Breast Cancer Res Treat (2013) 137:273–283
DOI 10.1007/s10549-012-2310-3

EPIDEMIOLOGY

# The association of breast density with breast cancer mortality in African American and white women screened in community practice

**Shengfan Zhang · Julie S. Ivy · Kathleen M. Diehl · Bonnie C. Yankaskas**

Received: 17 October 2012 / Accepted: 19 October 2012 / Published online: 10 November 2012


**Abstract** The effect of breast density on survival outcomes for American women who participate in screening remains unknown. We studied the role of breast density on both breast cancer and other cause of mortality in screened women. Data for women with breast cancer, identified from the community-based Carolina Mammography Registry, were linked with the North Carolina cancer registry and NC death tapes for this study. Cause-specific Cox proportional hazards models were developed to analyze the effect of several covariates on breast cancer mortality—namely, age, race (African American/White), cancer stage at diagnosis (in situ, local, regional, and distant), and breast density (BI-RADS® 1–4). Two stratified Cox models were considered controlling for (1) age and race, and (2) age and cancer stage, respectively, to further study the effect of density. The cumulative incidence function with confidence interval approximation was used to quantify mortality probabilities over time. For this study, 22,597 screened women were identified as having breast cancer. The non-stratified and stratified Cox models showed no significant statistical difference in mortality between dense tissue and fatty tissue, while controlling for other covariate effects ($p$ value = 0.1242, 0.0717, and 0.0619 for the non-stratified, race-stratified, and cancer stage–stratified models, respectively). The cumulative mortality probability estimates showed that women with dense breast tissues did not have significantly different breast cancer mortality than women with fatty breast tissue, regardless of age (e.g., 10-year confidence interval of mortality probabilities for whites aged 60–69 white: 0.056–0.090 vs. 0.054–0.083). Aging, African American race, and advanced cancer stage were found to be significant risk factors for breast cancer mortality (hazard ratio >1.0). After controlling for cancer incidence, there was not a significant association between mammographic breast density and mortality, adjusting for the effects of age, race, and cancer stage.

**Keywords** Breast cancer · Mortality · Breast density · Mammography screening

S. Zhang (✉)
Department of Industrial Engineering, University of Arkansas, Fayetteville, AR 72701, USA
e-mail: shengfan@uark.edu

J. S. Ivy
Edward P. Fitts Department of Industrial and Systems Engineering, North Carolina State University, Raleigh, NC 27695, USA
e-mail: jsivy@ncsu.edu

K. M. Diehl
Department of Surgery, Division of Surgery Oncology, University of Michigan Health Systems, Ann Arbor, MI 48109, USA
e-mail: kdiehl@med.umich.edu

B. C. Yankaskas
Department of Radiology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7510, USA
e-mail: bcy@med.unc.edu

B. C. Yankaskas
Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7510, USA

## Introduction

Approximately 75 % of women in their 40s have dense breast tissue, and the percentage diminishes with age, but still is sizeable: 54, 42, and 31 % for women in their 50s, 60s, and 70s, respectively [1]. Breast density is an accepted

risk factor for breast cancer and presents a challenge to screening, making it difficult to detect lesions on a mammogram [2–7]. There are few studies regarding the effect of breast density on mortality, particularly in American women. One study [8] using the Kopparberg randomized controlled trial in Sweden found that dense breast tissue (according to Tabar's classification) was significantly related to breast cancer incidence and mortality for Swedish women aged 45–59. However, they did not differentiate the incidence effect from the mortality effect. In a recent study, Gierach et al. [9] evaluated the relationship between density and risk of breast cancer death using the Breast Cancer Surveillance Consortium (BCSC) data between 1996 and 2005 with a sample size of 9,232. However, their study did not consider the role of race and produced a stationary risk estimate.

It is estimated that in 2012, there will be approximately 226,870 new cases of female breast cancer and 39,510 deaths from breast cancer [10]. The study of mortality is important not only for understanding disease risk, but it also informs decision-making regarding screening and treatment. Our study quantifies the risk of breast cancer mortality associated with breast density, controlling for the effects of age, race, and cancer stage.

While there are many mortality studies focused on predicting trends in breast cancer mortality [11–13], and quantifying the impact of treatment on breast cancer mortality [14, 15], our work is the first to estimate the effect of breast density on breast cancer and other cause mortality as a function of patient demographics over time, controlling for the effect of incidence. In contrast to the previous breast cancer mortality estimation models [16–19], we used a competing risk model framework to assess the density effect on mortality for women with breast cancer using a community-based mammography screening registry, adjusting for race, cancer stage, and age.

## Methods

### Introduction to data

This study used data from the community-based Carolina Mammography Registry (CMR). CMR is funded by National Cancer Institute [20] and is part of the BCSC, a collaborative research effort designed to study screening mammography in community practice (breastscreening.cancer.gov) [21]. Historically, CMR has the largest African American population among the BCSC member sites. CMR has been collecting prospective data on breast imaging performed in community-based mammography practices across North Carolina since 1994. All mammography records are linked to a breast pathology database and the North Carolina Central Cancer Registry. The CMR data are also linked to the North Carolina State Death Tapes for mortality information. At the time of this study, there were more than 2 million visit records on approximately 663,000 women, among whom more than 20,000 were diagnosed with breast cancer. The registry is reviewed annually and approved by the University of North Carolina, Chapel Hill, School of Medicine IRB, and complies with HIPAA requirements. Patients, radiologists, and facilities of CMR are also protected by a Public Health Service Certificate of Confidentiality.

