosed in a given calendar year, relative to the size of the population at risk and is described in terms of cases per 100,000 women per year. Age-adjusted mortality describes the number of women who die from breast cancer in a given calendar year, relative to the size of the population. It is described in terms of deaths per 100,000 women per year. The reference year is the year of death and the deaths are from breast cancer for patients who were treated *at any time in the past* (in this sense they reflect *prior* treatment protocols). Case-fatality describes the probability

* Corresponding author at: Women's College Research Institute, 790 Bay Street, 7th floor, Toronto, ON, Canada M5G 1N8.
Tel.: +1 416 351 3765; fax: +1 416 351 3767.
E-mail address: Steven.narod@wchospital.ca (S.A. Narod).

http://dx.doi.org/10.1016/j.jcpo.2015.03.002

of death from breast cancer for a patient diagnosed in a given year and reflects *current* treatment protocols; i.e., a woman who is diagnosed at age 38 and dies at age 42 is included in the under 40 group for case fatality but in the 40–50 group for mortality. In theory, case-fatality considers the remaining life of the patient (who ultimately dies of breast cancer or another cause) but for practical reasons it is often used to describe deaths which occur in a specific follow-up time period (e.g. five years or ten years following diagnosis). In the event that a new, effective treatment is introduced, the impact on case-fatality should be immediate, but there should be a lag of several years before an impact on mortality is noticed. In order to simplify the interpretation of these data (i.e., to remove the potential effect of demographic and ethnic change over the past 40 years) we restrict our analyses to white women.

Materials and methods

Data source and software

The Surveillance, Epidemiology and End Results (SEER) research database contains information on 2,899,726 women with invasive breast cancer. Since its inception in 1973, SEER has been a comprehensive source of cancer incidence and survival in the United States [13]. It encompasses approximately 26% of new breast cancer diagnoses in the country. For statistical purposes, various combinations of the SEER registries are available, depending on the time period and the specific registries included. For this study, we used the SEER 9 registry database (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) [14] and the SEER18 registry database (SEER13 [SEER9 plus Los Angeles, San Jose-Monterey, Rural Georgia, and the Alaska Native Tumor Registry] plus the Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia [15]. We used SEER*Stat version 8.1.5 to estimate incidence and survival rates from SEER databases [16].

Mortality

We used SEER mortality database to estimate age-adjusted breast cancer mortality rates (deaths from breast cancer per 100,000 women) for each year from 1975 to 2010 [17]. These analyses included all cases and subgroups defined by age of diagnosis.

Incidence

We used the SEER9 registry database to estimate the age-standardized incidence rates (adjusted to the 2000 US Standard Population) of breast cancer in women diagnosed with breast cancer for each year from 1975 to 2011. Given that Seattle-Puget Sound and Atlanta registries joined the SEER program in 1974 and 1975, respectively, we did not include the years 1973 and 1974 in our analyses. We included women who were classified as 'white' in the SEER 9 and had microscopically confirmed invasive breast cancer at diagnosis.

We used the Collaborative Staging Schema version 0204 to select 'breast' as primary site of cancer. For the cancer incidence analyses, we used the SEER historic stage A to define three categories of breast cancer stage at diagnosis: localized, regional and distant breast cancer. From the SEER*Stat software, we generated age-standardized incidence rates (cases per 100,000 per year) for localized, regional and distant breast cancers, and for all breast cancers combined. We performed subgroup analyses to estimate incidence rates of localized, regional and distant breast cancer (cases per 100,000) for women <50 years and women 50 years and above.

Survival

We used SEER18 registries database to estimate breast cancer-specific survival [15]. We selected women whose cancers were histologically confirmed, who had a known age at diagnosis and for whom follow-up data was available. We excluded women with missing survival time in the database and women with an unknown cause of death. From 1973 we used SEER historic stage A and estimated 10-year breast cancer-specific survival for localized, regional and distant breast cancers, and all cancers combined.

In order to estimate survival according to stage using a more granular staging system, we used Adjusted American Joint Committee on Cancer (AJCC) 6th Stage (1988+) and classified all invasive breast cancers into AJCC stages I–IV [18]. These data were available only for women diagnosed from 1988 on and it is premature to estimate ten years survival, hence we estimated 5-year breast cancer-specific survival for each stage. We performed subgroup analyses for women <50 years and women 50 years and above, and for women with estrogen receptor-positive and estrogen receptor-negative tumors. We used Kaplan–Meier method of survival estimation and calculated 95% confidence intervals.

Based on the 5-year breast cancer-specific survival estimates for the two years 1990 and 2006, we calculated the absolute increase in five-year survival over the 16-year period (percentage change in survival from 1990 to 2006 as well as the relative improvement in survival (%), the absolute reduction in mortality and the proportionate reduction in mortality. To estimate the number of deaths from breast cancer that were avoided in 2006, attributable to the improvement in survival, we first calculated the estimated number of deaths assuming 1990 five-year survival rates and compared these to the actual number of deaths reported in the 2006 cohort. Using the same approach we conducted subgroup analyses to estimate number of deaths avoided for women <50 years (ER-positive and ER-negative) and women 50 years and above (ER-positive and ER-negative).

Results

From 1990 to 2010, the age-adjusted breast cancer mortality rate from all breast cancers fell from 33.0 per 100,000 per year to 21.3 per 100,000 per year, a decline of 36% (Fig. 1). Prior to 1990, rates were stable. The decline was 41% for women under age 40, was 51% for women aged 40–49 and was 34% for women age 50 and older (Fig. 2).

Fig. 3 shows that during the period of rapid decline in mortality (1989–2009) there was no commensurate decline in cancer incidence. This effectively eliminates from consideration the possibility that there were fewer deaths from cancer because there were fewer cases of cancer.

