

Incident Malignancies Among Older Long-Term Breast Cancer Survivors and an Age-Matched and Site-Matched Nonbreast Cancer Comparison Group Over 10 Years of Follow-Up

Kerri M. Clough-Gorr, DSc, MPH^{1,2,3}; Soe Soe Thwin, PhD, MS^{2,4}; Jaclyn L. F. Bosco, PhD, MPH^{2,5}; Rebecca A. Silliman, MD, PhD^{2,6}; Diana S. M. Buist, PhD⁷; Pamala A. Pawloski, PharmD⁸; Virginia P. Quinn, PhD⁹; and Marianne N. Prout, MD, MPH⁶

BACKGROUND: Of the approximately 2.4 million American women with a history of breast cancer, 43% are aged ≥ 65 years and are at risk for developing subsequent malignancies. **METHODS:** Women from 6 geographically diverse sites included 5-year breast cancer survivors (N = 1361) who were diagnosed between 1990 and 1994 at age ≥ 65 years with stage I or II disease and a comparison group of women without breast cancer (N = 1361). Women in the comparison group were age-matched and site-matched to breast cancer survivors on the date of breast cancer diagnosis. Follow-up began 5 years after the index date (survivor diagnosis date or comparison enrollment date) until death, disenrollment, or through 15 years after the index date. Data were collected from medical records and electronic sources (cancer registry, administrative, clinical, National Death Index). Analyses included descriptive statistics, crude incidence rates, and Cox proportional hazards regression models for estimating the risk of incident malignancy and were adjusted for death as a competing risk. **RESULTS:** Survivors and women in the comparison group were similar: $>82\%$ were white, 55% had a Charlson Comorbidity Index of 0, and $\geq 73\%$ had a body mass index ≤ 30 kg/m². Of all 306 women (N = 160 in the survivor group, N = 146 in the comparison group) who developed a first incident malignancy during follow-up, the mean time to malignancy was similar (4.37 ± 2.81 years vs 4.03 ± 2.76 years, respectively; $P = .28$), whereas unadjusted incidence rates were slightly higher in survivors (1882 vs 1620 per 100,000 person years). The adjusted hazard of developing a first incident malignancy was slightly elevated in survivors in relation to women in the comparison group, but it was not statistically significant (hazard ratio, 1.17; 95% confidence interval, 0.94-1.47). **CONCLUSIONS:** Older women who survived 5 years after an early stage breast cancer diagnosis were not at an elevated risk for developing subsequent incident malignancies up to 15 years after their breast cancer diagnosis. *Cancer* 2013;119:1478-85. © 2012 American Cancer Society.

KEYWORDS: breast cancer, breast cancer survivors, incident malignancies, malignancy, multiple primary malignancies, older women, survivors.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer in American women, with an estimated 230,480 new cases of invasive breast cancer in 2011 and 50% of cases diagnosed in women aged ≥ 61 years.¹ Relative survival rates for women diagnosed with breast cancer in the United States are 89% 5 years after diagnosis, 82% after 10 years, and 77% after 15 years.¹ Thus, the vast majority of women with breast cancer will become long-term survivors and are at risk for developing subsequent malignancies. There are approximately 2.4 million women in the United States with a history of breast cancer, and 1 million of those women (43%) are aged ≥ 65 years.^{2,3} This group of older breast cancer survivors represents 17% of all older cancer survivors, yet their long-term survivorship has not been well studied.

One of the most serious events experienced by cancer survivors is the diagnosis of a new malignancy, but the epidemiology of new malignancies in older long-term cancer survivors is poorly understood. The risk of developing subsequent malignancies after an initial cancer diagnosis varies from 1% to 16%, depending on the primary cancer site.⁴ Breast cancer survivors represent 1 of the largest groups of survivors with subsequent malignancies, and the most common are

Corresponding author: Kerri M. Clough-Gorr, DSc, MPH, Boston Medical Center, 88 East Newton Street, Robinson 2, Boston, MA 02118; Fax: (617) 638-8387; kmclough@bu.edu

¹Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; ²Section of Geriatrics, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts; ³National Institute for Cancer Epidemiology and Registration, Zurich, Switzerland; ⁴Massachusetts Veterans Epidemiology Research and Information Center, Veterans Affairs Healthcare System, Boston, Massachusetts; ⁵Dana-Farber Cancer Institute, Boston, Massachusetts; ⁶Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts; ⁷Group Health Research Institute, Seattle, Washington; ⁸HealthPartners Research Foundation, Bloomington, Minnesota; ⁹Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California

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contralateral breast cancers.⁵ Yet it is unclear whether long-term breast cancer survivors are at increased risk of incident malignancies compared with their age-matched counterparts without a prior breast cancer diagnosis.