The following information from CMR was used for this study: birth date, race (white and African American), breast density at the time of the mammogram, cancer diagnosis date, cancer stage at diagnosis, vital status, death date, and cause of death (ICD code 174 in the 9th version [22] and C50 in the 10th version [23] for breast cancer death). Age was calculated based on the time difference between diagnosis date and birth date. The end of study time was assumed to be January 1, 2008, the last time the registry was linked to the death tapes prior to this study. Breast

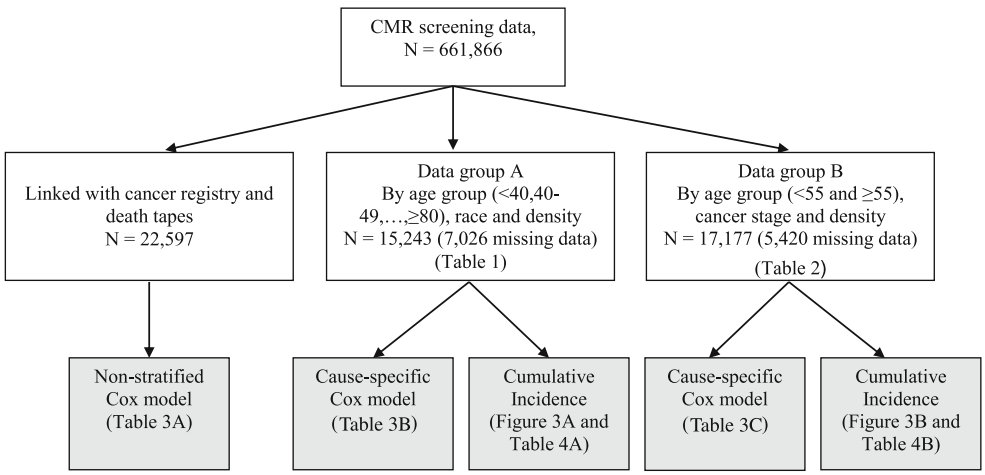


**Fig. 1** Summary of study design and data reduction, *Note* shaded boxes correspond to statistical analyses

density used the BI-RADS® codes from the American College of Radiology [24]; we dichotomized the codes into two categories, dense combining "heterogeneously dense" and "extremely dense," and fatty combining "almost entirely fat" and "scattered fibro-glandular densities."

In order to achieve an adequate sample size and control for other effects, the estimation for mortality probability was separated first by age and race and then by age and cancer stage. Since there were no patterns or bias associated with the missing observations, the records with missing values for race ($N = 2{,}692$), breast density ($N = 5{,}235$), and cancer stage ($N = 227$) were excluded from the analyses. A flow chart that summarizes the study design and sample size reduction is presented in Fig. 1. In data group A, age groups were categorized by 10-year increments. In data group B, these age groups were combined into two groups: pre-55 and 55 and older. This division is based on the age for menopause which ranges from 40 to 61 years [25] and affects breast density. By age 55, 96 % of women have reached menopause [26].

## Statistical analysis

In this study, deaths from causes other than breast cancer were modeled as competing risks for women with breast cancer. A two-proportion $z$ test was used to identify statistical differences in the proportion of African American and white women with dense tissue, and the proportion of women with dense breasts among the cancer stages. A competing risk Cox proportional hazards model and a cumulative incidence model with confidence intervals for the mortality estimates were developed to study the effect of breast density, controlling for the effects of age, race, and cancer stage at diagnosis.

A cause-specific Cox proportional hazards model [27] was developed to analyze the effects of the following covariates: age, race, breast density, and cancer stage on mortality. Binary variables were created for qualitative covariates. In order to adjust for the effect of breast density and cancer stage, two stratified Cox proportional hazards models were developed to allow for variation in the baseline hazard function across the levels of each stratification variable. The model was stratified on the following categories: (1) the age group and race (data group A), and (2) the age group and cancer stage (data group B). The baseline values for the race, cancer stage, and density variables were African American, unknown stage (this refers to those cancers that were categorized as "unknown," not missing data), and the fatty group, respectively. In these models, a baseline hazard function describes the instantaneous risk of dying from cause $j$, given the baseline values of covariates. In this study, we focused only on the risk of dying from breast cancer. Hazard ratio (HR) refers to the ratio of two hazard functions corresponding to the conditions described by two different values of a specific covariate. A value of HR greater than one indicates a higher risk of death from breast cancer.

In order to calculate the mortality probabilities from breast cancer and other causes, we used a nonparametric cumulative incidence function, an unbiased estimator for the breast cancer mortality probability in the presence of competing risks; in this case, non-breast cancer death [28–31]. Confidence intervals [32, 33] were constructed at the 95 % level. The cause-specific cumulative incidence at a given time was computed as a function of the number of deaths, the number of women at risk, and the Kaplan–Meier estimate of overall survival. Transformed log(−log) bounds were used to calculate the 95 % confidence interval [33] associated with each estimate. The log(−log) transformation is better for small sample sizes than other forms of transformation [32].

In comparison with a proportional hazards model, which estimates the effects of covariates on the hazard rate, the

**Table 1** Breast density distribution by age and race

| Age | White ($N = 12{,}632$) | | African American ($N = 2{,}611$) | | Total | Proportion difference (%)[a] | $p$ value[b] |
|---|---|---|---|---|---|---|---|
| | Dense $N$ (%) | Fatty $N$ (%) | Dense $N$ (%) | Fatty $N$ (%) | | | |
| <40 | 413 (64.6) | 226 (35.4) | 165 (63.0) | 97 (37.0) | 901 | 1.6 | 0.649 |
| 40–49 | 1,406 (60.6) | 915 (39.4) | 356 (58.0) | 258 (42.0) | 2,935 | 2.6 | 0.242 |
| 50–59 | 1,642 (52.6) | 1,479 (47.4) | 340 (51.2) | 324 (48.8) | 3,785 | 1.4 | 0.512 |
| 60–69 | 1,372 (43.0) | 1,818 (57.0) | 177 (33.8) | 346 (66.2) | 3,713 | 9.2 | <0.001 |
| 70–79 | 887 (36.8) | 1,524 (63.2) | 133 (35.8) | 239 (64.2) | 2,783 | 1.0 | 0.710 |
| ≥80 | 353 (37.2) | 597 (62.8) | 58 (33.0) | 118 (67.0) | 1,126 | 4.2 | 0.288 |
| Total | 6,073 (48.1) | 6,559 (51.9) | 1,229 (47.1) | 1,382 (52.9) | 15,243 | 1.0 | 0.352 |

[a] Difference of the dense tissue proportion in white versus African American by age group (e.g. age <40: 64.6–63 % = 1.6 %)

[b] Comparison of the proportion using two-proportion $z$ test

cumulative incidence model calculates the mortality probabilities over time. The confidence intervals for these probabilities are compared among different risk groups. The confidence intervals were used to identify statistically significant differences in mortality. An overlap in the 95 % confidence intervals for the respective mortality probabilities of two groups means there is insufficient evidence to suggest a statistically significant difference in those mortality probabilities; while no overlap means there is a statistically significant difference. The details of the statistical models can be found in Zhang [34].