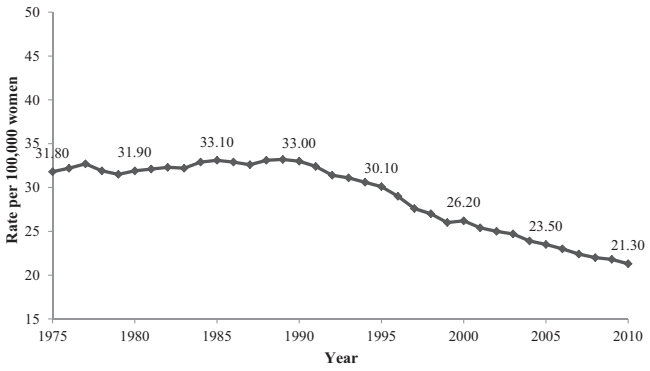

Fig. 1. Breast Cancer Mortality Rates in US White: SEER 1975–2010. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

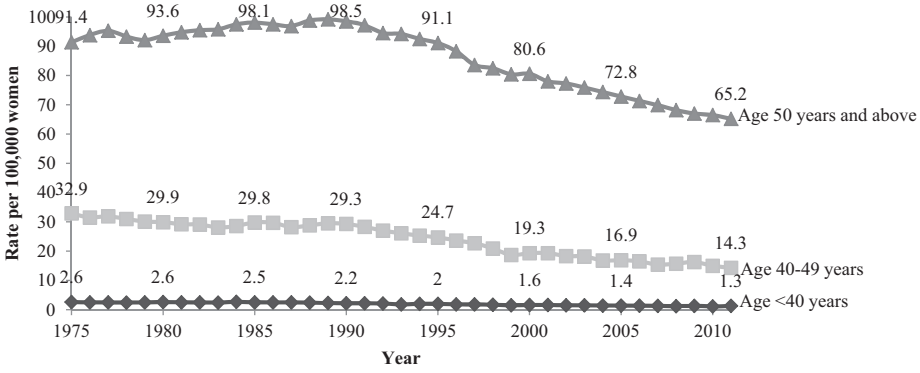

Fig. 2. Breast Cancer Mortality Rates in US White: SEER 1975–2010, by age group. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

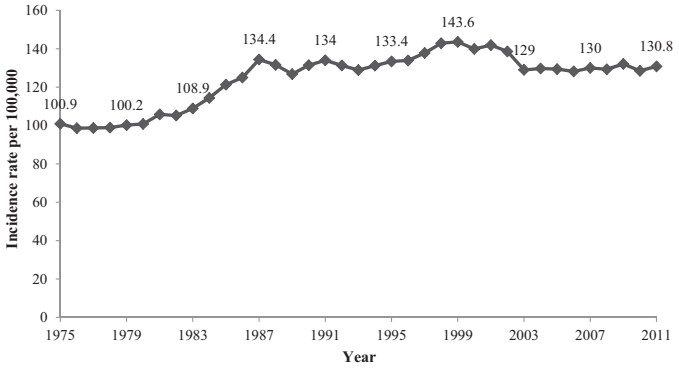

Fig. 3. Age-standardized incidence rates of breast cancer in the US White: SEER 9, 1975–2011. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

If the decline in mortality were the consequence of better screening – or more extensive screening – we would expect to see an increase in the incidence of early stage cancers and a compensatory decline in more advanced cancers. But (after a period of adjustment) the total incidence should remain the same. Fig. 4 shows the trends in localized cancer, in regional cancer and in distant cancer from 1975 to 2011. The incidence of localized cancer rose by 44 per 100,000 per year over this period, beginning in 1980 and peaking in 1999 but the incidence of advanced cancer fell by only 9 per 100,000 per year over the same period. The increase in the number of early cancers is not offset by a similar drop in the number of more advanced cancers, contrary to the proposition that screening is the main reason for the mortality decline. The shortfall is much greater for women over 50 (the target population for screening) (Fig. 5) than it is for women under 50 (few of whom had their cancer diagnosed through screening) (Fig. 6). Furthermore, mortality declined by 36% – far greater than the decline of 17% for advanced (regional and distant) cancers. The most plausible explanation is that the increase in early cancers was in fact, largely a consequence of screening, but given the small decrease in advanced cancers (Fig. 7) the data suggest that screening leads mainly to over-diagnosis, and not to early diagnosis.

The probability of a woman with breast cancer dying of breast cancer in a given time period is referred to as case-fatality and is distinguished from mortality, which refers to the probability of woman in the population at large dying of breast cancer in a given year. As is the case for mortality, improvements in case-fatality can be the result of screening (i.e., advancing diagnosis) or treatment. The complement (inverse) of case-fatality is survival and the sum of survival and case-fatality is 100%. Data on case-fatality can be presented in terms of deaths or in terms of survival. Changes in survival or in case-fatality can be expressed in absolute terms (deaths per 100 women) or in relative terms (percentage change in the number of deaths or survivors).

Trends in breast cancer-specific survival are presented in Fig. 8, by stage at presentation. The greatest absolute improvement in ten-year survival in the thirty-year period was for patients who presented with regional disease (an improvement of 23%), followed by localized disease (10%) and distant disease (3%). The rates of improvement, assuming a linear increase with time, are presented in Fig. 8b.

