ORIGINAL ARTICLE

# Clinical Characteristics of Breast Cancers in African-American Women with Benign Breast Disease: A Comparison to the Surveillance, Epidemiology, and End Results Program

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■ **Abstract:** Benign breast disease (BBD) is a very common condition, diagnosed in approximately half of all American women throughout their lifecourse. White women with BBD are known to be at substantially increased risk of subsequent breast cancer; however, nothing is known about breast cancer characteristics that develop after a BBD diagnosis in African-American women. Here, we compared 109 breast cancers that developed in a population of African-American women with a history of BBD to 10,601 breast cancers that developed in a general population of African-American women whose cancers were recorded by the Metropolitan Detroit Cancer Surveillance System (MDCSS population). Demographic and clinical characteristics of the BBD population were compared to the MDCSS population, using chi-squared tests, Fisher's exact tests, t-tests, and Wilcoxon tests where appropriate. Kaplan–Meier curves and Cox regression models were used to examine survival. Women in the BBD population were diagnosed with lower grade (p = 0.02), earlier stage cancers (p = 0.003) that were more likely to be hormone receptor-positive (p = 0.03) compared to the general metropolitan Detroit African-American population. In situ cancers were more common among women in the BBD cohort (36.7%) compared to the MDCSS population (22.1%, p < 0.001). Overall, women in the BBD population were less likely to die from breast cancer after 10 years of follow-up (p = 0.05), but this association was not seen when analyses were limited to invasive breast cancers. These results suggest that breast cancers occurring after a BBD diagnosis may have more favorable clinical parameters, but the majority of cancers are still invasive, with survival rates similar to the general African-American population. ■

**Key Words:** African-American, benign breast disease, breast cancer, risk, survival

Benign breast disease (BBD) is a very common condition, diagnosed in approximately half of all American women at some point in their lives (1). Along with age, reproductive factors and family history, it is well established that BBD raises long-term breast cancer risk (2–7). Different types of BBD have been associated with differentially elevated risk: nonproliferative lesions confer a relatively low level of additional risk, while proliferative lesions with atypia confer a much greater risk (7,8). However, although lesions differentially elevate breast cancer risk, little is known about whether different lesions predict the development of specific types of breast cancer (9).

There are known racial disparities between African-American and white women in the epidemiology of breast cancer. For example, African-American women develop breast cancer at a younger age and present with more advanced tumors (10–12). Despite these differences, recent research has suggested that the

association between BBD and breast cancer first described in white women also applies to African-American women (8,13). BBD and breast cancer may even be more strongly associated in African-American women than they are in white women (14). Therefore, it is important to better characterize the association between BBD and breast cancer in African-American women.

Although it is well known that BBD elevates risk of breast cancer, no studies have compared the breast cancer characteristics of women with a history of BBD to the breast cancer characteristics of the general population. Such a comparison is of interest because women with BBD are at elevated risk for breast cancer, so it is important to determine whether their tumors are clinically different from those of the general population. It is possible that because women who have been diagnosed with BBD have established access to medical care and some awareness of breast health, their cancers will be diagnosed earlier. In this study, we will compare the characteristics of breast cancers in women with a history of BBD to the characteristics of breast cancers in a large population-based sample of women.

## MATERIALS AND METHODS

### Populations Studied

The BBD cohort was composed of women who self-reported African-American/black race from metropolitan Detroit, MI, who had been diagnosed with BBD between 1997 and 2003 at hospitals and clinics associated with the Detroit Medical Center. The BBD cohort was previously described by Cote et al. (13). In brief, exclusion criteria included: a previous breast biopsy, a history of invasive or in situ breast carcinoma prior to, or within 6 months, of the BBD biopsy, unilateral or bilateral mastectomy prior to or at diagnosis, prior breast reduction surgery, lipoma, fat necrosis, epidermal cysts, hematoma, accessory structure, phyllodes tumor, or a lymph node biopsy with no breast tissue. Women from the BBD cohort who subsequently developed breast cancer before the second quarter of 2013 comprised the BBD population.