## Results

### Prevalence of dense breast tissue in women with cancer

There were 15,243 women with breast cancer in the registry with known age, race, and breast density; 47.9 % (7302/15243) of whom had dense breast tissue (BI-RADS three or four dense breast tissue); see Table 1 and Fig. 2A. The difference in the proportion of white and African American women with dense tissue was not significant ($p = 0.352$) (Table 1). When stratified by age group, there

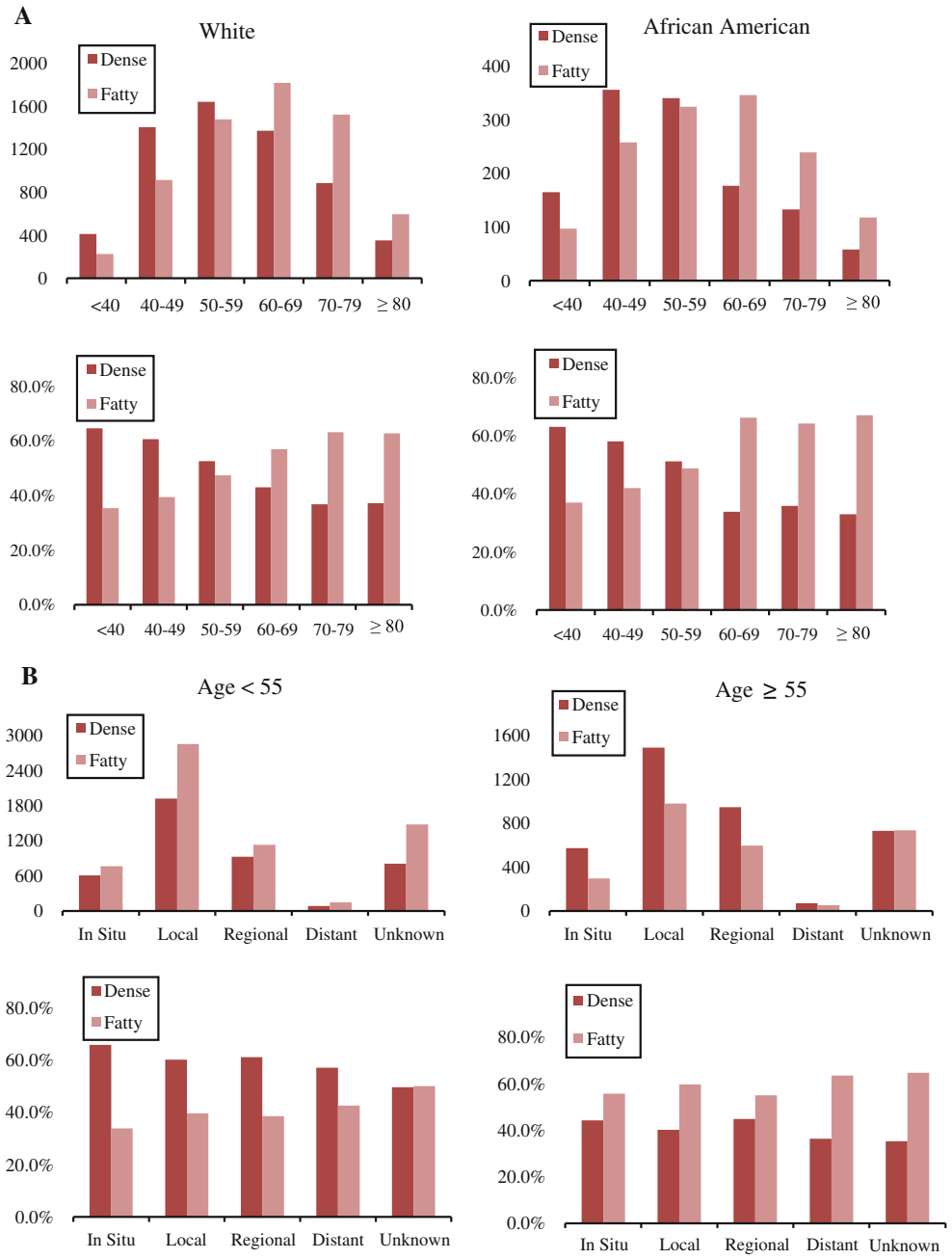


**Fig. 2** Distribution of population breast density by **A** race and age, and **B** cancer stage and age group

were also no significant differences in the proportion of white and African American women with dense tissue ($p$ values all greater than 0.1), except for women aged 60–69 ($p < 0.0001$).

There were 17,177 women with records of age, density, and cancer stage at diagnosis, of whom 37.6 % (6464/17177) were younger than 55 (Table 2; Fig. 2B). As would be expected, a higher proportion of women of age <55 years, 58.9 % (3805/6464) had dense tissue. The opposite pattern was seen in women if age ≥55, 40.5 % (4340/10713) with dense breast tissue [5]. Comparing women of age <55 years with those of age ≥55, we see that the proportion of the women of age <55 with dense tissue was higher in women with in situ cancer than in women with local invasive disease, regional disease, and distant metastases ($p$ values = 0.003, 0.023, and 0.057, respectively) (Table 2). For women of age ≥55, those who have in situ cancer did not have a significantly higher proportion of dense breast tissue compared with women who are in the regional stage ($p$ value = 0.692). While the proportion of women of age <55 with dense tissue was not significantly different between local and regional or distant stage diagnoses ($p$ value > 0.1), for women of age ≥55, the proportion with dense breast tissue in the local stage was significantly lower than that in the regional stage ($p$ value = 0.0003). When comparing the regional and distant stages, there is not a significant difference in the proportion of women of age <55 with dense breast tissue, but the proportion is significantly higher in the regional stage than the proportion in the distant stage for women of age ≥55 (Table 2).