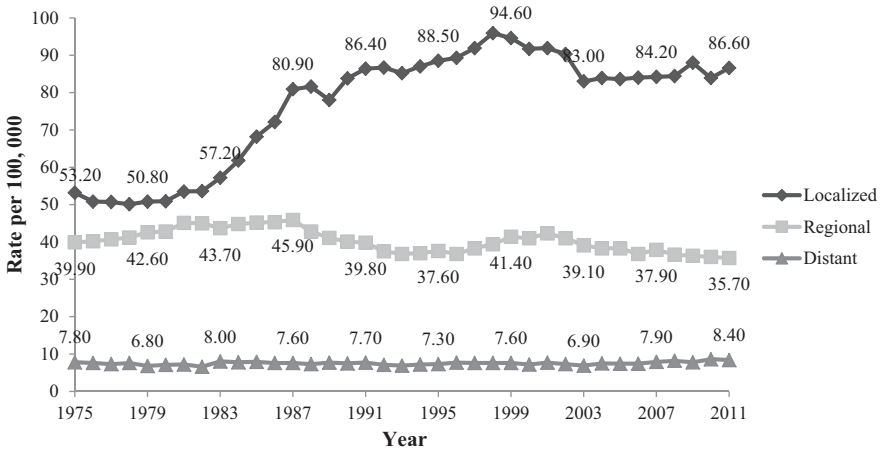

Fig. 4. Age-standardized incidence rates of localized, regional and distant breast cancers in US White: SEER 9, 1975–2011, all ages. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

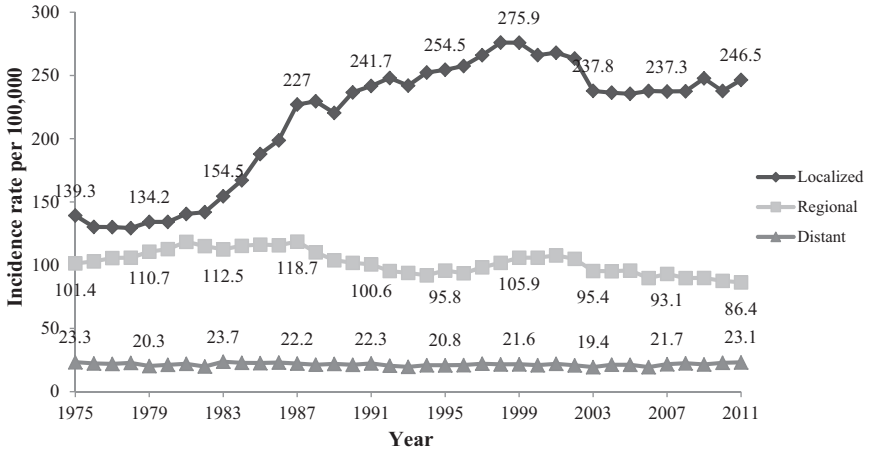

Fig. 5. Age-standardized incidence rates of localized, regional and distant breast cancers in US White: SEER 9, 1975–2011, age ≥50 years. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

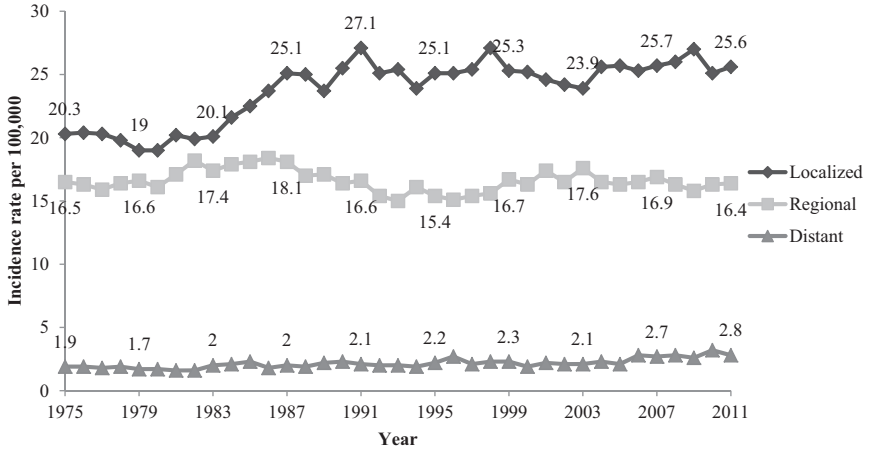

Fig. 6. Age-standardized incidence rates of localized, regional and distant breast cancers in US White: SEER 9, 1975–2011, age <50 years. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

The improvement in breast cancer survival is perhaps best illustrated by examining ten-year case-fatality. In absolute terms, ten-year case fatality (all stages) declined by 22.2% – the same as the absolute improvement in survival (Fig. 9). However, when expressed in relative terms, the decline in case-fatality is much greater than the improvement in survival (56% and 37%, respectively). Note that, as expected, the decline in mortality became apparent much later than the decline in case fatality (Fig. 1 above). The lag period was about six years.

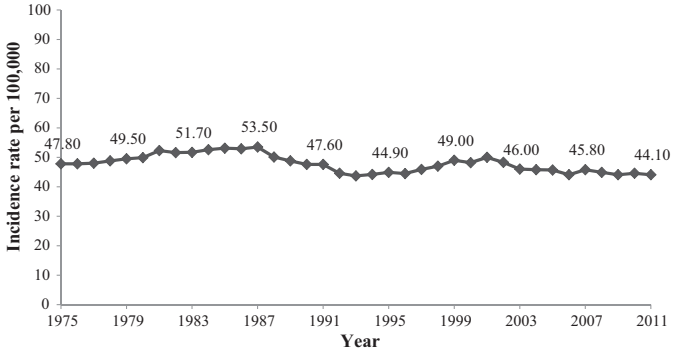

Fig. 7. Age-standardized incidence rates of advanced (regional and distant) breast cancer in the US White: SEER 9, 1975–2011. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

From 1975 to 2003, patients with localized disease experienced a 58% decline in ten-year case-fatality (compared to a 12% increase in survival), patients with regional disease experienced a 48% decline in ten-year case-fatality (and a 43% increase in survival) and patients with distant disease experienced a 4% decline in ten-year case-fatality (and a 25% increase in survival) (Fig. 10).

