JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Declining Incidence of Contralateral Breast Cancer in the United States From 1975 to 2006

Hazel B. Nichols, Amy Berrington de González, James V. Lacey Jr, Philip S. Rosenberg, and William F. Anderson

A B S T R A C T

Purpose
Contralateral breast cancer (CBC) is the most frequent new malignancy among women diagnosed with a first breast cancer. Although temporal trends for first breast cancers have been well studied, trends for CBC are not so well established.

Patients and Methods
We examined temporal trends in CBC incidence using US Surveillance, Epidemiology, and End Results database (1975 to 2006). Data were stratified by estrogen receptor (ER) status of the first breast cancer for the available time period (1990+). We estimated the annual percent change (EAPC) in CBC rates using Poisson regression models adjusted for the age at and time since first breast cancer diagnosis.

Results
Before 1985, CBC incidence rates were stable (EAPC, 0.27% per year; 95% CI, −0.4 to 0.9), after which they declined with an EAPC of −3.07% per year (95% CI, −3.5 to −2.7). From 1990 forward, the declines were restricted to CBC after an ER-positive cancer (EAPC, −3.18%; 95% CI, −4.2 to −2.2) with no clear decreases after an ER-negative cancer. Estimated current age-specific CBC rates (per 100/year) after an ER-positive first cancer were: 0.45 for first cancers diagnosed before age 30 years and 0.25 to 0.37 for age 30 years or older. Rates after an ER-negative cancer were higher: 1.26 before age 30 years, 0.85 for age 30 to 35 years, and 0.45 to 0.65 for age 40 or older.

Conclusion
Results show a favorable decrease of 3% per year for CBC incidence in the United States since 1985. This overall trend was driven by declining CBC rates after an ER-positive cancer, possibly because of the widespread usage of adjuvant hormone therapies, after the results of the Nolvadex Adjuvant Trial Organisation were published in 1983, and/or other adjuvant treatments.

J Clin Oncol 29:1564-1569. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Because of advances in breast cancer detection and treatment, overall 5-year survival rates now approach 90%, and 10-year survival rates exceed 80%.[1] Research efforts are increasingly directed toward optimizing health surveillance and medical care delivery[2,3] for the more than 2.4 million US women living with a personal history of breast cancer.[4,5] Among breast cancer survivors, developing a new malignancy in the contralateral breast is the most frequent second-cancer event.[6]

Temporal trends in contralateral breast cancer (CBC) are not as well established as those for first breast cancers. Recent reports from cancer registries in the US and abroad have suggested potential declines in age-adjusted CBC incidence rates (IR) over the past 20 to 30 years.[7-9] Age-specific CBC IR are also debated as either constant (annual rate approximately 0.7 cases per 100[10,11]) or inversely associated with age.[7,8,12,13] These studies did not examine trends with respect to the estrogen receptor (ER) status of the first breast cancer, and also did not account for potential confounding by age at diagnosis of the first breast cancer, year of diagnosis, and time since diagnosis of the first breast cancer.

We examined CBC IR according to age at diagnosis and year of diagnosis of the first breast cancer with adjustment for time since diagnosis, using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database. SEER is one of the few large-scale and population-based cancer registries that routinely records breast cancer laterality and ER status for the assessment of contralateral tumors.

PATIENTS AND METHODS

Study Participants

Female invasive breast cancer case and population data were obtained from the SEER 9 Registries Database (SEER9, November 2008 submission), whose registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) covered approximately 10% of the US population (Fig 1). We excluded breast cancers diagnosed before age 25 years, or 85 years and older, because of under-reporting of second cancers among elderly patients,[14] and those based only on autopsy reports or death certificates. Of the 369,169 potentially eligible women diagnosed with a unilateral first breast cancer with known laterality between January 1, 1975, and December 31, 2005, and followed through December 31, 2006, we excluded another 26,165 women (7.1%) who had fewer than 12 months of follow-up, resulting in 343,004 breast cancers for analyses.