## Effect of density on breast cancer mortality controlling for age, race, and stage

Table 3 summarizes the results from the cause-specific Cox proportional hazards models that assess the relative breast cancer mortality (BC mortality) hazard (risk). When controlling for the effects of race and stage, in the non-stratified Cox model, we found that the BC mortality increased by 0.7 % per year as women aged (Table 3A), and white women had lower BC mortality than African American women ($p < 0.0001$). Women with in situ and local cancers had lower BC mortality than women with cancers of unknown stage (HR: 0.155 and 0.631, respectively, and both $p$ values < 0.0001). The diagnosis of a regional cancer increased the BC mortality almost three-fold (HR: 2.868, $p$ value < 0.0001), and the BC mortality increased more than 19-fold for distant cancers (HR: 19.27, $p$ value < 0.0001). Most important, we found no significant difference in BC mortality between women with dense and fatty breast tissue ($p$ value = 0.12).

By allowing the baseline hazard to vary across different age and racial groups, the stratified model showed that regional and distant cancer stage increased the hazard of dying from breast cancer (HR: 2.839 and 18.383,

**Table 2** Breast density distribution by age and cancer stage

| Cancer stage | Age <55 ($N$ = 6,464) | | Age ≥55 ($N$ = 10,713) | | Total |
|---|---|---|---|---|---|
| | Dense $N$ (%) | Fatty $N$ (%) | Dense $N$ (%) | Fatty $N$ (%) | |
| In situ | 572 (66.0) | 295 (34.0) | 606 (44.2) | 764 (55.8) | 2,237 |
| Local | 1,488 (60.3) | 979 (39.7) | 1,922 (40.2) | 2,855 (59.8) | 7,244 |
| Regional | 945 (61.3) | 596 (38.7) | 924 (44.9) | 1,133 (55.1) | 3,598 |
| Distant | 71 (57.3) | 53 (42.7) | 83 (36.4) | 145 (63.6) | 352 |
| Unknown | 729 (49.8) | 736 (50.2) | 805 (35.3) | 1,476 (64.7) | 3,746 |
| Total | 3,805 (58.9) | 2,659 (41.1) | 4,340 (40.5) | 6,373 (59.5) | 17,177 |

| Pairwise comparison | Proportion difference (%)[a] | $p$ value[b] | Proportion difference (%) | $p$ value |
|---|---|---|---|---|
| I–L | 5.7 | 0.003 | 4.0 | 0.008 |
| I–R | 4.7 | 0.023 | −0.7 | 0.692 |
| I–D | 8.7 | 0.057 | 7.8 | 0.027 |
| L–R | −1.0 | 0.525 | −4.7 | 0.0003 |
| L–D | 3.1 | 0.497 | 3.8 | 0.249 |
| R–D | 7.5 | 0.372 | 1.1 | 0.014 |

*I* in situ, *L* local, *R* regional, *D* distant, − pair-wise difference

[a] Difference of dense tissue proportion in cancer stages by age groups (e.g., age <55, I-L: 66–60.3 % = 5.7 %)

[b] Comparison of the proportion using two-proportion $z$ test

**Table 3** Effect of breast density on mortality controlling for other factors using Cox proportional hazards model

| Covariate | Parameter estimate | *P* value | Hazard ratio |
|---|---|---|---|
| **A.** Non-stratified Cox model | | | |
| Age | 0.00664 | 0.0045 | 1.007 |
| White | −0.60038 | <0.0001 | 0.549 |
| In situ | −1.86234 | <0.0001 | 0.155 |
| Local | −0.46056 | <0.0001 | 0.631 |
| Regional | 1.05354 | <0.0001 | 2.868 |
| Distant | 2.95857 | <0.0001 | 19.270 |
| Dense | −0.09597 | 0.1242 | 0.908 |
| Baseline case: age 18, African American, unknown cancer stage, and fatty breast | | | |
| **B.** Controlling for age group[a] and race | | | |
| In situ | −1.84934 | <0.0001 | 0.157 |
| Local | −0.46880 | <0.0001 | 0.626 |
| Regional | 1.04340 | <0.0001 | 2.839 |
| Distant | 2.91140 | <0.0001 | 18.383 |
| Dense | −0.11301 | 0.0717 | 0.893 |
| Baseline case: unknown cancer stage, and fatty breast; stratified on age group[a] and race | | | |
| **C.** Controlling for age group[b] and cancer stage | | | |
| White | −0.56532 | <0.0001 | 0.568 |
| Dense | −0.11622 | 0.0619 | 0.890 |
| Baseline case: African American, and fatty breast; stratified on age group[b] and cancer stage | | | |

[a] Age group: <40, 40–49, 50–59, 60–69, 70–79, ≥80

[b] Age group: <55, ≥55

respectively) (Table 3B). African American women had a higher BC mortality when stratified by age group and cancer stage. In both stratified models, there was not a significant difference in the BC mortality between women with dense and fatty breast tissue at a 5 % significance level, $p$ value = 0.0717 and 0.0619, respectively (Table 3C).

## Estimation of mortality probabilities over time

The curves for the cumulative mortality probabilities for each group are presented in Fig. 3A (by age, race, and density) and 3B (by age, cancer stage, and density) with corresponding summary statistics in Table 4A, B, respectively. For each graph, the estimated mortality probabilities over time for breast cancer (pink) and other causes (black) are plotted with solid lines, while confidence intervals are plotted with dashed lines. The $y$-axis corresponds to the cumulative mortality probability, and the $x$-axis is the time since diagnosis (in months). The mortality probabilities are plotted over a 160-month horizon (approximately 13 years) unless otherwise noted. The number of deaths and estimates of the BC and other cause (OC) of mortality probabilities with the associated 95 % confidence intervals (CIs) at 5, 10, and 13 years are summarized in Table 4A, B.

African American women had a statistically higher probability of dying from BC than white women, particularly for women diagnosed between the ages of 40 and 59 (for all three mortality estimates at 5, 10, and 13 years). In fact, for African American women with dense breast tissue between the ages of 40 and 49, the CI for 10-year BC mortality (0.111, 0.202) was significantly higher than for white women (0.049, 0.080). The effect of breast density was most apparent for women aged 70–79. There was a significant difference in the BC mortality between African American and white women with fatty breast tissue (a 10-year mortality probability between (0.112, 0.223) compared to (0.065, 0.097), but not for African American and white women with dense breast tissue [e.g., (0.095, 0.243) compared to (0.053, 0.098)]). For the other age groups, although the point estimate for the BC mortality probability was always higher for African American women, no statistically significant differences could be identified.