In order to better understand the underlying basis for the decline in breast cancer mortality, additional analyses were done focusing on the SEER data from 1988 to 2008. In 1988, the AJCC staging system was introduced, thereby increasing the number of categories from three (localized, regional, distant) to four (stage I to stage IV). However, given that ten-year survival data can only be determined for patients diagnosed in 2003 and earlier, we used five-year survival (and changes in five-year survival) as the principal endpoints of interest

In 2008, the five year survival for stage I breast cancer was 97.8%, up from 96.7% in 1988 (Table 1). A small increase of 1% appears to be trivial, but in fact represents a 30% decline in case-fatality. Patients with stage II cancers experienced a 6% increase in survival and a 47% decline in case fatality. For patients with stage III cancer there was an increase of 11% in survival and a decline of 30% in case-fatality. For women diagnosed with stage III cancer under age 50, the increase in survival was 19% and the decline in case fatality

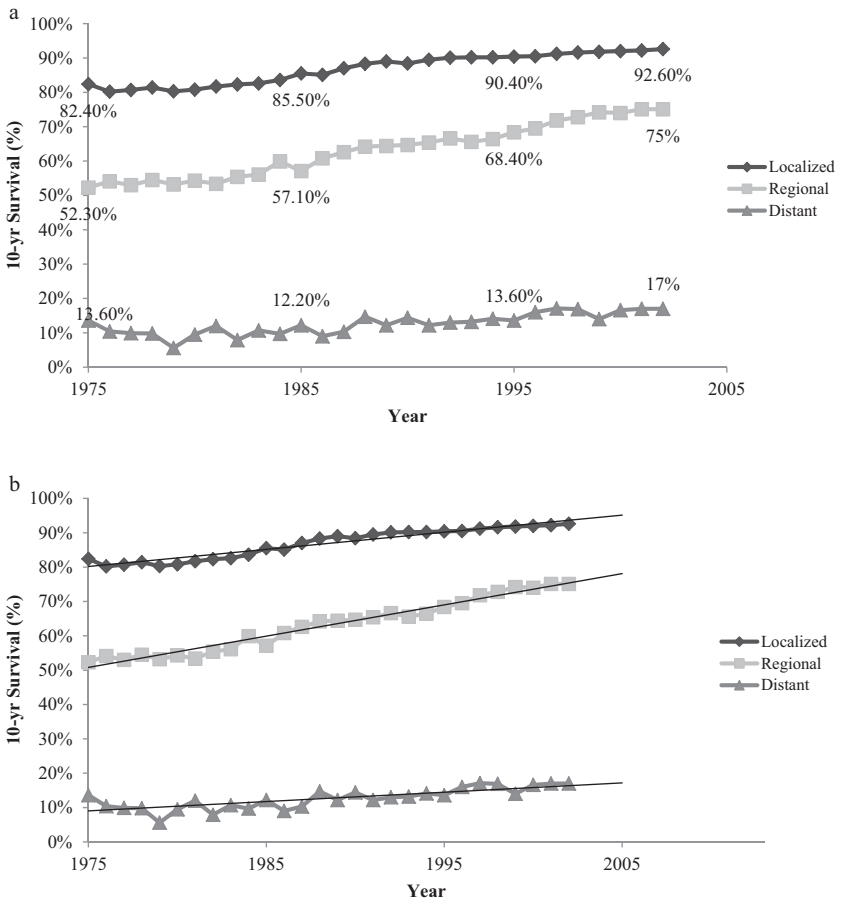

Fig. 8. (a) 10-year breast cancer-specific survival for localized, regional and distant breast cancer in the US White: SEER 18, 1975–2003. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results. (b) 10-year breast cancer-specific survival for localized, regional and distant breast cancer from 1973–2002, with linear trendline.

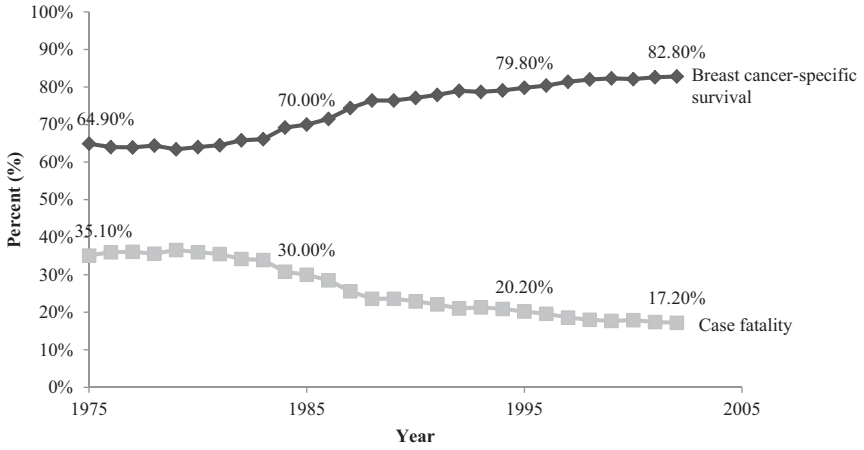

Fig. 9. 10-Year breast cancer-specific survival (%) and case fatality (%) (all stages combined) in US white: SEER 18: 1975–2002. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

Table 1
Percent increase in 5-year survival and number of deaths avoided in stage 1–3 breast cancer in US, 1990–2006.*

AJCC stage	Number of cases in 2006	% of all cases	Survival in 1990 (%)	Fatality in 1990 (%)	Survival in 2006 (%)	Fatality in 2006 (%)	Absolute increase in survival (%)	Relative improvement in survival (%)	Proportionate reduction in fatality (%)	Number of deaths avoided
I	15,578	50.4	96.1	3.9	97.8	2.2	1.7	1.7	43.6	265
II	11,136	36	86.9	13.1	92.3	7.7	5.4	5.9	41.2	601
III	4194	13.6	66.5	33.5	76.1	23.9	9.6	12.6	28.7	403
I–III	30,908	100	87.8	12.2	92.9	7.1	5.1	5.5	41.8	1269

Abbreviations: AJCC, American Joint Committee on Cancer.
* Cases restricted to women with known estrogen receptor and progesterone receptor status.