CBC was defined as an invasive second breast cancer diagnosed in the opposite breast 12 months or more after the first invasive breast cancer diagnosis. The first 12 months of follow-up were excluded to minimize the potential for misclassification of metastases or undetected synchronous bilateral breast cancer as CBC. Person-months were accrued from 12 months after the date of diagnosis of the first breast cancer until date of death, CBC, other second invasive malignancy, or administrative censoring on December 31, 2006. Overall 15,643 women had a second invasive breast cancer of which 12,886 were classified as a CBC based on our definition.

Demographic and tumor characteristics included year of diagnosis and age at diagnosis of the first breast cancer, attained age at diagnosis for CBC, and ER expression (positive, negative, or unknown) for the first breast cancer. ER status was not recorded by SEER until 1990. Method of ER detection was not reported by SEER, but would largely consist of immunohistochemical staining during this time period.

Statistical Methods

We used Poisson regression models to examine annual IR for CBC according to the year of diagnosis of the first breast cancer in continuous 1-year increments (YEAR). CBC IR were adjusted for age at the first breast cancer in 5-year age groups (ages 25 to 29, 30 to 34, …, 80 to 84 years with 50 to 54 years as the referent age) and time since first cancer diagnosis in continuous 1-year increments. To obtain flexible but smooth IR estimates, regression splines with knots were selected using Akaike's information criteria.[15] Our final model included a cubic function for year, a cubic function for age, and a linear term for latency. We also examined the CBC rates before and after 1985 to assess the impact of the widespread usage of adjuvant hormone therapies after the results of the Nolvadex Adjuvant Trial Organisation (NATO) in 1983.[16] We calculated the estimated annual percentage change (EAPC) in CBC rates as the antilog of the regression coefficient for YEAR minus 1 times 100 (ie, EAPC equals (exponential (YEAR) − 1) × 100). P values $\leq .05$ were considered to be statistically significant. We estimated average CBC rates and the corresponding variances for recently diagnosed women whose first breast cancer occurred between 2001 and 2005 using the delta method applied to the parameter estimates and variance-covariance matrix for the full model of the log rates.

RESULTS

From 1975 through 2006, there were 2,560,590 person-years contributed by 339,790 women with a first breast cancer (average follow-up, 7.5 years) and 12,886 (4%) of these women developed an invasive CBC (Fig 1 and Table 1). Approximately 40% of CBC diagnoses occurred within 1 to 4 years of the first breast cancer diagnosis, 30% between 5 and 9 years, and 30% 10 years or later. Overall 2,430 CBC diagnoses (19%) occurred among women with a first breast cancer diagnosed before age 45 years, 6,629 (51%) among women with a first breast cancer between 45 and 64 years, and 3,827 (30%) among women whose first breast cancer was diagnosed between 65 and 84 years of age.