The referent population was selected from the Metropolitan Detroit Cancer Surveillance System (MDCSS) data base, a founding member of the Surveillance, Epidemiology, and End Results (SEER) program. The MDCSS population was composed of African-American women who were diagnosed with breast cancer between 1998 and 2012 and who lived in the tri-county Metropolitan Detroit area. The SEER program collected estrogen receptor (ER) and progesterone receptor (PR) status during this time period, but HER2 status was not a required variable until 2010 and thus is not included in this analysis for either population. To ensure comparability between the BBD population and the MDCSS population, girls under the age of 18 and women diagnosed with inflammatory breast cancer or Paget's Disease were excluded from analysis. In addition, to ensure that analyses reflected the experiences of women with breast cancer, women who died less than 2 months after breast cancer diagnosis were excluded from both populations. Data were accessed on June 12, 2013.

### Statistical Analysis

Demographic and clinical characteristics of the BBD population were compared to the MDCSS population, using chi-squared tests, Fisher's exact tests, t-tests, and Wilcoxon tests where appropriate. Known predictors of survival (age, hormone receptor status, tumor grade, tumor stage, in situ or invasive behavior, tumor size, and treatment variables) were evaluated. Age was evaluated in 10-year intervals (<40 years, 40–49 years, 50–59 years, 60–69 years, ≥70 years) in descriptive statistics, and as a continuous variable in the Cox regression models. Hormone receptor status was divided into two categories: ER or PR positive versus both ER and PR negative, in accordance with clinically significant differences in hormone receptor status (15). Tumor grade was recorded from the MDCSS and coded as I, II, or III/IV. Tumor stage was recorded from the MDCSS and categorized as in situ, localized, regional, or distant. Tumor size was categorized in accordance with American Joint Committee on Cancer (AJCC) guidelines (≤20 mm, >20–50 mm, >50 mm) (16). Radiation and surgery were both evaluated as dichotomous variables. Other characteristics, namely marital status and number of previous cancers, were also evaluated. Characteristics were examined overall and stratified by in situ or invasive status. Variables in which more than 15% of observations were unknown were evaluated both with and without the unknown category in descriptive statistics, and with the unknown category in the Cox regression models.

Kaplan–Meier curves were used to evaluate overall and breast cancer-specific survival over a 10-year follow-up, in all women and in women with invasive breast cancer only. Hazard ratios for overall survival

and breast cancer-specific survival were estimated using Cox regression models adjusted for age, marital status, number of previous cancers, hormone receptor status (ER−/PR−, ER+ and/or PR+, or Unknown), tumor grade (I, II, or III/IV), stage (in situ, localized, regional, or distant), size (divided according to AJCC staging guidelines), radiation, and surgery. SAS 9.2 (Cary, NC) was used for all analyses.

## RESULTS

### Population Characteristics

The BBD population consisted of 109 women with a history of BBD, who were diagnosed with breast cancer before the second quarter of 2013. BBD population women were aged 29–85 years (median age = 59.0 years) at time of cancer diagnosis (median survival among deceased = 2.9 years). The MDCSS population was composed of 10,601 African-American women within the MDCSS catchment area. MDCSS women were aged 18–107 years (median age = 58.0 years) at time of cancer diagnosis (median survival among deceased = 2.9 years). Women in the BBD population did not differ from the MDCSS population in age, marital status at breast cancer diagnosis, number of previous cancers, length of survival after diagnosis among deceased, or in breast cancer treatment (surgery or radiation; Table 1).

### Tumor Characteristics

Women in the BBD population did not differ from the MDCSS population with respect to tumor size, but were significantly more likely to develop breast cancers that were hormone receptor-positive (excluding unknown group, 81.7% versus 69.6%, p = 0.027), in situ rather than invasive (36.7% versus 22.1%, p < 0.001), early stage (37.7% versus 22.6%, p = 0.003), and low grade (25.0% versus 14.5%, p = 0.020), when compared to the MDCSS population (Table 1).

In stratified analysis examining invasive cancers only, the BBD population remained more likely to be diagnosed with hormone receptor-positive tumors (excluding unknown group, 78.0% versus 66.5%, p = 0.062) and more likely to be alive at last follow-up (75.4% versus 63.6%, p = 0.044), although the length of survival after diagnosis among deceased individuals did not differ between populations. Among in situ cancers only, BBD women were more likely to be

diagnosed with low-grade tumors (45.2% versus 24.0%, p = 0.021; Table 2).