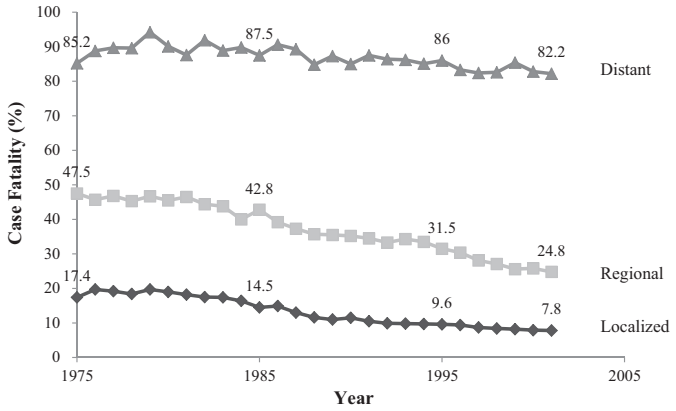

Fig. 10. 10-Year case-fatality (%) of localized, regional and distant breast cancer: SEER 18: 1975–2003. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

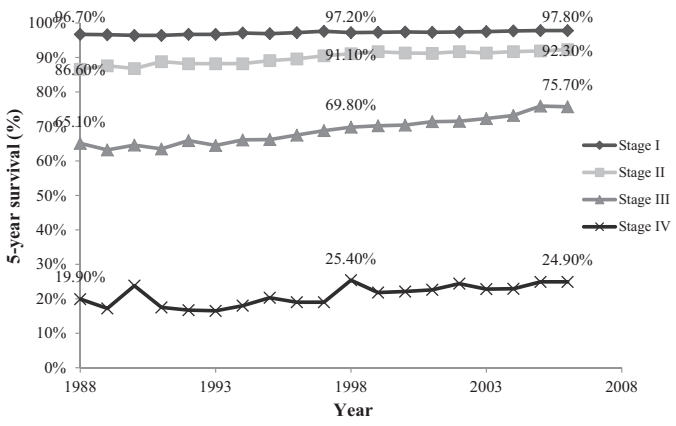

Fig. 11. 5-Year breast cancer-specific survival for stage I–IV breast cancer in US White: SEER 18, 1988–2006. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

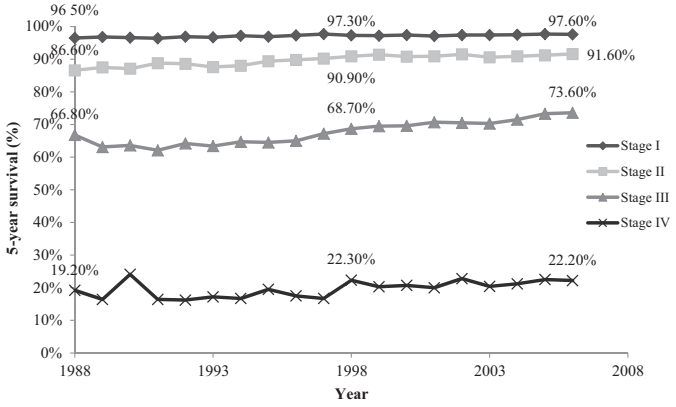

Fig. 12. 5-Year breast cancer-specific survival for stage I–IV breast cancer in US White: SEER 18, 1988–2006, age ≥50 years. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

was 50%. Among women with stage III breast cancers, the decline in case-fatality was 37% for women with estrogen receptor positive cancers and was 22% for women with estrogen receptor negative cancers. There was no appreciable decline in the case-fatality for women with stage IV cancers (Fig. 11) and these are not considered in the remaining analyses.

From Figs. 11–15 we can estimate how many fewer deaths have occurred in the SEER cohort of white women in the five year period

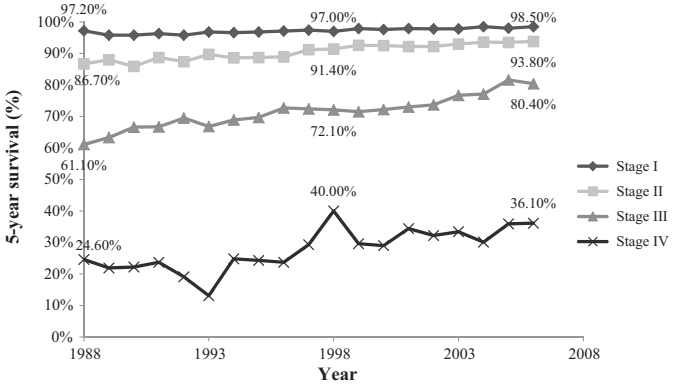

Fig. 13. 5-Year breast cancer-specific survival for stage I–IV breast cancer in US White: SEER 18, 1988–2006, age <50 years. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

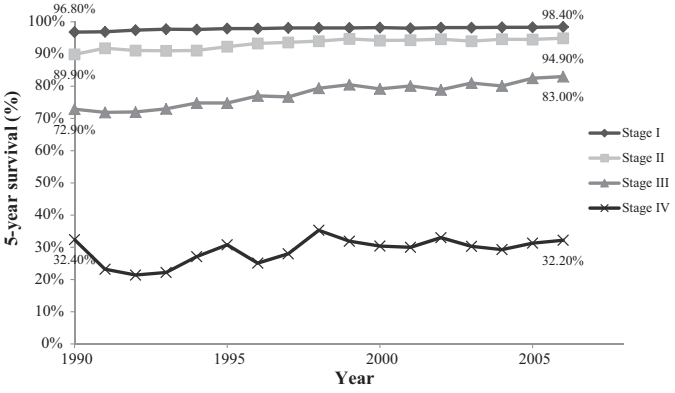

Fig. 14. 5-Year breast cancer-specific survival for stage I–IV breast cancer in US White: SEER 18, 1990–2006, estrogen receptor-positive tumors. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