For the time period where ER status was recorded (1990 forward), there were 1,173,505 person-years contributed by
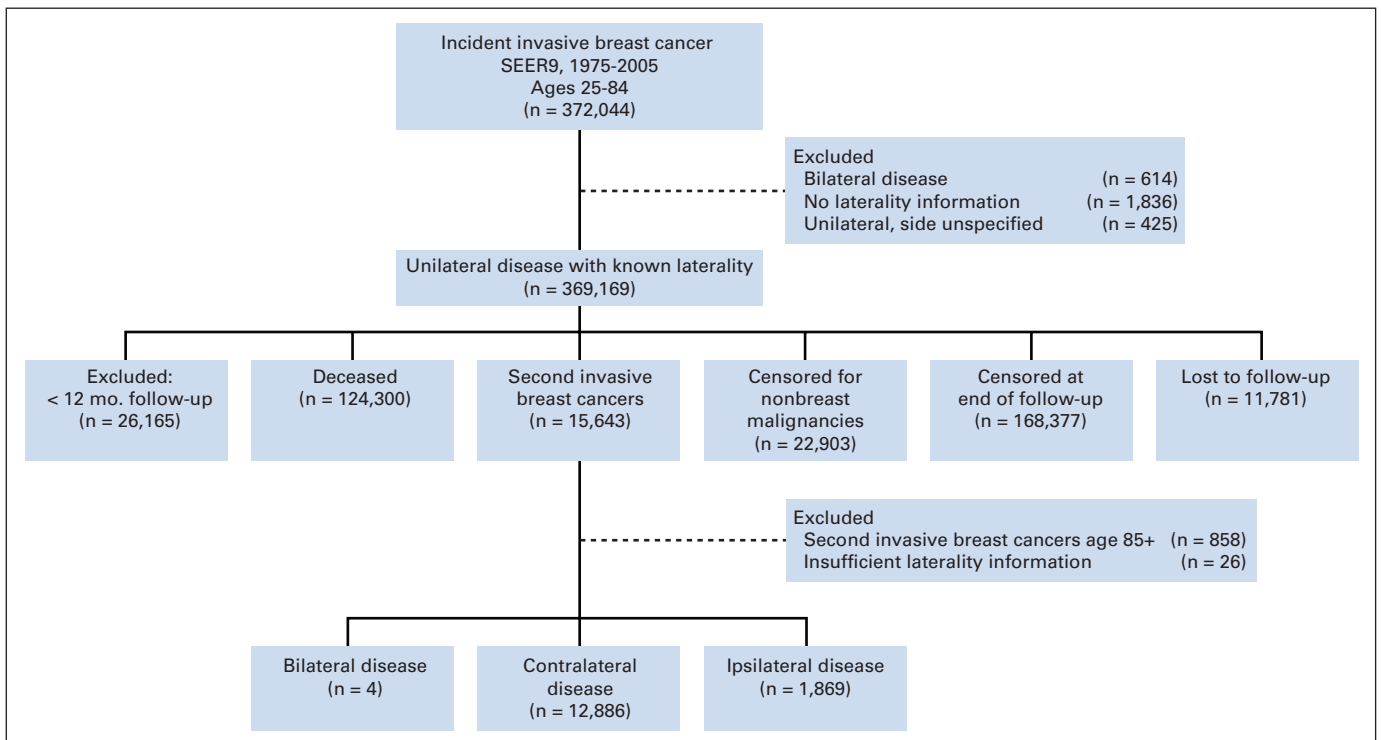

Fig 1. Identification of contralateral breast cancer cases in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 9 registries database (1975 to 2006; see Patients and Methods for details).

Table 1. Characteristics of First Primary and CBCs in the SEER9 Cancer Registries, 1975 to 2006

Characteristic	No. of First Primary Breast Cancers	No.of CBCs	% of Total CBCs	Person-Years
Total	339,790	12,886	100.0	2,560,590
Latency (time between diagnoses, months)				
12-59	NA	5,305	41.2	1,083,769
60-119	NA	3,980	30.9	784,293
120+	NA	3,601	27.9	692,528
Age, years				
First primary < 45	**53,096**	**2,430**	**18.9**	**488,108**
CBC < 45	NA	1,051	8.2	172,588
CBC 45-64	NA	1,333	10.3	304,695
CBC 65-84	NA	46	0.4	10,826
First primary 45-64	**160,680**	**6,629**	**51.4**	**1,365,229**
CBC 45-64	NA	3,623	28.1	817,780
CBC 65-84	NA	3,006	23.3	547,449
First primary 65-84	**126,014**	**3,827**	**29.7**	**707,253**
CBC 65-84	NA	3,827	29.7	707,253
Calendar period				
1975-1979	36,561	310	2.4	412,053
1980-1984	41,866	1,060	8.2	438,291
1985-1989	53,299	1,905	14.8	536,741
1990-1994	58,873	2,465	19.1	518,034
1995-1999	66,897	2,819	21.9	433,366
2000-2005*	82,294	4,327	33.6	222,105
ER status†				
First primary ER+	**135,901**	**2,998**	**59.4**	**752,852**
CBC ER+	NA	2,023	40.1	752,852
CBC ER−	NA	500	9.9	752,852
CBC Unknown	NA	475	9.4	752,852
First primary ER−	**40,722**	**1,182**	**23.4**	**219,826**
CBC ER+	NA	472	9.4	219,826
CBC ER−	NA	507	10.1	219,826
CBC unknown	NA	203	4.0	219,826
First primary ER unknown	**31,441**	**864**	**17.1**	**200,827**
CBC ER+	NA	472	9.4	200,827
CBC ER−	NA	203	4.0	200,827
CBC Unknown	NA	189	3.7	200,827

NOTE. Bold font indicates total of numbers listed below.
Abbreviations: CBC, contralateral breast cancer; SEER, Surveillance, Epidemiology, and End Results; NA, not available; ER, estrogen receptor.
*Includes CBC diagnosed through December 31, 2006.
†ER status information is restricted to the 5,044 cases of CBC diagnosed after 1990.