Subsequent incident malignancies may reflect late sequelae of treatment as well as the effects of aging, lifestyle factors, environmental exposures, host factors, and combinations of influences, including gene-environment and gene-gene interactions.^{6,7} The majority of studies of incident malignancies in breast cancer survivors have focused on treatment as a risk factor and on contralateral breast cancer.⁸⁻¹³ Especially lacking are comparisons with older women without breast cancer. This information is important for helping women and their providers with clinical decision-making about priorities for surveillance for other cancers beyond their initial breast cancer. However, it is equally important in helping clinicians decide whether they should consider a different surveillance approach for older breast cancer survivors than that for older women in general. The objective of the current study was to examine incident malignancies in a cohort of older long-term (5-year) breast cancer survivors and a matched comparison group of women without a breast cancer diagnosis over 10 years of follow-up.

MATERIALS AND METHODS

The protocol for this study was reviewed and approved by the institutional review boards at each participating health care site and at the Boston University Medical Campus. The study was conducted in compliance with all federal regulations governing the protection and privacy of human subjects.

Data Collection

Demographic, health-related, breast cancer-related, history of cancer, incident malignancies, and follow-up for mortality variables were collected from medical records and electronic sources (cancer registry, administrative and clinical records, and National Death Index). Standardized medical record reviews were conducted by trained medical record abstractors, and data were entered directly into a computer-based, menu-driven data-collection system.¹⁴

Study Population

We conducted a longitudinal cohort study of women (total study population, $N = 2722$) who received care in 1 of 6 Health Maintenance Organization Cancer Research Network-integrated health care sites: Group Health Cooperative, Western Washington; Kaiser Permanente Southern California; Lovelace Health System, New Mexico; Henry Ford Hospital and Health System, Michigan;

HealthPartners, Minnesota; and Reliant Medical Group, Massachusetts. These 6 sites were chosen to achieve diversity in geography, system size, and patient populations while maintaining study feasibility. Four of the 6 Cancer Research Network sites collected cancer data for the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, and 2 collected cancer data for state cancer registries. Long-term breast cancer survivors (the survivor cohort; $N = 1361$) included women diagnosed with early stage breast cancer (TNM stage I, IIA, or IIB) between January 1, 1990 and December 31, 1994 who survived for 5 years. Women for the nonbreast cancer comparison cohort ($N = 1361$) were selected from the source population and were matched (1:1) on breast cancer survivors' age at initial breast cancer diagnosis and site. We defined the index date as either the date of a survivor's initial breast cancer diagnosis or the date of a matched comparison woman's enrollment. To be eligible for the study, both 5-year breast cancer survivors and matched comparison women had to be cancer-free (ie, no invasive malignant cancer diagnosis) during the period from 1 to 5 years before the (pre-)index date. Study follow-up began 5 years after the (post-)index date and continued until death, disenrollment, or through 10 years of follow-up (6-15 years postindex date) (see Fig. 1).

Analytic Variables

Breast cancer characteristics were collected at the time of diagnosis. Demographic and health-related variables were collected at 5 years postindex date.

Demographic characteristics

We gathered information on each woman's age (for groups ages 70-74 years, 75-79 years, and ≥ 80 years), race, and ethnicity. We classified race/ethnicity (white non-Hispanic, African-American, Asian, Hispanic) at all sites using the SEER coding instructions for consistency.¹⁵ We recategorized race as white versus other for modeling.

Health-related characteristics

At 5 years after the index date, we collected information on comorbid conditions to calculate the Charlson Comorbidity Index (CCI)¹⁶ modified to exclude initial breast cancer, plus body mass index (BMI) in kg/m^2 ($\text{BMI} < 25 \text{ kg}/\text{m}^2$, $25\text{-}29 \text{ kg}/\text{m}^2$, and $\geq 30 \text{ kg}/\text{m}^2$) and smoking history (never, current, former).