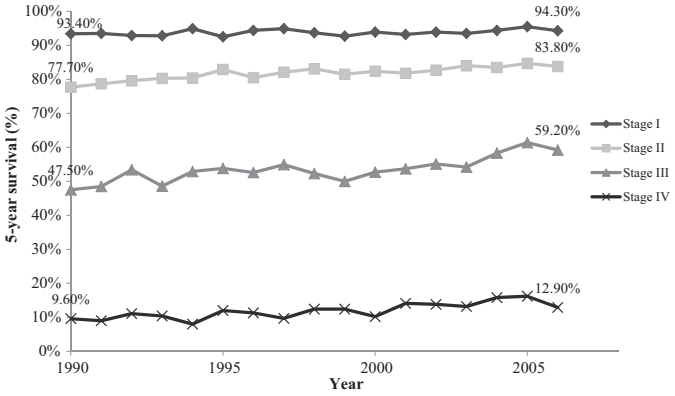

Fig. 15. 5-Year breast cancer-specific survival for stage I–IV breast cancer in US White: SEER 18, 1990–2006, estrogen receptor-negative tumors. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

following a diagnosis of invasive breast cancer (stages I–III) as a consequence of the decline in case fatality from 1990 to 2006. There were 30,908 women diagnosed in 2006; assuming a five-year case-fatality of 12.2% (the 1990 figure) we would have expected 3771 deaths in the cohort. Assuming the five-year case fatality of 7.1% (the 2006 figure) we would expect 2194 deaths. The difference is 1577 fewer deaths, or 5.1 fewer deaths per 100 patients. Of the 1577 deaths avoided, the largest number was in stage 2 patients (601 fewer deaths) followed by stage 3 patients (403 fewer deaths) and stage I patients (265 fewer deaths). These data are broken down

Table 2
Number of lives saved according to age and hormone receptor status; 1990–2006.*

AJCC stage	Age <50 years		Age ≥50 years		Total cases
	ER+ Number of lives saved	ER− Number of lives saved	ER+ Number of lives saved	ER− Number of lives saved	
I	61	6	172	14	253
II	164	68	263	96	591
III	102	29	194	129	454
I–III	327	103	629	239	1298

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
* Cases restricted to women with known estrogen receptor and progesterone receptor status

further in Table 2 (the total number of deaths is fewer because estrogen receptor status was not available for all patients). Approximately one-half of the deaths avoided were among women over 50 with estrogen-receptor positive cancers. About one third of the deaths avoided were in young women (<50), who comprised 25% of the cohort. Approximately one-quarter of the deaths avoided were in women with estrogen receptor negative breast cancers, who comprised 20% of the cohort.

Discussion

SEER data for white women diagnosed with invasive breast cancer between 1975 and 2011 provide compelling evidence that deaths from breast cancer have declined significantly, despite a dramatic increase in the number of breast cancers diagnosed over the same period. The period of greatest decline was 1989–2009, which saw a fall in annual mortality from 33 per 100,000 women to 21 per 100,000 women. There was little evidence to suggest that the decline could be attributed to prevention or screening – there was no decline in the incidence of all cancers and only a small decline in advanced stage cancers – rather, the drop could be accounted for by declining case-fatality.

A large increase in the rate of early cancers, in the absence of a similar decline in the rate of advanced cancers, is an indicator of over-diagnosis. These data have been reviewed in more detail by Welch and Bleyer [8]. The trends in incidence do not support the position that screening greatly reduces breast cancer mortality, results consistent with those of the recent Canadian National Breast Screening study [19,20]. In that randomized trial, five annual mammography screens resulted in the identification of 212 non-palpable breast cancers, and an excess of 142 cancers in the screening group compared to the control group, but no reduction in the number of deaths from breast cancer (180 versus 171). Notably, fifteen years after the screening period stopped, the excess of cancers in the group assigned to screening persisted, pointing to overdiagnosis (criticisms of the study which have been numerous and are addressed in [21]).

Given that the number of early breast cancers nearly doubled in the USA from 1980 to 1998 (the period when mammography use was expanding) health promotion efforts based on advocating screening and breast cancer awareness have been highly successful in terms of finding more early cancers. The lack of a major decline in more advanced cancers, however, suggests that finding cancers when small is not enough to impact on mortality. It is possible that MRI screening will prevent cancer deaths [22–24], but the number of women who qualify for MRI screening at present is probably too small to have an impact on overall mortality rates.

These data suggest further that efforts directed toward the prevention of breast cancer have not yet had an impact on mortality. One must consider several possibilities; e.g. that a specific intervention is ineffective, that the risk factor to be avoided is rare or that the uptake of the prevention option is poor. However, more fundamentally, it is not necessarily the case that a program that results in fewer breast cancers will result in fewer cancer deaths. To date, studies on prevention have focused on cancer incidence and not on mortality because there are many more cases of cancer than deaths from cancer and for statistical reasons, incidence is easier to study. But in terms of prevention, not all cancers are equal; for example, a drug which prevents small ER-positive cancers is expected to have much less impact on mortality than a drug that prevents large ER-negative cancers. One would have to prevent 20 localized ER-positive cancers in order to prevent a single cancer death. Tamoxifen has been shown to prevent estrogen receptor-positive breast cancer [25,26], but to date, no study has shown that tamoxifen used in the preventive setting reduces breast cancer mortality [27]. This may be due to the statistical power of the studies, or tamoxifen may preferentially prevent those breast cancers which carry a favorable prognosis. The five-year survival of women with small, estrogen receptor positive, node-negative breast cancers is excellent (stage I: 98.4%; stage II: 94.9%); but these may recur for up to 20 years after diagnosis and the full impact of preventing these, in terms of reducing mortality may be delayed [28]. Aromatase inhibitors are an alternative to tamoxifen for preventing ER-positive breast cancers, but there are currently no chemopreventive agents which have been shown to prevent ER-negative breast cancers.