208,064 women with a first invasive breast cancer and 5,044 invasive CBC events. Approximately 60% of the CBC diagnoses were among women whose first breast cancer was ER positive, 24% among women with a first ER-negative breast cancer, and 17% among first breast cancers with unknown ER status. Of the 2,998 CBC diagnoses after an ER-positive first breast cancer, 2,023 (67%) were concordant for an ER-positive second breast cancer. CBCs after an ER-negative first breast cancer (n = 1,182) had similar proportions of ER-positive (40%) and ER-negative (43%) tumors.

Temporal Trends in CBC Incidence

Overall, the CBC rates declined with an EAPC of −1.77% per year (95% CI, −1.95 to −1.55) from 1975 to 2006, after adjustment for age at first breast cancer diagnosis and time since the first breast cancer diagnosis. However, when we examined CBC rates before and after 1985 (Fig 2A), CBC incidence was stable from 1975 to 1985 with an EAPC of 0.27% per year (95% CI, −0.4 to 0.9) but declined after 1985 with an EAPC of −3.07% per year (95% CI,

−3.5 to −2.7). This drop in CBC incidence after 1985 reflected an absolute decline in rates per 100 woman years from 0.57 (95% CI, 0.5 to 0.6) for cancers diagnosed in 1985 to 0.26 (95% CI, 0.2 to 0.3) for cancers diagnosed in 2005. The greatest percentage changes for CBC were observed during the first 1 to 4 years after first breast cancer diagnosis (EAPC, −2.32% per year; 95% CI, −2.6 to −2.0). This downward trend was somewhat attenuated with increasing time since diagnosis: −1.32% per year 5 to 9 years (95% CI, −1.8 to −0.9) and −1.59% (95% CI, −2.2 to −1.0) per year 10 years or more after the first breast cancer diagnosis.