### Survival

Compared to the MDCSS population, BBD population women had a moderately lower risk of death

## Table 1. Demographic and Clinical Characteristics of MDCSS and BBD Population Women

| Characteristic | MDCSS population ($n = 10,601$) | BBD population ($n = 109$) | p-value |
|---|---|---|---|
| Percentage of total | 99.0% | 1.0% | |
| **Age at diagnosis** | | | |
| <40 years | 639 (6.0) | 4 (3.7) | 0.321 |
| 40–49 years | 2083 (19.7) | 16 (14.7) | |
| 50–59 years | 2887 (27.2) | 38 (34.9) | |
| 60–69 years | 2289 (21.6) | 24 (22.0) | |
| ≥70 years | 2703 (25.5) | 27 (24.8) | |
| Median age (years) | 58.0 ± 0.1 | 59.0 ± 1.2 | 0.724 |
| **Marital status at diagnosis[1]** | | | |
| Single | 3020 (30.0) | 34 (32.4) | 0.873 |
| Married | 3477 (34.6) | 35 (33.3) | |
| Other | 3556 (35.4) | 36 (34.3) | |
| **No. of previous cancers** | | | |
| 0 | 8115 (76.6) | 85 (78.0) | 0.408 |
| 1 | 1214 (11.4) | 15 (13.8) | |
| ≥2 | 1272 (12.0) | 9 (8.3) | |
| **Vital status as of 2012** | | | |
| Alive | 7241 (68.3) | 87 (79.8) | 0.010* |
| Deceased | 3360 (31.7) | 22 (20.2) | |
| Survival (years) among deceased[2] | 2.9 ± 0.1 | 2.9 ± 0.5 | 0.406 |
| **Hormone receptor status** | | | |
| ER+ or PR+ | 5677 (53.5) | 58 (53.2) | 0.002*/0.027*[8] |
| ER−/PR− | 2479 (23.4) | 13 (11.9) | |
| Unknown | 2445 (23.1) | 38 (34.9) | |
| **Tumor grade[3]** | | | |
| I | 1340 (14.5) | 22 (25.0) | 0.020* |
| II | 3240 (35.1) | 29 (33.0) | |
| III/IV | 4648 (50.4) | 37 (42.0) | |
| **Tumor stage[4]** | | | |
| In situ | 2347 (22.6) | 40 (37.7) | 0.003* |
| Localized | 4382 (42.2) | 36 (34.0) | |
| Regional | 2994 (28.8) | 25 (23.6) | |
| Distant | 668 (6.4) | 5 (4.7) | |
| **Tumor behavior** | | | |
| In situ | 2347 (22.1) | 40 (36.7) | <0.001* |
| Invasive | 8254 (77.9) | 69 (63.3) | |
| **Tumor size[5]** | | | |
| ≤20 mm | 4929 (53.8) | 47 (50.5) | 0.816 |
| >20–50 mm | 3194 (34.9) | 35 (37.6) | |
| >50 mm | 1037 (11.3) | 11 (11.8) | |
| **Radiation[6]** | | | |
| Yes | 5137 (50.0) | 61 (57.0) | 0.152 |
| No | 5127 (50.0) | 46 (43.0) | |
| **Surgery[7]** | | | |
| Yes | 9548 (90.3) | 99 (90.8) | 0.867 |
| No | 1020 (9.7) | 10 (9.2) | |

Percentages may not sum to 100% due to rounding. Plus-minus values are medians ± SE.
Missing observations among all women: [1]548; [2]37; [3]1373; [4]210; [5]1441; [6]337; [7]33.
Missing observations among biopsied women: [1]4; [3]c21; [4]3; [5]16; [6]2.
[8]The first p-value indicates the chi-squared probability including the "Unknown" group. The second p-value indicates the chi-squared probability excluding the "Unknown" group.

from any cause (p = 0.084) and a lower risk of death from breast cancer specifically (p = 0.047) over 10 years of follow-up after diagnosis. However, when analyzing invasive cancers only, the BBD and MDCSS populations did not differ in risk of death from any cause or from breast cancer (Fig. 1).