Two factors should be considered when examining stage distribution (and shift in stage distribution) over time. More intensive surveillance of health women and more sensitive imaging techniques after a diagnosis of breast cancer may cause stage shifts in either direction. More frequent screening, more women screened and more sensitive screening tests will increase the number of early breast cancers detected and increase the proportion of cancers that are detected at stage I. On the other hand, after a diagnosis of breast cancer, close scrutiny of lymph nodes for micro-metastases using molecular and immunohistochemical techniques will increase the number of women determined to have local spread. More and better imaging in the context of staging will lead to the detection of small metastases and an upward shift in stage for some patients. Of note, the CT scan came into routine use for staging in the 1980s. The sizes of these stage shifts are not expected to be large and are not possible to quantitate using the current data set.

Perhaps the single most relevant risk factor to consider when reviewing national cancer incidence trends is hormone replacement therapy [29–31]. The decline in the use of postmenopausal hormone therapy was followed rapidly by a short but steep decline in the incidence of postmenopausal breast cancer, but a commensurate decline in mortality is not seen, even if a lag time is taken into consideration (Fig. 16). The rapid decrease in the incidence of breast cancer following cessation of HRT suggests that many of the cancers that are 'prevented' are actually induced to regress; this is a characteristic of the least aggressive types of breast cancer (e.g. luminal A) i.e., those that are least likely to be fatal [32].

Over the last thirty years, through the study of dietary consumption patterns, migration patterns and cancer incidence it was supposed by many epidemiologists that nutrition played a key role

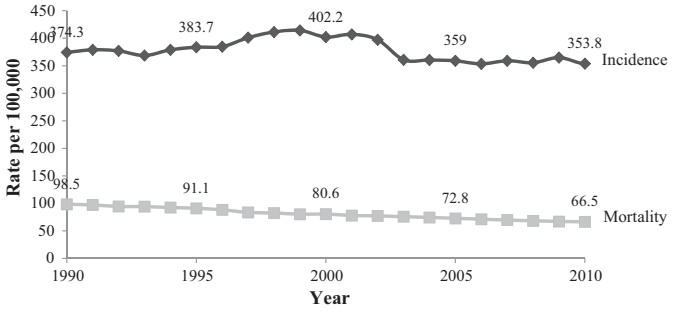

Fig. 16. Cancer incidence and mortality for women aged 50 and above, 40, 1990 to present. *Abbreviations*: SEER, Surveillance, Epidemiology and End Results.

in breast cancer etiology [33,34]. It followed that if a woman could be persuaded to change her diet, she could lower her risk of breast cancer. A 'healthy diet' was one that was low in fat and high in fruit and vegetables [35]. Several randomized trials and observational studies were conducted but these failed to confirm the hypothesis. Notable among these studies were the lack of cancer prevention associated with a low fat diet in a randomized controlled trial of dietary intervention for breast cancer prevention among Canadian women [36], the Nurses' Health Study [34], and the lack of impact of fruit and vegetables on breast cancer risk in the EPIC study [37]. Recently, a cohort study of circulating vitamin D levels in the Nurses' Health Study proved negative as well [38]. To a large extent, exercise and obesity, rather than diet per se have replaced the concept of a 'healthy' diet in the modern breast cancer advocacy movement [39]. Breast cancer advocates and funding agencies also hope to realize the goal of cancer prevention through control of environmental hazards such as toxic workplace exposures and low level radiation. In 2012, the National Academy of Sciences published a report entitled "Breast Cancer and the Environment, a Life Course approach" [40]. The principal recommendations were to avoid smoking (active and passive), to avoid alcohol, to avoid menopausal hormonal therapy and to avoid radiation and workplace chemicals. Smoking is not a proven breast cancer carcinogen [41] and the contribution of alcohol is modest and is limited to postmenopausal ER-positive breast cancers [42–44]. HRT is discussed above. The proportions of breast cancers attributable to radiation exposure or to workplace exposures in the United States are unknown but are undoubtedly very small and there is no reason to expect that control measures that pertain to a few percent of the population will have an impact on overall cancer mortality. In spite of mounting evidence that increasing awareness does not save lives, the EARLY act was passed in 2010 by the US Congress with the stated goals of educating and increasing breast cancer awareness among women younger than age 45 [45]. The legislators hope that through increasing awareness and educating young women about modifiable risk factors, they might promote (positive) behavioral change. Unfortunately, the underlying premise that we can prevent deaths from breast cancer risk by changing behavior is unproven and the incidence of advanced breast cancer has not decreased.

The observed reductions in mortality are consistent with the observed reductions in case-fatality. The decline in mortality from 1990 to 2001 was 27% for women under age 40, 34% for women aged 41–50 and was 20% for women age 50 and older. The corresponding decline in case fatality was 18% for women under age 40, was 25% for women aged 41–50 and was 24% for women age 50 and older. The use of survival as an indicator of treatment efficacy is more common than case-fatality, possibly because it connotes a positive message, but the term does not do justice to the progress that has been made since 1975. For example, a one percent increase in survival for women with localized breast cancer corresponds to a 30% reduction in case-fatality.

In aggregate, the data in this study indicate that the decline in mortality is attributable to a decline in case-fatality. For each stage and for each age group, the probability of a patient dying of her breast cancer has fallen. This decline cannot be attributable to shifting of patients from a higher stage to a lower stage. The greatest improvement in survival has been in women with regional disease.

Fig. 17 indicates that the period of greatest decline in case-fatality was after the introduction of CMF, and tamoxifen in 1970s [28,46,47]. The decline continued throughout the 1980s, possibly due to the addition of anthracyclines [48,49] and to the expansion of the number of patients treated with tamoxifen and chemotherapy. The 1990s saw the introduction of adjuvant taxanes [50]. Taxanes were introduced into adjuvant therapy in the mid-1990s and are now in widespread use. While effective, taxanes offer a relatively small marginal benefit over existing chemotherapy regimens. Since 2000, the most notable changes in therapy were the introduction of adjuvant trastuzumab [51] and of the aromatase inhibitors [52]. Trastuzamab was introduced as a treatment for patients with metastatic disease in 1998 and then became standard as adjuvant therapy for all women with Her2-positive cancer in 2005. The decline in case fatality continued, but the rate of decline did not appear to accelerate after the introduction of these drugs.