For women whose first breast cancer was ER positive, the estimated EAPC from 1990 through 2005 was −3.18% per year (95% CI, −4.2 to −2.2; Fig 2B). Among women whose first breast cancer was ER negative, there was a marginally significant rise of 1.68% per year (95% CI, 0.0 to 3.4), although the pattern was nonlinear and estimates were less precise due to the smaller sample size. For CBC that was diagnosed during the period 1 to 4 years after an ER-positive first breast cancer, EAPC was −3.71% per year (95% CI, −4.9 to −2.5).
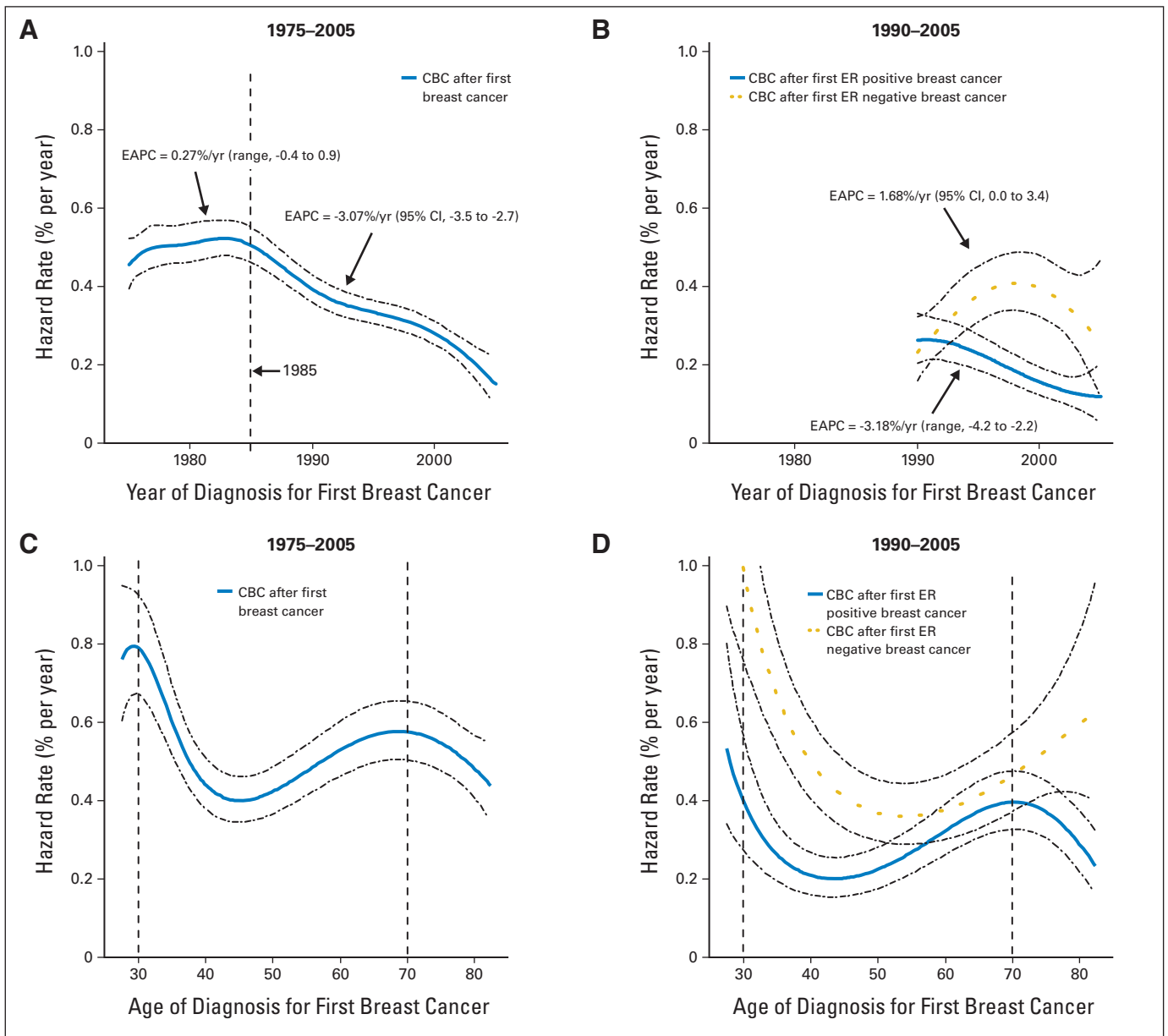
Fig 2. Annual hazard rates for contralateral breast cancer (CBC) over time and across age from 1975 to 2005 after a first breast cancer (A,C). Annual hazard rates for CBC over time and across age from 1990 to 2005 after a first estrogen receptor (ER) –positive or first ER-negative breast cancer (B, D). Estimated annual percentage change (EAPC) is the EAPC in the hazard rates per year of calendar-time.

Age-Specific IR for CBC

Age-specific rates for CBC overall were not constant but instead showed early and late incidence peaks near ages 30 and 70 years, respectively (Fig 2C). CBC IR per 100 woman-years were 0.81 (95% CI, 0.7 to 0.9), 0.48 (95% CI, 0.4 to 0.5), and 0.63 (95% CI, 0.6 to 0.7) near ages 30, 45, and 70 years, respectively. The overall 22% decline in CBC rates from age 30 to 70 corresponds to a 0.5% drop in incidence with each yearly increase of age at the first breast cancer diagnosis. A similar bimodal pattern was observed after an ER-positive but not ER-negative breast cancer (Fig 2D).

The age-specific rates shown in Figure 2 are averaged across all time periods. Estimated current CBC rates (per 100/year) after first breast cancers diagnosed between 2001 and 2005 are presented in

Table 2. Estimated current CBC rates after an ER-positive cancer were: 0.45 for diagnoses before age 30 years and 0.25 to 0.37 for diagnoses at age 30 years or older (Table 2). Rates after an ER-negative cancer were higher: 1.26 before age 30 years, 0.85 at age 30 to 35 years, and 0.45 to 0.64 for diagnoses at age 40 or older.