For white women, while the BC mortality probabilities did not indicate significant differences between age groups, younger women were more likely to die from BC while older women had a significantly higher probability of dying from OC, regardless of breast density. Within an age group, there was not a significant difference in mortality (BC or OC) between the dense and fatty groups [e.g., (0.056, 0.090) vs. (0.054, 0.083) for 60–69 age group].

For African American women, while BC mortality probabilities were significantly higher than OC mortality in younger ages, for those 60 years and older there was not enough evidence to indicate significant differences in the BC and OC mortality probabilities. The CIs had similar patterns with respect to the BC and OC mortality curves between dense and fatty groups across all ages, except for those over 80. In this age group, the 10-year mortality 95 % CI for BC (0.091, 0.349) and OC (0.213, 0.460) overlapped in the dense group, while in the fatty group the 95 % CIs are (0.078, 0.238) and (0.407, 0.594) respectively, which suggested significant differences.

As shown in Fig. 3B, the more advanced the stage at diagnosis, the higher the BC mortality probability. However, for women with dense breasts, the 95 % CI for the distant BC stage overlapped with the regional stage for women aged <55 [(0.184, 0.747) vs. (0.159, 0.222)], and similarly for women aged ≥55 [(0.084, 0.861) vs. (0.138, 0.201)]. On the contrary, the CIs did not overlap for the fatty group. The two density groups behave similarly with respect to all other aspects, controlling for age and cancer stage.

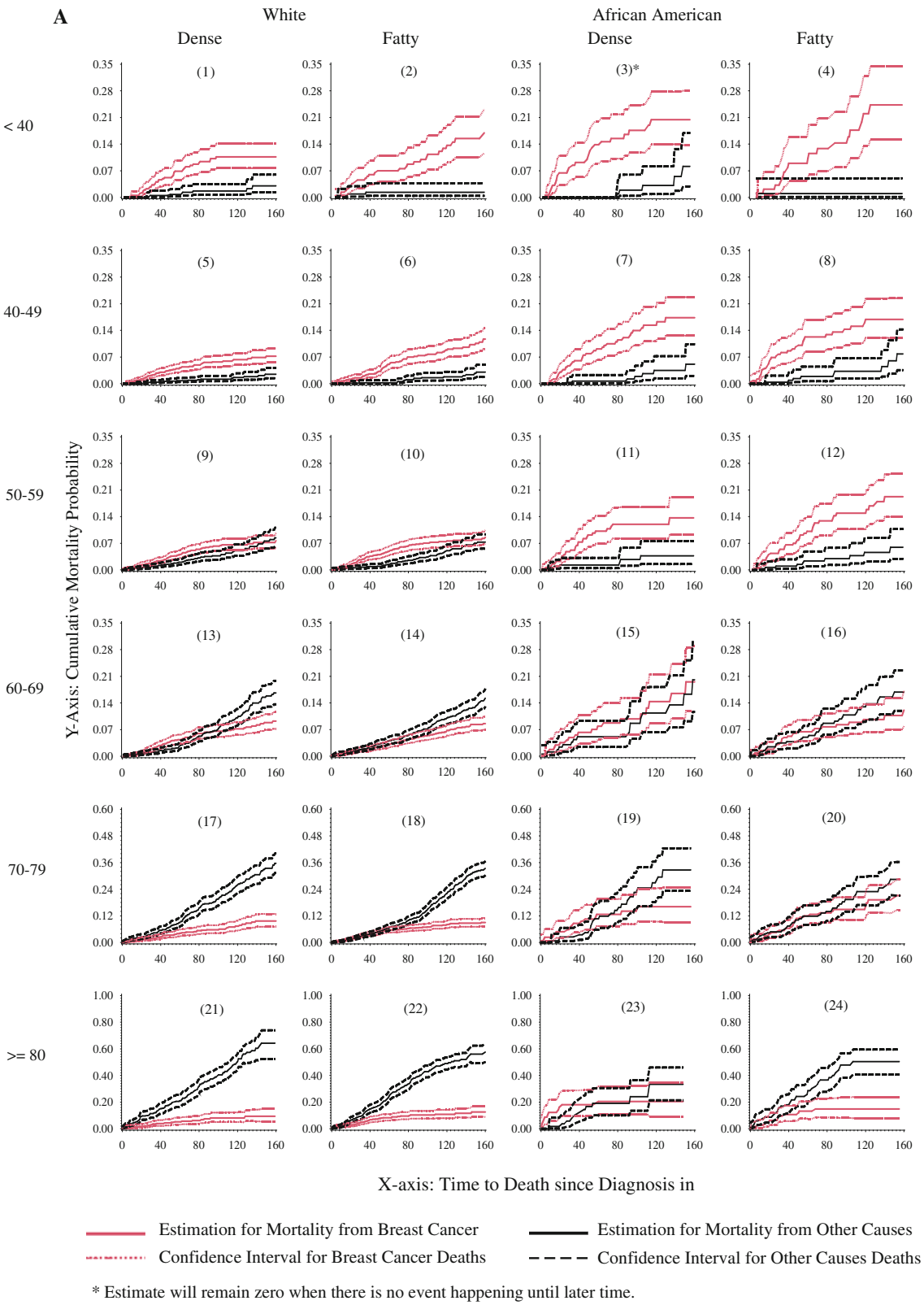


**Fig. 3** Mortality probability with confidence interval by **A** age group, race, and density, **B** age group, cancer stage, and density