In both the MDCSS population and the BBD population, risk of death from any cause was significantly associated with known predictors of survival: increasing age at breast cancer diagnosis, hormone receptor-negativity, increasing grade, increasing stage, increasing tumor size, not receiving radiation or surgery, and at least one previous cancer diagnosis (Table 3). All of these factors, with the exception of having had a previous cancer diagnosis, also significantly elevated risk of breast cancer-specific death in the adjusted models (Table 3). Membership in the BBD population was not significantly associated with risk of death in the adjusted models (Table 3).

**Table 2. Demographic and Clinical Characteristics of Cancers in MDCSS and BBD Women, Stratified by Invasive Versus In Situ Disease**

| Characteristic | Invasive cancer | | | In situ cancer | | |
|---|---|---|---|---|---|---|
| | MDCSS population | BBD population | p-value | MDCSS population | BBD population | p-value |
| Age at diagnosis | | | | | | |
| <40 years | 569 (6.9) | 3 (4.3) | 0.378 | 70 (3.0) | 1 (2.5) | 0.510 |
| 40–49 years | 1624 (19.7) | 8 (11.6) | | 459 (19.6) | 8 (20.0) | |
| 50–59 years | 2173 (26.3) | 21 (30.4) | | 714 (30.4) | 17 (42.5) | |
| 60–69 years | 1746 (21.2) | 18 (26.1) | | 543 (23.1) | 6 (15.0) | |
| ≥70 years | 2142 (26.0) | 19 (27.5) | | 561 (23.9) | 8 (20.0) | |
| Median age (years) | 58.0 ± 0.2 | 61.0 ± 1.5 | 0.297 | 59.0 ± 0.3 | 56.0 ± 1.8 | 0.334 |
| Marital status at diagnosis[1] | | | | | | |
| Single | 2380 (30.4) | 20 (30.3) | 0.680 | 640 (28.7) | 14 (35.9) | 0.428 |
| Married | 2600 (33.3) | 19 (28.8) | | 877 (39.3) | 16 (41.0) | |
| Other | 2840 (36.3) | 27 (40.9) | | 716 (32.1) | 9 (23.1) | |
| No. of previous cancers | | | | | | |
| 0 | 6406 (77.6) | 54 (78.3) | 0.907 | 1709 (72.8) | 31 (77.5) | 0.298 |
| 1 | 883 (10.7) | 8 (11.6) | | 331 (14.1) | 7 (17.5) | |
| ≥2 | 965 (11.7) | 7 (10.1) | | 307 (13.1) | 2 (5.0) | |
| Vital status as of 2012 | | | | | | |
| Alive | 5254 (63.6) | 52 (75.4) | 0.044* | 1987 (84.7) | 35 (87.5) | 0.621 |
| Deceased | 3000 (36.4) | 17 (24.6) | | 360 (15.3) | 5 (12.5) | |
| Survival (years) among deceased[2] | 2.7 ± 0.1 | 2.3 ± 0.5 | 0.605 | 5.2 ± 0.2 | 5.7 ± 1.3 | 0.783 |
| Hormone receptor status | | | | | | |
| ER+ or PR+ | 4685 (56.8) | 46 (66.7) | 0.176/0.062*[8] | 992 (42.3) | 12 (30.0) | 0.062/0.625[8] |
| ER−/PR− | 2363 (28.6) | 13 (18.8) | | 116 (4.9) | 0 (0) | |
| Unknown | 1206 (14.6) | 10 (14.5) | | 1239 (52.8) | 28 (70.0) | |
| Tumor grade[3] | | | | | | |
| I | 901 (12.2) | 8 (14.0) | 0.730 | 439 (24.0) | 14 (45.2) | 0.021* |
| II | 2478 (33.5) | 21 (36.8) | | 762 (41.6) | 8 (25.8) | |
| III/IV | 4019 (54.3) | 28 (49.1) | | 629 (34.4) | 9 (29.0) | |
| Tumor stage[4] | | | | | | |
| In situ | – | – | 0.976 | 2347 (100.0) | 40 (100.0) | – |
| Localized | 4382 (54.5) | 36 (54.6) | | – | – | |
| Regional | 2994 (37.2) | 25 (37.9) | | – | – | |
| Distant | 668 (8.3) | 5 (7.6) | | – | – | |
| Tumor size[5] | | | | | | |
| ≤20 mm | 3700 (49.0) | 25 (39.1) | 0.280 | 1229 (76.4) | 22 (75.9) | 0.987 |
| >20–50 mm | 2941 (38.6) | 30 (46.9) | | 280 (17.4) | 5 (17.2) | |
| >50 mm | 938 (12.4) | 9 (14.1) | | 99 (6.2) | 2 (6.9) | |
| Radiation[6] | | | | | | |
| Yes | 4100 (51.5) | 43 (64.2) | 0.039* | 1037 (45.0) | 18 (45.0) | 0.997 |
| No | 3861 (48.5) | 24 (35.8) | | 1266 (55.0) | 22 (55.0) | |
| Surgery[7] | | | | | | |
| Yes | 7316 (89.0) | 62 (89.9) | 0.819 | 2232 (95.1) | 37 (92.5) | 0.446 |
| No | 905 (11.0) | 7 (10.1) | | 115 (4.9) | 3 (7.5) | |