Sensitivity Analyses

EAPC for CBC was attenuated but not altered qualitatively if the CBC was expanded to include in situ tumors (EAPC, −1.30% per year; 95% CI, −1.5 to −1.1). Results also did not change materially if the cutoff period for CBC was reduced from 12 to 6 months (EAPC, −1.92% per year; 95% CI, −2.2 to −1.7) or expanded from 12 to 24 months (EAPC, −1.79% per year; 95% CI, −2.1 to −1.5) after the

Table 2. Estimated* Annual Contralateral Breast Cancer Incidence Rates (per 100/year) for First Breast Cancers Diagnosed Between 2001 and 2005: According to Age at First Breast Cancer Diagnosis and ER Status of the First Breast Cancer

Age at Diagnosis for First Breast Cancer (years)	ER-Positive First Cancer		ER-Negative First Cancer	
	Per 100/Year	95% CI	Per 100/Year	95% CI
25-29	0.45	0.30 to 0.60	1.26	0.88 to 1.64
30-34	0.31	0.25 to 0.37	0.85	0.68 to 1.02
35-39	0.25	0.22 to 0.29	0.64	0.53 to 0.74
40-45	0.24	0.21 to 0.26	0.53	0.44 to 0.61
45-49	0.24	0.22 to 0.27	0.47	0.39 to 0.54
50-54	0.26	0.24 to 0.29	0.45	0.38 to 0.52
55-59	0.30	0.27 to 0.33	0.45	0.38 to 0.52
60-64	0.34	0.30 to 0.37	0.47	0.39 to 0.55
65-69	0.36	0.32 to 0.40	0.51	0.42 to 0.59
70-74	0.37	0.33 to 0.41	0.55	0.45 to 0.64
75-79	0.33	0.29 to 0.38	0.60	0.47 to 0.73
80-84	0.26	0.21 to 0.32	0.63	0.40 to 0.86

Abbreviation: ER, estrogen receptor.
*Estimated using the Poisson regression model with adjustment for time since first breast cancer diagnosis.

first breast cancer. CBC incidence rates also were not impacted by changing the adjustment for time since diagnosis of the first breast cancer from continuous 1-year increments to three categorical cut points (1 to 4, 5 to 9, and 10+ years). CBC trend after a first breast cancer with unknown ER expression fell between rates after ER-negative and ER-positive first breast cancers (EAPC, −1.68; 95% CI, −3.7 to 0.3).

DISCUSSION

Our analysis shows a favorable temporal trend in CBC IR since 1985, a time period that corresponds to the widespread uptake of tamoxifen adjuvant therapy in the US after the results of the NATO trial in 1983.[16,17] Moreover, CBC rates fell more than 3% per year after a first ER-positive breast cancer. There was no significant decrease in CBC incidence after a first ER-negative breast cancer.

Notably, CBC rates varied according to age at the first breast cancer diagnosis, demonstrating a bimodal pattern overall after a first ER-positive breast cancer with an overall decline in the rates of about 0.5% with each yearly increase in age. Early and late peak incidence rates for CBC near ages 30 and 70 years contrasted somewhat with the bimodal peaks for primary breast cancer near ages 50 and 70 years.[18] These results are in agreement with recent registry-based reports in the US and Europe[7,8,12,13] and disagree with earlier reports of a constant incidence rate of CBC of approximately 0.5% to 1% per year.[10,11,19]

Our results support and extend the previous analysis by Bernstein et al,[7] which also found a downward temporal trend in CBC incidence in the US during 1984 to 1998. The current analysis expanded the follow-up by 8 years (through 2006) and included an examination of variation according to ER status for first breast cancers. A 30% decline in CBC incidence between 1980 and 2000 was also reported in Sweden,[8] and preliminary data suggests an annual 3.5% decline in CBC during 1990 to 2001 in the California Cancer Registry[9] (only part of that registry, San Francisco and Oakland, was included in the current analysis).