History of cancer before the start of follow-up

Information on invasive malignancies that occurred before the start of study follow-up was divided into 3

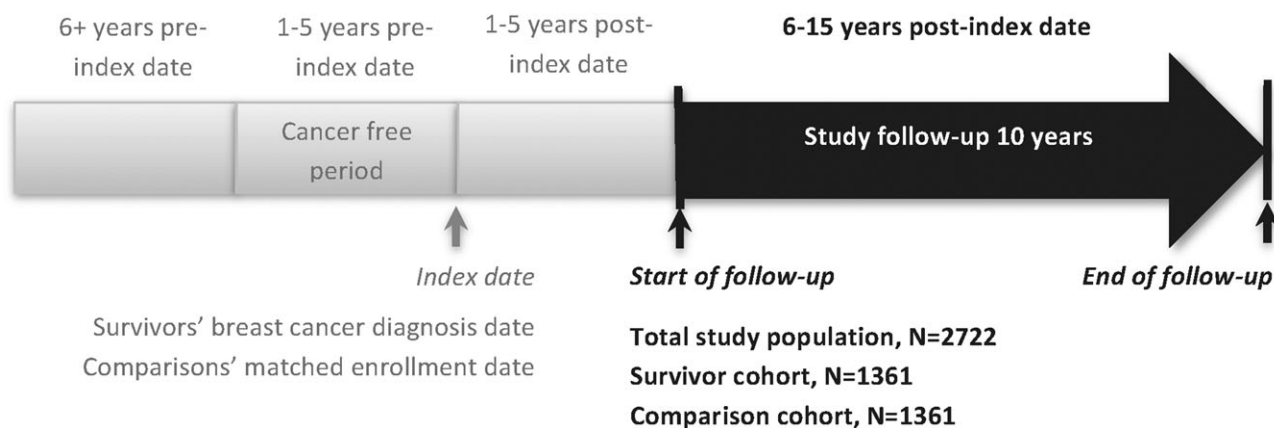


Figure 1. The study timeline is illustrated.

periods (see Fig. 1). Data were collected for the periods >5 years preindex date (history of cancer, yes/no) and 1 to 5 years postindex date (date of diagnosis, cancer type, and stage). Because of eligibility criteria, all women had to be cancer-free for 1 to 5 years before the index date.

Incident malignancies that occurred during follow-up

We recorded all incident invasive malignancies that were diagnosed over 10 years of study follow-up (6-15 years postindex date). Incident malignancy variables included date of diagnosis, mean time to diagnosis, number of incident malignancies (ie, first incident malignancy, >1 incident malignancy), type of malignancy (breast, lung, colorectal, melanoma skin, lymphoma/leukemia, gynecologic, or other cancer), and SEER stage (local, regional, distant, unstaged).¹⁵ All breast cancers that occurred during follow-up on the same side as the breast cancer survivors' primary cancer (ie, ipsilateral events) were classified as recurrences.

Analytic Methods

We examined the descriptive characteristics in the total population and compared the distributions between the survivor and comparison cohorts using the Student *t* test for continuous variables and the chi-square test for categorical variables to test for statistically significant differences. Rates of incident malignancy were calculated in the total study population and in each cohort as crude measures by summing the number of incident malignancies per cohort and dividing by the total number of person-years (PY) contributed by women in the total population and in each cohort; these were converted to estimates per 100,000 PY. Women who remained alive

were censored at the date of first incident malignancy, disenrollment, or end of follow-up, whichever occurred first. Variables with missing values for >5% of women were missing similarly in both cohorts and, thus, were assumed to be missing at random. Unadjusted and multivariable adjusted Cox proportional hazards regression models were fitted adjusting for death as a competing risk to estimate the risk of incident malignancy as a hazard ratio (HR) with 95% confidence interval (CI) in long-term breast cancer survivors relative to the matched comparison cohort.^{17,18} Model selection was based on 2 criteria: 1) a theoretical basis for, or knowledge of, a relation between causal variables and effects, and 2) statistical testing (ie, elimination of highly correlated variables, inclusion of a necessary minimum set of statistically meaningful variables, and overall model fit).¹⁹ A matched analysis was conducted (ie, age and site were included in models) to control for residual confounding.