Percentages may not sum to 100% due to rounding. Plus-minus values are medians ± SE. Missing observations among in situ cancers: MDCSS women: [1]114; [2]1; [3]517; [5]739; [6]44. BBD women: [1]1; [3]9; [5]11. Missing observations among invasive cancers: MDCSS women: [1]434; [2]36; [3]856; [4]210; [5]702; [6]293; [7]33. BBD women: [1]3; [3]12; [4]3; [5]5; [6]2.
[8]The first p-value indicates the chi-squared probability including the "Unknown" group. The second p-value indicates the chi-squared probability excluding the "Unknown" group.
*indicates statistical significance.
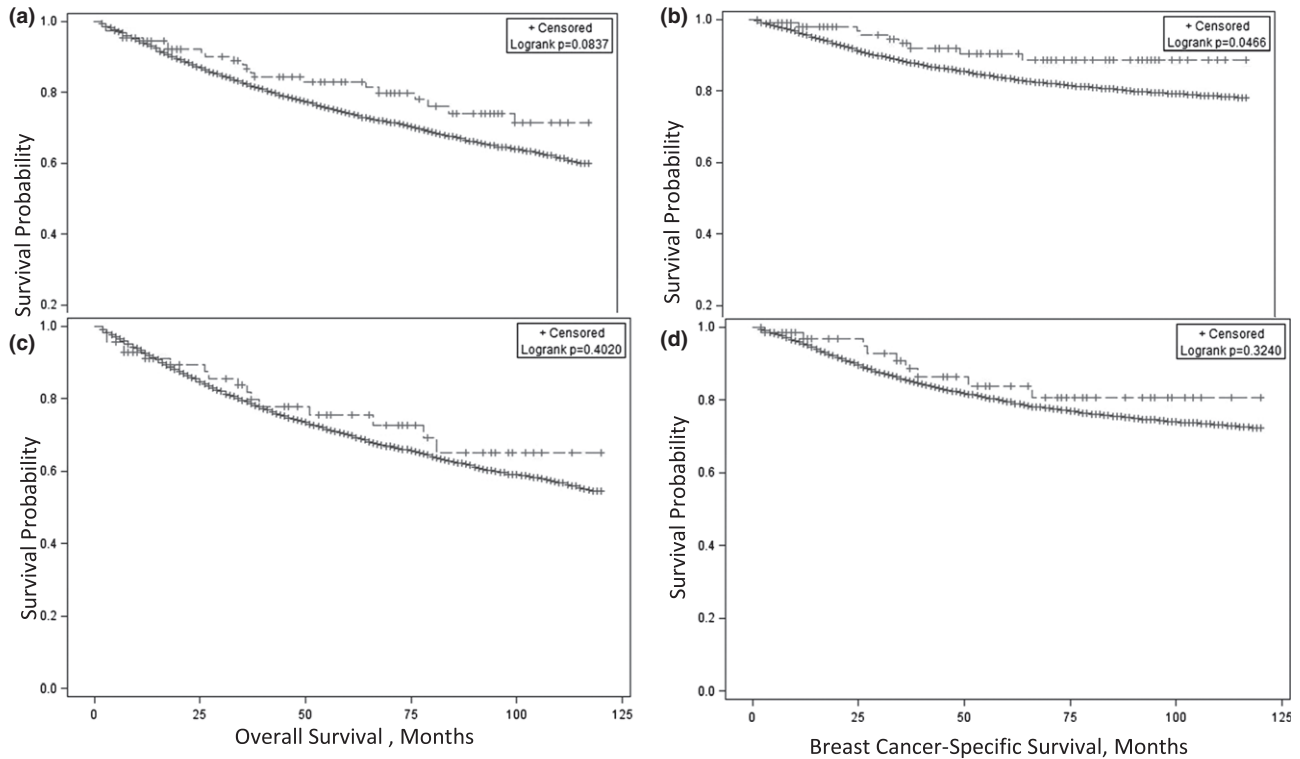
**Figure 1.** Survival curves comparing observed survival time of women in the BBD population (dashed line) and women in the MDCSS population (solid line). (a) Ten-year survival curves comparing observed survival time of all BBD population women and all MDCSS population women. (b) Ten-year survival curves comparing observed breast cancer-specific survival time of BBD population women and MDCSS population women. (c) Ten-year survival curves comparing observed survival time of women with invasive breast cancer from the BBD and the MDCSS populations. (d) Ten-year survival curves comparing observed breast cancer-specific survival time of women with invasive breast cancer from the BBD and the MDCSS populations.