Our findings disagree with the interpretation by Kurian et al[20] that there were no clear trends in CBC by hormone receptor status

and calendar year from 1992 to 2004 in the SEER data. They did find some evidence of a decrease during the 1990s after a hormone receptor–positive cancer diagnosed age 50+, but the trend did not clearly continue into 2000 to 2004. There were two important differences in our methodologic approach that might explain the discrepancy. Firstly, we examined the patterns by year of the first cancer diagnosis rather than by the year of the CBC diagnosis, which was used by Kurian et al. We used the year of diagnosis of the first cancer as a proxy for treatment that has greater clinical utility. Furthermore, we examined trends in the IR, whereas Kurian et al analyzed the changes in the standard incidence ratios (ie, the patterns in the second cancer rates in relation to the patterns in the breast cancer rates in the general population). Other more minor differences include their use of 2 rather than 12 months as the cutoff period for CBC and use of progesterone receptor status also to define hormone receptor positive cancers.

In the Early Breast Cancer Trialists' Collaborative Group's analysis of 12 randomized trials, use of tamoxifen for approximately 5 years reduced CBC risk by 39% (95% CI, 0.27% to 0.50%) among women with ER-positive or ER-unknown breast cancer.[21] Tamoxifen use was widely adopted in the US during the late 1980s after the NATO trial.[16] Patterns of use are complicated though as they depend on age and stage at diagnosis as well as ER status and use is also correlated with receipt of chemotherapy,[17,22] which can also prevent CBC if used premenopausally.[16] Furthermore, in the early 2000s, use of aromatase inhibitors (AI) increased as results from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial became available.[23] Reports from the ATAC trial[24] and others[25-27] indicate 32% to 43% reductions in CBC incidence with primary, sequential, or extended AI treatment strategies compared to tamoxifen. All of these factors make it difficult to formally assess the correlation between hormone therapy trends and CBC IR. Nevertheless, the fact that the strongest declines in CBC incidence rates were within the first 5 years after diagnosis of an ER-positive tumor is consistent with current practice guidelines for 5 years of adjuvant endocrine therapy with tamoxifen and/or AIs after an incident ER-positive breast cancer.[28,29] Long-term follow-up of the randomized trials shows that the period of greatest tamoxifen efficacy

is during current use, although benefits continue at least up to 10 years.[21]

As well as adjuvant hormone therapies and chemotherapy, other factors, such as mammography screening and/or postmenopausal hormone-replacement therapy, may also have contributed to declining CBC trends, if they detect and/or promote indolent tumors less likely to be associated with CBC. Bernstein et al,[7] however, found similar CBC rates after in situ and invasive first cancers.

Our study has the usual limitations of descriptive epidemiology with retrospective analysis, missing data, lack of individual-level risk factors, and nonstandardized definitions. Nonetheless, SEER's large-scale and population-based design, long-term follow-up, breast cancer laterality, and ER status provided a unique opportunity to assess temporal trends for CBC. Another major strength of the study was that CBC IR were examined according to age at and year of diagnosis of the first breast cancer with adjustment for potential confounding by time since diagnosis of the first breast cancer. Details of hormone treatment were not available in SEER, but our annual percentage declines of higher than 3% after ER-positive first cancers suggest an important role for the widespread usage of adjuvant therapies, especially hormone treatments.

In summary, our results show a favorable decrease in the order of 3% per year for CBC incidence in the US since 1985. This overall trend was largely driven by declining CBC rates after an ER-positive first breast cancer, possibly due to the widespread usage of adjuvant hormone therapies. Although this decline represents a notable success, CBC rates overall remain high especially after a first ER-negative breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Hazel B. Nichols, Amy Berrington de González, Philip S. Rosenberg, William F. Anderson
Collection and assembly of data: Hazel B. Nichols, Amy Berrington de González, William F. Anderson
Data analysis and interpretation: Hazel B. Nichols, Amy Berrington de González, James V. Lacey Jr, Philip S. Rosenberg, William F. Anderson
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. American Cancer Society: Cancer Facts & Figures 2009. Atlanta, GA, American Cancer Society, 2009

2. Snyder CF, Frick KD, Kantsiper ME, et al: Prevention, screening, and surveillance care for breast cancer survivors compared with controls: Changes from 1998 to 2002. J Clin Oncol 27:1054-1061, 2009