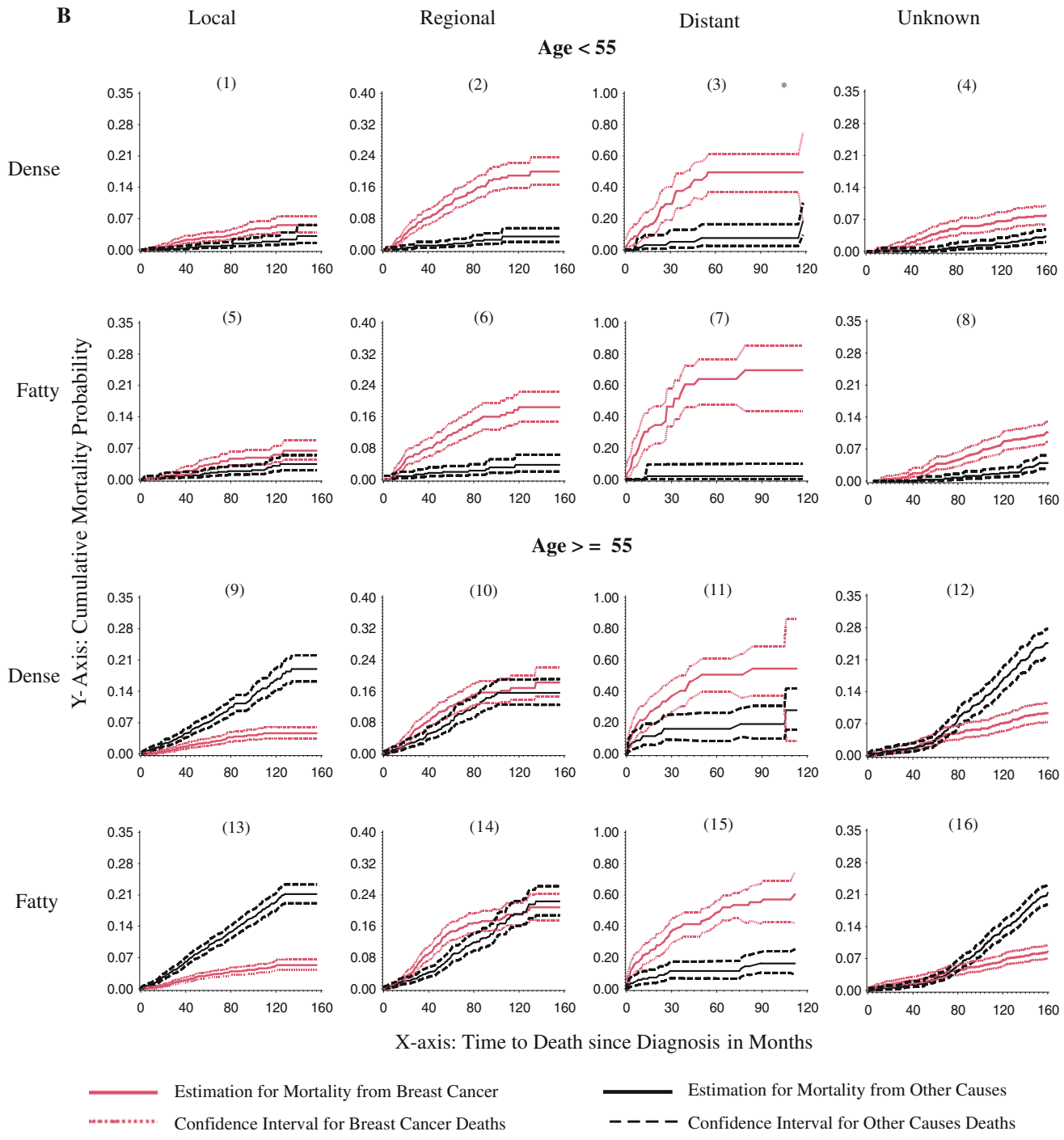


**Fig. 3** continued

## Discussion

Our results suggest that although women with dense breast tissue are known to have a higher risk of developing breast cancer, density does not have a significant effect on mortality for women with breast cancer after controlling for incidence. While the effects of various breast cancer risk factors on mortality have been well studied in the literature [1, 10, 16–18], the role of breast density has not been extensively explored, although it is an important breast cancer risk factor. We explored the effect of breast density on mortality outcomes for women, while controlling for the

**Table 4** Summary of study population and estimation of mortality probabilities with 95 % confidence interval by (**A**) age, race, and density; (**B**) age, cancer stage, and density