In addition, because study inclusion criteria allowed a history of cancer during the first 5 years of survival (1-5 years postindex date) we conducted 2 sets of sensitivity analyses to explore its potential effects. First, we excluded all women (in the survivor cohort or the comparison cohort) who had a history of cancer in years 1 to 5 after the index date (N = 143). Second, we excluded any matched comparison and survivor pair in which 1 woman or both women had a history of cancer 1 to 5 years after the index date (N = 278). Finally, in a sensitivity analysis to explore the effect of potential differences in outcome data, we re-evaluated results excluding non-SEER sites (N = 322). All analyses were performed using SAS software (version 9.2; SAS Institute, Inc., Cary, NC), and all *P* values were from 2-sided tests.²⁰

TABLE 1. Characteristics of the Total Study Population and the Survivor and Comparison Cohorts 5 Years After the Index Date^a

| Characteristic | No. of Women (%) | | | <i>P</i> ^b |
|----------------------------|-------------------------------|------------------------------|--------------------------------|-----------------------|
| | Total Population, N = 2722 | Survivor Cohort, N = 1361 | Comparison Cohort, N = 1361 | |
| Age group, y ^c | | | | |
| 70-74 | 1004 (37) | 502 (37) | 502 (37) | 1.0 |
| 75-79 | 834 (31) | 417 (31) | 417 (31) | |
| ≥80 | 884 (32) | 442 (32) | 442 (32) | |
| Race/ethnicity | | | | |
| White non-Hispanic | 2276 (84) | 1115 (82) | 1161 (85) | .05 ^d |
| African American | 262 (9.6) | 137 (10) | 125 (9.2) | |
| Asian | 64 (2.4) | 37 (2.7) | 27 (2) | |
| Hispanic | 120 (4.4) | 72 (5.3) | 48 (3.5) | |
| Charlson Comorbidity Index | | | | |
| 0 | 1528 (56) | 757 (56) | 771 (57) | .82 |
| 1 | 977 (36) | 492 (36) | 485 (36) | |
| ≥2 | 217 (8) | 112 (8) | 105 (8) | |
| BMI, kg/m ² | | | | |
| <25 | 861 (40) | 414 (38) | 447 (42) | .08 |
| 25-29 | 754 (35) | 377 (35) | 377 (35) | |
| ≥30 | 536 (25) | 291 (27) | 245 (23) | |
| Missing | 571 | 279 | 292 | |
| Smoking status | | | | |
| Never | 731 (27) | 363 (27) | 368 (27) | .67 |
| Current | 166 (6.1) | 77 (5.7) | 89 (6.5) | |
| Former | 1674 (62) | 849 (62) | 825 (61) | |
| No mention or missing | 151 (5.6) | 72 (5.3) | 79 (5.8) | |

Abbreviations: BMI, body mass index; y, years.

^aThe index date was either the date of the survivor's diagnosis or the date of the matched comparison woman's enrollment.

^b*P* values reflect differences between long-term breast cancer survivors and the nonbreast cancer comparison cohort.

^cSurvivors and members of the comparison group were age-matched.

^dWhites were compared with nonwhites.

RESULTS

Population Characteristics

Table 1 lists the characteristics of the total study population, the long-term breast cancer survivor cohort, and the matched comparison cohort at the beginning of study follow-up (5 years postindex date). Approximately 1/3 of the total study population was in each age category. The survivor and comparison cohorts had very similar characteristics. The majority of both survivors and comparison women were white (>82%), had a CCI of 0 (55%), and had a BMI ≤30 kg/m² (≥73%). Greater than 61% of women reported being former smokers. Slight differences were observed for race/ethnicity categories: the survivor cohort was 82% white and 5.3% Hispanic, whereas the comparison cohort was 85% white and 3.5% Hispanic (*P* = .05).

Malignancy Characteristics

Table 2 provides the history of cancer before study follow-up began as well as the characteristics of incident malignancies that developed over the 10 years of study follow-up. No difference was observed in history of cancer for the period >5 years before the index date between cohorts (survi-

vors, 2.2%; comparison group, 2.1%; *P* = .89). However, 6.8% of survivors had a history of cancer during the period from 1 to 5 years after the index date compared with 3.8% of women in the comparison group (*P* < .001). Furthermore, a higher proportion of survivors than women in the comparison group had either a breast cancer (40% vs 28%) or a gynecologic cancer (15% vs 8%) diagnosed during the period from 1 to 5 years after the index date before study follow-up began (data not shown).