## DISCUSSION

This is the first known study to compare the clinical characteristics of breast cancers in women with a history of BBD to those in the general population. In addition, this study was done in a population of African-American women, which adds a new perspective to the literature on BBD and breast cancer that has largely been done in white populations.

The cancers diagnosed in the BBD population were much more likely to be in situ than were the cancers diagnosed in the MDCSS population. In addition, many of the differences between BBD population cancers and MDCSS population cancers appear to be due to this difference in tumor behavior. For example, the breast cancers developed by BBD women differed in hormone receptor status, grade, stage, and in situ versus invasive disease from the breast cancers developed by the MDCSS population, but the differences between the BBD population and the MDCSS population disappeared almost entirely after controlling for in situ versus invasive disease. Similarly, BBD population women were significantly less likely than MDCSS population women to die from breast cancer over 10 years of follow-up in overall survival analysis, but the survival differences between the populations were greatly reduced after excluding women with in situ cancers from analysis.

Interestingly, women in the BBD population were more likely than women in the MDCSS population to develop hormone receptor-positive breast cancer tumors, although results were somewhat limited by the large proportion of tumors without records of hormone receptor status. We included the unknown group in the final analyses to maintain sufficient power for the models. Previous studies that have attempted to correlate tumor hormone receptor status with history of BBD have reported null results (17) or had insufficient data to draw a clear conclusion (18). However, some research indicates that estradiol is elevated in BBD tissue (19), and the ER-alpha gene is more highly expressed in some types of BBD tissue (20), perhaps favoring the later development of ER+ tumors in women with BBD. Information regarding hormone therapy use was not available for either cohort.