It is too early to speculate on the global impact these two adjuvant agents on cancer mortality or case fatality. A further possible cause of reduced case-fatality rates from the 1970s through the 1990s has been the increasing use radiation therapy. It has now been shown that regional radiotherapy reduces the rates of distant recurrence and death to a small extent [9,10].

The incidence of advanced stage breast cancer is relatively stable (Fig. 7). Similarly, the mean survival of patients from the time

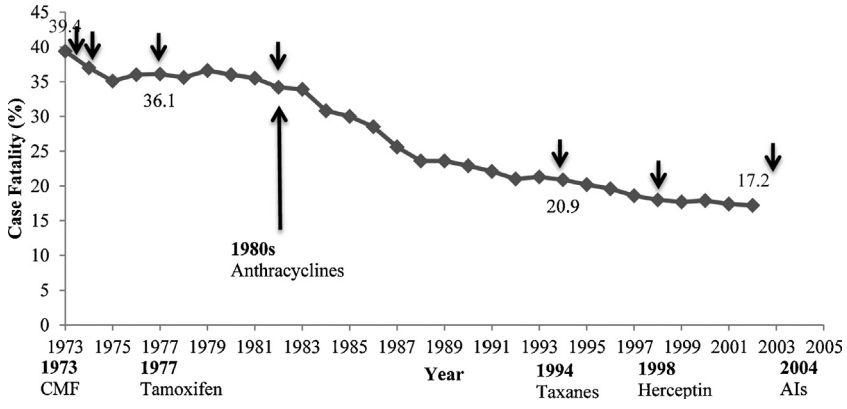

Fig. 17. 10-Year breast cancer case fatality and historical timeline of breast cancer chemotherapy.

of development of metastatic disease until death has not increased over this extended time period [53,54]. To some extent, this may be an unintended consequence of the better treatments, i.e. as case fatality decreases, fewer women will develop metastatic disease, but those who do experience a distant recurrence may have cancers with an unfavorable histologic/molecular profile and which are intrinsically aggressive.

It is perhaps not unexpected that the oldest drugs should have had the greatest impact. In general, CMF and anthracyclines were introduced in an era when the standard of care was no chemotherapy, whereas taxanes and other new therapies were introduced as an adjunct to other chemotherapies and the incremental benefit of a new drug versus a conventional drug appears smaller, compared to the incremental benefit of chemotherapy versus no chemotherapy. Currently a CMF or an anthracycline and/or taxane-based combination is recommended for most breast cancer patients. If we assume that all breast cancer patients with the exception of women with postmenopausal women with small ER-positive cancers are eligible for chemotherapy, then this comprises approximately 70% of all women diagnosed with breast cancer in 2009. In contrast, only about 15% of breast cancer patients are eligible for trastuzamab and the impact of trastuzamab on the total burden of mortality is therefore expected to be much smaller.

In this study, we have estimated the number of cancer deaths that were avoided because of the drop in case-fatality, by age of diagnosis, by stage and by ER-status (12 categories in total). The number of deaths avoided in a given category is determined by the relative proportion of breast cancers that fall into that category and the decline in five year case-fatality from 1990 to 2006. In this analysis we see that the total benefit is a composite of the benefits in all 12 categories combined and that each category contributes to the total. The largest number of deaths avoided was in the category of post-menopausal women with ER-positive stage II and stage III breast cancers; these women accounted for 27% of the cohort but for 35% of the lives saved. This is perhaps not surprising as these women are candidates for both tamoxifen and cytotoxic chemotherapy.

There are several limitations to our study. Stage was introduced in 1998 and therefore we do not have detailed information on stage for the entire cohort. As a consequence, our comparisons of deaths were based on five-year mortality and these statistics will underestimate the total number of deaths experienced in the cohort (and of deaths avoided). It is not clear if the distributions of death by age, stage and ER-status after five years are similar to the distributions in years one to five. In particular, it is expected that the proportion of women who are ER-positive will be higher among women who die in years five to fifteen than in years one to five. It will be important to readdress this cohort after five more years of follow-up so that most of the women who eventually die from their breast cancer will be identified. It is possible that the five-year rates will not reflect ultimate cure and it is important to readdress this cohort in five years. The most recent group of women studied here is that of women who were treated in 2003. It is too early to measure the impacts of drugs, such as trastuzamab, taxanes and the aromatase inhibitors on mortality in these women. Moreover, we did not have detailed information on the treatments received and our speculations regarding the underlying causes of the decline in mortality are based on summary statistics. Our conclusions regarding mammography are based on the incidence of localized and distant cancers and we do not have specific information regarding which cancers were palpable and/or detected by mammography. We restricted our analysis to white women for simplicity of analysis and it may be that the trends in African American or Asian women are different. The category of white women included Hispanics and non-Hispanics and we might have obscured relevant ethnic differences if they exist.

In conclusion, the data presented here suggest that the decline in case-fatality that became apparent in 1980 was followed by a prolonged decline in breast cancer mortality that began approximately 10 years later. The lack of a decline in advanced cancers in the face of an increase in localized cancers suggests that public health initiatives aimed at prevention and early detection, while highly successful in terms of implementing a stage shift, have not contributed to the decline in mortality. The observed decline in mortality is based to a large extent on drugs introduced in the 1970s and 1980s. The protracted decline in case fatality was likely due to incremental adjustments in the drug doses and duration (alone and in combination) as well as a gradual expansion in the number of women who were candidates to receive adjuvant hormonal and/or chemotherapy.

Conflict of interest statement

The authors declare no conflict of interest exists.

Acknowledgements

We thank Dr. Kathleen Pritchard and Dr. Jonas Bergh for review of the manuscript and helpful comments.

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