Three hundred six women (N = 160 survivors; N = 146 comparison women; *P* = .40) developed a first incident malignancy during study follow-up. Unadjusted incidence rates were slightly higher among survivors (1882.1 vs 1620.6 per 100,000 PY), whereas the mean time (±standard deviation) to first incident malignancy was similar between the survivor and comparison cohorts (4.37 ± 2.81 years vs 4.03 ± 2.76 years, respectively; *P* = .28). During follow-up, breast cancer was the most commonly occurring incident malignancy in both cohorts (≥27%) followed by the general "other" category (25%). However, the third most frequently diagnosed malignancy differed between cohorts (lung in the survivor

TABLE 2. History of Cancer Before the Start of Follow-Up (>5 Years Before the Index Date or 1-5 Years After the Index Date) and Characteristics of Incident Malignancies Over 10 Years of Follow-Up (6-15 Years After the Index Date) for the Total Study Population and the Survivor and Comparison Cohorts^a

| Characteristic | No. of Women (%) | | | <i>P</i> ^b |
|---|-------------------------------|------------------------------|--------------------------------|-----------------------|
| | Total Population, N = 2722 | Survivor Cohort, N = 1361 | Comparison Cohort, N = 1361 | |
| History of cancer before the start of follow-up: Before the index date or 1-5 y after the index date ^a | | | | |
| History of cancer >5 y before index date ^a | 59 (2.2) | 30 (2.2) | 29 (2.1) | .89 |
| History of cancer 1-5 y after index date ^a | 143 (5.3) | 92 (6.8) | 51 (3.8) | .0004 |
| Incident malignancies that occurred during follow-up: At 6-15 y after the index date ^a | | | | |
| First incident malignancy | 306 (11) | 160 (12) | 146 (11) | .40 |
| First incident malignancy rate, PY | 1748/100,000 | 1882/100,000 | 1620/100,000 | |
| Time to first incident malignancy: Mean ± SD, y | 4.21±2.78 | 4.37±2.81 | 4.03±2.76 | .28 |
| Type of first incident malignancy | | | | |
| Breast | 80 (26) | 43 (27) | 37 (25) | .61 |
| Colorectal | 47 (15) | 18 (11) | 29 (20) | |
| Gynecologic | 17 (5.6) | 12 (7.5) | 5 (3.4) | |
| Lymphoma/leukemia | 25 (8.2) | 15 (9.4) | 10 (6.9) | |
| Lung | 45 (15) | 24 (15) | 21 (14) | |
| Melanoma | 12 (3.9) | 6 (3.8) | 6 (4.1) | |
| Other | 79 (26) | 42 (26) | 37 (25) | |
| Stage of first incident malignancy ^c | | | | |
| Local | 64 (34) | 24 (25) | 40 (43) | .05 |
| Regional | 64 (34) | 39 (40) | 25 (27) | |
| Distant | 32 (17) | 18 (19) | 14 (15) | |
| Unstaged | 29 (15) | 16 (16) | 13 (14) | |
| No. of incident malignancies | | | | |
| 0 | 2416 (89) | 1201 (88) | 1215 (89) | .51 |
| 1 | 289 (11) | 153 (11) | 136 (10) | |
| 2 | 16 (0.6) | 7 (0.5) | 9 (0.7) | |
| 3 | 1 (0.04) | 0 (0) | 1 (0.07) | |

Abbreviations: PY, person years; SD, standard deviation; y, years.

^aThe index date was either the date of the survivor's diagnosis or the date of the matched comparison woman's enrollment.

^b*P* values reflect differences between long-term breast cancer survivors and the nonbreast cancer comparison cohort.

^cStage was restricted to solid tumors (breast, lung, colorectal, gynecologic).