| Age | Race | Density | Counts | | Mortality at 5-year (60 months) | | Mortality at 10-year (120 months) | | Mortality at 13-year (156 months) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Grp | | | BCD | OCD | BC prob est(CI) | OC prob est(CI) | BC prob est(CI) | OC prob est(CI) | BC prob est(CI) | OC prob est(CI) |
| **A** | | | | | | | | | | |
| <40 | W | Dense | 38 | 8 | 0.069 (0.046–0.097) | 0.008 (0.002–0.022) | 0.106 (0.077–0.141) | 0.017 (0.007–0.035) | 0.106 (0.077–0.141) | 0.031 (0.013–0.060) |
| | | Fatty | 31 | 3 | 0.070 (0.041–0.109) | 0.014 (0.004–0.037) | 0.137 (0.092–0.191) | 0.014 (0.004–0.037) | 0.155 (0.106–0.212) | 0.014 (0.004–0.037) |
| | AA | Dense | 26 | 5 | 0.138 (0.089–0.199) | 0[a] | 0.204 (0.139–0.277) | 0.032 (0.009–0.082) | 0.204 (0.137–0.280) | 0.081 (0.029–0.169) |
| | | Fatty | 18 | 1 | 0.102 (0.051–0.175) | 0.010 (0.001–0.050) | 0.220 (0.135–0.318) | 0.010 (0.001–0.050) | 0.243 (0.153–0.344) | 0.010 (0.001–0.050) |
| 40–49 | W | Dense | 71 | 21 | 0.041 (0.031–0.054) | 0.008 (0.004–0.015) | 0.063 (0.049–0.080) | 0.016 (0.009–0.027) | 0.072 (0.055–0.092) | 0.025 (0.014–0.041) |
| | | Fatty | 79 | 16 | 0.051 (0.037–0.068) | 0.002 (0.001–0.008) | 0.088 (0.068–0.111) | 0.018 (0.010–0.031) | 0.119 (0.085–0.137) | 0.031 (0.017–0.050) |
| | AA | Dense | 40 | 8 | 0.091 (0.062–0.127) | 0.007 (0.001–0.022) | 0.154 (0.111–0.202) | 0.035 (0.014–0.072) | 0.173 (0.126–0.227) | 0.051 (0.020–0.104) |
| | | Fatty | 34 | 10 | 0.123 (0.084–0.168) | 0.019 (0.006–0.045) | 0.169 (0.120–0.224) | 0.033 (0.013–0.066) | 0.169 (0.119–0.225) | 0.078 (0.035–0.143) |
| 50–59 | W | Dense | 78 | 60 | 0.041 (0.031–0.053) | 0.020 (0.013–0.029) | 0.066 (0.052–0.082) | 0.051 (0.037–0.068) | 0.072 (0.056–0.090) | 0.080 (0.059–0.105) |
| | | Fatty | 96 | 70 | 0.049 (0.038–0.062) | 0.015 (0.010–0.023) | 0.076 (0.061–0.092) | 0.051 (0.038–0.067) | 0.080 (0.064–0.097) | 0.073 (0.056–0.094) |
| | AA | Dense | 30 | 7 | 0.102 (0.069–0.143) | 0.013 (0.004–0.031) | 0.120 (0.083–0.165) | 0.037 (0.015–0.076) | 0.137 (0.092–0.190) | 0.037 (0.015–0.076) |
| | | Fatty | 40 | 11 | 0.101 (0.069–0.141) | 0.024 (0.010–0.048) | 0.149 (0.107–0.198) | 0.046 (0.022–0.084) | 0.192 (0.139–0.252) | 0.060 (0.029–0.108) |
| 60–69 | W | Dense | 79 | 111 | 0.044 (0.033–0.057) | 0.027 (0.019–0.039) | 0.072 (0.056–0.090) | 0.101 (0.081–0.124) | 0.089 (0.069–0.111) | 0.163 (0.134–0.194) |
| | | Fatty | 103 | 173 | 0.031 (0.023–0.041) | 0.040 (0.031–0.051) | 0.068 (0.054–0.083) | 0.100 (0.084–0.118) | 0.083 (0.067–0.101) | 0.146 (0.124–0.169) |
| | AA | Dense | 20 | 17 | 0.079 (0.043–0.128) | 0.051 (0.024–0.093) | 0.144 (0.086–0.215) | 0.114 (0.063–0.181) | 0.195 (0.119–0.285) | 0.163 (0.092–0.252) |
| | | Fatty | 27 | 38 | 0.064 (0.040–0.095) | 0.050 (0.029–0.079) | 0.096 (0.064–0.137) | 0.130 (0.090–0.177) | 0.107 (0.070–0.152) | 0.169 (0.119–0.226) |
| 70–79 | W | Dense | 48 | 160 | 0.041 (0.029–0.058) | 0.090 (0.070–0.112) | 0.074 (0.053–0.098) | 0.259 (0.223–0.297) | 0.097 (0.070–0.128) | 0.335 (0.293–0.378) |
| | | Fatty | 97 | 270 | 0.056 (0.044–0.070) | 0.067 (0.054–0.081) | 0.080 (0.065–0.097) | 0.221 (0.195–0.248) | 0.090 (0.073–0.110) | 0.327 (0.296–0.358) |
| | AA | Dense | 16 | 23 | 0.126 (0.073–0.195) | 0.107 (0.058–0.174) | 0.161 (0.095–0.243) | 0.269 (0.182–0.364) | 0.161 (0.092–0.247) | 0.327 (0.232–0.425) |
| | | Fatty | 32 | 42 | 0.120 (0.080–0.168) | 0.119 (0.079–0.167) | 0.163 (0.112–0.223) | 0.229 (0.168–0.296) | 0.212 (0.147–0.284) | 0.285 (0.211–0.363) |
| ≥80 | W | Dense | 21 | 116 | 0.052 (0.030–0.082) | 0.211 (0.167–0.259) | 0.081 (0.050–0.123) | 0.506 (0.445–0.563) | 0.093 (0.053–0.147) | 0.643 (0.523–0.739) |
| | | Fatty | 50 | 187 | 0.083 (0.061–0.110) | 0.247 (0.210–0.285) | 0.108 (0.079–0.142) | 0.490 (0.444–0.534) | 0.126 (0.090–0.167) | 0.561 (0.492–0.624) |
| | AA | Dense | 11 | 11 | 0.204 (0.110–0.318) | 0.192 (0.100–0.305) | 0.204 (0.091–0.349) | 0.334 (0.213–0.460) | 0.204 (0.091–0.349) | 0.334 (0.213–0.460) |
| | | Fatty | 14 | 39 | 0.132 (0.075–0.205) | 0.286 (0.205–0.373) | 0.148 (0.078–0.238) | 0.504 (0.407–0.594) | 0.148 (0.078–0.238) | 0.504 (0.407–0.594) |
| **B** | | | | | | | | | | |
| <55 | L | Dense | 47 | 17 | 0.028 (0.019–0.038) | 0.008 (0.004–0.015) | 0.051 (0.037–0.069) | 0.019 (0.010–0.031) | 0.055 (0.040–0.074) | 0.031 (0.015–0.055) |
| | | Fatty | 38 | 19 | 0.032 (0.021–0.046) | 0.013 (0.007–0.023) | 0.055 (0.039–0.075) | 0.030 (0.018–0.048) | 0.064 (0.045–0.088) | 0.034 (0.020–0.054) |
| | R | Dense | 119 | 18 | 0.117 (0.096–0.141) | 0.014 (0.008–0.025) | 0.190 (0.159–0.222) | 0.034 (0.020–0.054) | 0.200 (0.166–0.236) | 0.034 (0.020–0.054) |
| | | Fatty | 76 | 14 | 0.114 (0.088–0.143) | 0.019 (0.010–0.034) | 0.184 (0.147–0.225) | 0.037 (0.020–0.063) | 0.184 (0.147–0.225) | 0.037 (0.020–0.063) |
| | D | Dense | 27 | 5 | 0.495 (0.369–0.609) | 0.075 (0.025–0.163) | 0.495 (0.184–0.747) | 0.183 (0.092–0.297) | NA[b] | NA |
| | | Fatty | 29 | 1 | 0.642 (0.476–0.767) | 0.022 (0.002–0.098) | 0.698 (0.437–0.855) | 0.022 (0.002–0.100) | NA | NA |
| | U | Dense | 61 | 28 | 0.037 (0.025–0.053) | 0.003 (0.001–0.010) | 0.066 (0.049–0.086) | 0.018 (0.010–0.030) | 0.077 (0.059–0.099) | 0.031 (0.019–0.046) |
| | | Fatty | 92 | 34 | 0.035 (0.023–0.050) | 0.003 (0.001–0.010) | 0.084 (0.065–0.106) | 0.017 (0.009–0.029) | 0.100 (0.079–0.124) | 0.039 (0.027–0.056) |