3. Snyder CF, Frick KD, Peairs KS, et al: Comparing care for breast cancer survivors to non-cancer controls: A five-year longitudinal study. J Gen Intern Med 24:469-474, 2009

4. De Angelis R, Tavilla A, Verdecchia A, et al: Breast cancer survivors in the United States: Geographic variability and time trends, 2005-2015. Cancer 115:1954-1966, 2009

5. American Cancer Society: Breast Cancer Facts & Figures 2007-2008. Atlanta, GA, American Cancer Society, 2009

6. Curtis RE, Freedman DM, Ron E, et al: New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD, National Cancer Institute, 2006

7. Bernstein JL, Lapinski RH, Thakore SS, et al: The descriptive epidemiology of second primary breast cancer. Epidemiology 14:552-558, 2003

8. Hartman M, Czene K, Reilly M, et al: Incidence and prognosis of synchronous and metachronous bilateral breast cancer. J Clin Oncol 25:4210-4216, 2007

9. Marshall SF, Ziogas A, Castaneda J, et al: Changing incidence of second primary breast cancer in California. Am J Epidemiol 169:S4, 2009

10. Rosen PP, Groshen S, Kinne DW, et al: Contralateral breast carcinoma: An assessment of risk and prognosis in stage I (T1N0M0) and stage II (T1N1M0) patients with 20-year follow-up. Surgery 106:904-910, 1989

11. Peto J, Mack TM: High constant incidence in twins and other relatives of women with breast cancer. Nat Genet 26:411-414, 2000

12. Vaittinen P, Hemminki K: Risk factors and age-incidence relationships for contralateral breast cancer. Int J Cancer 88:998-1002, 2000

13. Bertelsen L, Mellemkjaer L, Christensen J, et al: Age-specific incidence of breast cancer in breast cancer survivors and their first-degree relatives. Epidemiology 20:175-180, 2009

14. Fraumeni JF, Curtis RE, Edwards BK, et al: Introduction, New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD, National Cancer Institute, 2006

15. Rosenberg PS, Katki H, Swanson CA, et al: Quantifying epidemiologic risk factors using non-parametric regression: Model selection remains the greatest challenge. Stat Med 22:3369-3381, 2003

16. NATO: Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer: Interim analysis at four years by Nolvadex Adjuvant Trial Organisation. Lancet 1:257-261, 1983

17. Mariotto A, Feuer EJ, Harlan LC, et al: Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999. J Natl Cancer Inst 94:1626-1634, 2002

18. Anderson WF, Jatoi I, Sherman ME: Qualitative age interactions in breast cancer studies: Mind the gap. J Clin Oncol 27:5308-5311, 2009

19. Healey EA, Cook EF, Orav EJ, et al: Contralateral breast cancer: Clinical characteristics and impact on prognosis. J Clin Oncol 11:1545-1552, 1993

20. Kurian AW, McClure LA, John EM, et al: Second primary breast cancer occurrence according to hormone receptor status. J Natl Cancer Inst 101:1058-1065, 2009

21. Early Breast Cancer Trialists' Collaborative Group: Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365:1687-1717, 2005

22. Jordan VC, Morrow M: Re: Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999. J Natl Cancer Inst 95:683-684, 2003; author reply 684-5

23. Svahn TH, Niland JC, Carlson RW, et al: Predictors and temporal trends of adjuvant aromatase inhibitor use in breast cancer. J Natl Compr Canc Netw 7:115-121, 2009

24. Forbes JF, Cuzick J, Buzdar A, et al: Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 9:45-53, 2008

25. Coombes RC, Kilburn LS, Snowdon CF, et al: Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): A randomised controlled trial. Lancet 369:559-570, 2007

26. Ingle JN, Tu D, Pater JL, et al: Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA. 17. Ann Oncol 19:877-882, 2008

27. Jakesz R, Greil R, Gnant M, et al: Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: Results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 99:1845-1853, 2007

28. Burstein HJ, Prestrud AA, Seidenfeld J, et al: American society of clinical oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 28:3784-3796, 2010

29. National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology: Breast Cancer. National Comprehensive Cancer Network, 2009