TABLE 3. The Risk of Incident Malignant Cancer in the Survivor Cohort Compared With the Comparison Cohort Adjusted for the Competing Risk of Death Over 10 Years of Follow-Up (6 to 15 Years After the Index Date), N = 2722^a

| | HR _{crude} (95% CI) | HR _{adjusted} (95% CI) ^b |
|-------------------------------------|------------------------------|--|
| First incident all-cause malignancy | 1.16 (0.93-1.46) | 1.17 (0.94-1.47) |
| Type of first incident malignancy | | |
| Breast | 1.26 (0.81-1.95) | 1.28 (0.83-1.99) |
| Colorectal | 0.66 (0.37-1.19) | 0.66 (0.37-1.20) |
| Gynecologic | 2.53 (0.89-7.18) | 2.72 (0.96-7.74) |
| Lymphoma/leukemia | 1.33 (0.62-2.84) | 1.28 (0.59-2.75) |
| Lung | 1.21 (0.68-2.18) | 1.25 (0.69-2.25) |
| Melanoma | 1.01 (0.36-3.32) | 0.93 (0.29-2.94) |
| Other | 1.20 (0.77-1.87) | 1.19 (0.77-1.86) |

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aThe index date was either the date of the survivor's diagnosis or the date of the matched comparison woman's enrollment.

^bAdjusted models included site, age, race, comorbidity, and history of cancer.

cohort, colorectal in the comparison group). Fewer long-term breast cancer survivors than women in the matched comparison group had local disease.

During the 10 years of follow-up, 17 women in the total population (N = 7 survivors; N = 10 comparison women) developed more than 1 incident malignancy (N = 16 had 2 incident malignancies; N = 1 had 3 incident malignancies). Among those who developed a second incident malignancy, the mean time from first to second incident malignancy was 3.79 ± 1.59 years for the survivor cohort and 2.98 ± 2.68 years for the comparison cohort (*P* = .49; data not shown). Unadjusted incidence rates for more than 1 malignancy during follow-up were lower in long-term breast cancer survivors than in the matched comparison group (1452.3 vs 2469.6 per 100,000 PY; data not shown).

Risk of Incident Malignancies

Table 3 describes the risk of incident malignancy adjusted for death as a competing risk in long-term breast cancer survivors compared with the matched comparison group

during the follow-up period of 6 to 15 years postindex date. The adjusted hazard of developing a first incident malignancy controlling for site, age, race, comorbidity, and history of cancer was slightly elevated in survivors relative to the comparison group but was not statistically significant (HR, 1.17; 95% CI, 0.94-1.47). Similar cancer-specific models indicated the most pronounced increased risk for incident gynecologic malignancy (HR, 2.72; 95% CI, 0.96-7.74) and a decreased risk of colorectal malignancy (HR, 0.66; 95% CI, 0.37-1.20) in a comparison of the survivor and comparison cohorts.

Sensitivity Analyses

The results from sensitivity analysis differed minimally from the main findings (data not shown).

DISCUSSION

In this study, we compared incident malignancies in older long-term breast cancer survivors versus women in a matched comparison group without a previous breast cancer diagnosis to determine whether cancer risk 5 to 15 years after diagnosis was similar or different. We observed that older women who survived 5 years after an early stage breast cancer diagnosis were similar to comparison women without breast cancer with respect to the risk of developing an incident malignancy over follow-up (ie, no/slight increased risk). However, the risk of a cause-specific incident malignancy differed. During follow-up, survivors had a nonstatistically significant increased risk of incident gynecologic malignancy and a decreased risk of colorectal malignancy.

Our results are consistent with findings of no excess risk of first incident malignancy and an increased risk of subsequent uterine malignancies in older women diagnosed with breast cancer compared with the general population.²¹⁻²³ However, the risk of incident gynecologic malignancies in our study was higher than the gynecologic malignancy risk previously reported by individual disease sites (eg, uterine, ovary, cervix) for older survivors. Differences may be attributed to the finding that we included only 5-year survivors, women with a history of cancer (>5 years before the index date and 1-5 years after the index date), and used less specific malignancy groupings (ie, uterine, ovary, cervix combined as gynecologic). Previous studies have reported conflicting results for colorectal cancer risk after primary breast cancer.²²⁻²⁸ Our findings are in keeping with more recent studies indicating no overall increased risk and specifically with the results reported by Newschaffer et al, who similarly observed a decreased risk of colorectal cancer in older breast cancer survivors.^{25,27}

However, caution should be used when comparing our findings with previous studies given differences in study designs and our smaller numbers and less precise cause-specific results.