**Table 3. Hazard of Death from Any Cause and Death from Breast Cancer Specifically, for Selected Variables**

| Characteristic | Overall survival[†] H.R. (95% CI) | p-value | Breast cancer survival H.R. (95% CI) | p-value |
|---|---|---|---|---|
| Population | | | | |
| MDCSS | Ref. | – | Ref. | – |
| BBD | 1.10 (0.67, 1.80) | 0.71 | 0.97 (0.46, 2.05) | 0.946 |
| Age at diagnosis | 1.03 (1.03, 1.03) | <0.001* | 1.01 (1.00, 1.01) | <0.001* |
| Marital status at diagnosis | | | | |
| Single | Ref. | – | Ref. | – |
| Married | 0.86 (0.77, 0.96) | 0.007* | 0.88 (0.76, 1.02) | 0.072 |
| Other | 1.01 (0.90, 1.13) | 0.874 | 1.02 (0.88, 1.18) | 0.814 |
| No. of previous cancers | | | | |
| 0 | Ref. | – | Ref. | – |
| 1 | 1.19 (1.05, 1.34) | 0.006* | 0.88 (0.73, 1.06) | 0.190 |
| ≥2 | 1.34 (1.19, 1.52) | <0.001* | 1.17 (0.97, 1.41) | 0.097 |
| Hormone receptor status | | | | |
| ER+ or PR+ | Ref. | | Ref. | – |
| ER−/PR− | 1.46 (1.37, 1.64) | <0.001* | 1.74 (1.53, 1.98) | <0.001* |
| Unknown | 1.26 (1.11, 1.42) | <0.001* | 1.39 (1.15, 1.68) | <0.001* |
| Tumor grade | | | | |
| I | Ref. | – | Ref. | – |
| II | 1.25 (1.06, 1.47) | 0.008* | 2.24 (1.57, 3.21) | <0.001* |
| III/IV | 1.62 (1.38, 1.91) | <0.001* | 3.23 (2.27, 4.59) | <0.001* |
| Tumor stage | | | | |
| In situ | Ref. | – | Ref. | – |
| Localized | 1.64 (1.37, 1.95) | <0.001* | 3.70 (2.43, 5.62) | <0.001* |
| Regional | 2.81 (2.35, 3.36) | <0.001* | 9.34 (6.18, 14.13) | <0.001* |
| Distant | 6.66 (5.31, 8.35) | <0.001* | 23.72 (15.20, 37.02) | <0.001* |
| Tumor size | | | | |
| ≤20 mm | Ref. | – | Ref. | – |
| >20–50 mm | 1.55 (1.40, 1.72) | <0.001* | 2.04 (1.76, 2.38) | <0.001* |
| >50 mm | 2.32 (2.03, 2.64) | <0.001* | 3.16 (2.64, 3.78) | <0.001* |
| Radiation | | | | |
| Yes | Ref. | – | Ref. | – |
| No | 1.50 (1.37, 1.64) | <0.001* | 1.36 (1.21, 1.54) | <0.001* |
| Surgery | | | | |
| Yes | Ref | – | Ref. | – |
| No | 2.38 (2.04, 2.77) | <0.001* | 2.39 (1.97, 2.89) | <0.001* |

All values represent 10 year survival. Hazard ratios adjusted for population, age, marital status, no. of previous cancers, hormone receptor status, grade, stage, size, radiation, and surgery. [†]Sample size (n) for both models = 7,745 observations. Overall events: 2,205. Breast cancer-specific events: 1,189.
*indicates statistical significance.

The breast cancer literature has not reached a consensus as to whether in situ breast tumors represent a stage in the multi-stage carcinogenesis pathway leading to invasive breast cancers, or instead represent a risk marker indicating elevated risk in all breast tissue (21). This uncertainty allows several possible explanations for our results. The difference may indicate that women who receive medical attention for BBD are more likely to have an established relationship with the health care system, and therefore are screened more frequently and are likely more aware of their own breast health. These factors could lead to earlier tumor detection of in situ cancers that would eventually have become invasive. This explanation is supported by the better 10-year breast cancer-specific survival among BBD women reported in this study. Alternatively, the difference may indicate that women who have received a BBD diagnosis are more likely to be subsequently over-screened, resulting in detection of more subclinical in situ cancers that would not have progressed, while not conferring a survival benefit to women with invasive cancers. This explanation may be supported by the greater proportion of in situ cancers found in BBD population women, and the identical median survival after diagnosis among the deceased from both populations reported in this study.

This study had several limitations. First, the SEER registry does not collect information on BBD in women who develop breast cancer. We were therefore unable to distinguish which women in the MDCSS population may have been previously diagnosed with BBD. This misclassification would bias results toward the null. In addition, the SEER registry does not collect detailed information about chemotherapy treatment, limiting

our analysis of treatment to radiation therapy or surgery. Furthermore, power was limited by the small number of women in the BBD population. Finally, although women in the BBD population were diagnosed with BBD in Detroit hospitals, not all women in the BBD population live in the Detroit metro area. Therefore, a small number of women in the BBD population may not have been included in the MDCSS upon developing cancer, leading to a slight underestimate of the subsequent cancers in the cohort. Underreporting of the cancer outcome would be unlikely to bias our results, as we have no reason to suspect that women who do not live in the metropolitan Detroit area develop cancers that differ from women who do.

In conclusion, although previous research indicates that women with a history of BBD are at higher risk of developing breast cancer, their cancers may differ in clinically important ways from those of the general population. Women with a history of BBD appear to develop cancers that are more likely to be in situ than invasive, more likely to be hormone receptor positive, and less likely to cause death within 10 years of follow-up. Additional study to identify higher risk benign lesions is warranted, and could identify a subset of women who would be more likely to derive benefit from closer surveillance.

## Acknowledgments

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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