Several unmeasured factors may have contributed to our findings and, thus, are worthy of mention. First, we collected no information on cancer screening in the survivor and comparison cohorts. Higher rates of colorectal screening in the survivor cohort may have contributed to the lower rate of colorectal cancer in the survivor cohort compared with the comparison cohort. Second, lung cancer incidence and smoking status did not differ between the cohorts. However, smoking status (never, current, former) does not provide a full picture of smoking risk. A more specific dose measurement (ie, pack-years) indicating elevated tobacco use may have identified an association with other smoking-related subsequent malignancies. Finally, the observed slight increases in breast and gynecologic malignancies as well as the decrease in colorectal malignancies may have been influenced by unmeasured hormone factors.

We designed this study specifically to address a knowledge gap regarding the long-term risk of subsequent incident malignancy in older women with breast cancer. We collected information on whether or not women had history of a cancer diagnosis in 2 separate periods before study follow-up began. It is noteworthy that we observed no difference between cohorts in the period >5 years before the index date (ie, before the initial breast cancer diagnosis). However, during the first 5 years after diagnosis, more survivors were diagnosed with cancer, and particularly breast and gynecologic cancers, than women in the comparison group. This pattern warrants further research. Unfortunately, it could not be examined in this study, because breast cancer survivors and women in the age-matched/site-matched comparison group who did not survive for 5 years were excluded by study design. It is conceivable that, because we only included 5-year survivors and malignancies from that point forward, a different picture may have emerged if we had included all women and examined incident malignancies during short-term and long-term follow-up (ie, follow-up from the index date forward).

The major strengths of this study are the sample size, the diversity of sites of care and their locations, the comprehensive long-term follow-up of survivors and women in the matched comparison group, and the competing risk for death analyses. Our breast cancer and comparison cohorts were nearly identical across the spectrum of study characteristics collected. We believe this is

because of similar selection factors for both groups for participation, strengthening comparisons but limiting the generalizability of results outside this setting. Another potential limitation of these findings is that we only included women who survived for 5 years after their initial breast cancer diagnosis. Nonetheless, women with a breast cancer diagnosis and their matched comparisons had to survive for 5 years after the index date, suggesting that similar selection factors affected both cohorts. By study design, breast cancer survivors were only at risk for a second breast cancer in the contralateral breast, whereas women in the comparison group were at risk in either breast. Moreover, a greater proportion of survivors had a history of breast cancer 1 to 5 years after the index date. Both factors may have inestimably attenuated the breast cancer-specific risk among survivors over follow-up. There were also 2 potential, unquantifiable sources of incident malignancy misclassification: 1) women who had missing or unknown data for history of cancer were eligible, but small numbers were missing data nondifferentially in the 2 cohorts; and 2) capture of new malignancies may have differed between SEER sites and non-SEER sites, although all sites have state cancer registries, and sensitivity analyses indicated no effect. We controlled for history of cancer in the models, and any residual effect should be minor, because sensitivity analyses that excluded women with a history of cancer produced no meaningful change in the results. Finally, given the small numbers of cause-specific outcomes and of women who developed more than 1 incident malignancy over follow-up, we were unable to conduct statistically stable analyses for more than 1 incident malignancy. Additional studies with larger populations are needed.

In conclusion, our results suggest that the risk of developing an incident malignancy is similar between 5-year breast cancer survivors and nonbreast cancer comparison women for 6 to 15 years after a breast cancer diagnosis. The number of incident malignancies, the incidence rate, and the time to incident malignancy were comparable between cohorts, but disease stage and type of malignancy differed. The lack of a significant increase in the incidence of subsequent malignancies in long-term breast cancer survivors suggests that follow-up care does not need to be different from that for women without a previous breast cancer. Furthermore, the risk of incident malignancies in older long-term cancer survivors in relation to older women in general is crucial because of the growth of our aging population, its lengthening life expectancy, and the overall increased risk of malignancy associated with older age. These trends will result in more women with

breast cancer living longer after a breast cancer diagnosis. Earlier diagnosis of breast cancer through screening and the development of new cancer treatments also will increase the population of breast cancer survivors at risk for subsequent malignancies. Research like this, describing subsequent malignancies in older long-term survivors, provides essential information for clinicians and older patients.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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