**Table 4** continued

| Age Grp | Race | Density | Counts | | Mortality at 5-year (60 months) | | Mortality at 10-year (120 months) | | Mortality at 13-year (156 months) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | BCD | OCD | BC prob est(CI) | OC prob est(CI) | BC prob est(CI) | OC prob est(CI) | BC prob est(CI) | OC prob est(CI) |
| ≥55 | L | Dense | 53 | 174 | 0.025 (0.018–0.034) | 0.070 (0.058–0.084) | 0.046 (0.034–0.060) | 0.165 (0.141–0.191) | 0.046 (0.034–0.060) | 0.190 (0.162–0.220) |
| | | Fatty | 92 | 338 | 0.030 (0.024–0.038) | 0.094 (0.082–0.106) | 0.051 (0.041–0.063) | 0.194 (0.175–0.214) | 0.053 (0.042–0.065) | 0.212 (0.191–0.234) |
| | R | Dense | 103 | 83 | 0.122 (0.099–0.148) | 0.086 (0.066–0.108) | 0.168 (0.138–0.201) | 0.157 (0.126–0.190) | 0.183 (0.147–0.221) | 0.157 (0.126–0.191) |
| | | Fatty | 153 | 122 | 0.146 (0.124–0.170) | 0.083 (0.066–0.103) | 0.190 (0.162–0.220) | 0.192 (0.161–0.225) | 0.208 (0.176–0.243) | 0.224 (0.188–0.263) |
| | D | Dense | 35 | 14 | 0.507 (0.397–0.607) | 0.161 (0.083–0.263) | 0.545 (0.084–0.861) | 0.279 (0.155–0.418) | NA | NA |
| | | Fatty | 67 | 19 | 0.483 (0.403–0.558) | 0.114 (0.065–0.176) | 0.604 (0.419–0.746) | 0.163 (0.092–0.253) | 0.604 (0.291–0.814) | 0.202 (0.127–0.289) |
| | U | Dense | 136 | 350 | 0.035 (0.024–0.050) | 0.032 (0.021–0.046) | 0.070 (0.053–0.090) | 0.165 (0.140–0.193) | 0.091 (0.072–0.113) | 0.239 (0.210–0.270) |
| | | Fatty | 208 | 443 | 0.031 (0.023–0.040) | 0.026 (0.019–0.035) | 0.066 (0.054–0.080) | 0.134 (0.116–0.152) | 0.082 (0.069–0.098) | 0.206 (0.186–0.228) |

*Grp* group, *W* white, *AA* African American, *BCD* breast cancer death, *OCD* other cause death, *Prob Est* probability Estimate, *CI* confidence interval

[a] When there is no event observed, the probability estimate is zero with no confidence interval

[b] There is no event (mortality or censoring) observed beyond this time point

effect of breast cancer incidence, using data from the community-based CMR that was linked with the state cancer registry and death tapes. Previous research does not differentiate the effect of density on incidence and mortality with respect to patient demographics [8, 9]. Our study separates the effect of breast density on incidence to identify the effect of breast density on mortality over time as a function of race.

The effects of age, race, and cancer stage on breast cancer and other cause mortality were consistent with earlier estimates [1, 10, 12, 16] that did not consider density. The proportion of dense breast is similar between white and African American, but differs by cancer stage. For younger women, significantly more women with dense breast tissue were diagnosed at the in situ stage. This may be due to the fact that calcifications, but not masses, are more easily seen in dense tissue and are associated with DCIS. Women with dense and fatty breast tissues have similar mortality probabilities after adjusting for age, race, incidence, and cancer stage effects. This suggests that women with breast cancer and dense breast tissue do not have poorer survival than those with fatty breast tissue. The risk factor dense breast tissue only affects the diagnosis. In general, African American women have a higher mortality probability compared to white women, but the difference in mortality is not attributed to breast density, except possibly for women 70–79. Density may potentially reduce the effect of race on mortality in this age group.

The methods in this study differ from prior research [17–19]. In this paper, deaths from other causes are modeled as competing risks for women with breast cancer to not overestimate the breast cancer mortality risk by failing to compensate for competing risk. The research by Schairer et al. [16] used surveillance, epidemiology, and end results (SEER) data to calculate the short-term and long-term cumulative mortality probabilities by age, race, breast cancer stage, and estrogen receptor status and concluded that these selected covariates had different impacts on mortality probabilities from breast cancer and other causes. Our study extends the Schairer et al. study to include breast density, and confidence interval approximation for the mortality estimates. Our method provides an estimate for the mortality probabilities so that risks may be visually compared among different groups.

There are some limitations to this study. Small sample sizes may affect some of the confidence intervals. This means that the point estimate should not be ignored when comparing probabilities among different groups. Another limitation is that lifetime follow-up for the women is not available as the CMR started in 1994. We also did not consider comorbidities, though comorbidities should not differ by breast density. Future research should estimate long-term mortality for women with breast cancer with different risk

information and study the effect of additional risk factors on mortality for breast cancer patients.

In conclusion, our study results suggest that mammographic breast density, though a risk factor for breast cancer in women, is not associated with breast cancer mortality for African American or white women, when the effect of cancer incidence is accounted for and removed.

**Acknowledgments** We would like to thank the Carolina Mammography Registry for providing onsite access to the data for this study. We also thank Dr. James Wilson at North Carolina State University for reading and reviewing our manuscript.

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. McCormack VA, dos Santos Silva I (2006) Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemol Biomarkers Prev 5:1159–1169
2. American Cancer Society. What are the risk factors for breast cancer? Available at: http://www.cancer.org/Cancer/BreastCancer/DetailedGuide/breast-cancer-risk-factors. Accessed 30 June 2010
3. Carney PA, Miglioretti DL, Yankaskas BC et al (2003) Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. Ann Intern Med 138:168–175
4. Kerlikowske K, Ichikawa L, Miglioretti DL et al (2007) Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer. J Natl Cancer Inst 99:386–395
5. Boyd NF, Guo H, Martin LJ et al (2007) Mammographic density and the risk and detection of breast cancer. N Engl J Med 356:227–236
6. Olsen AH, Bihrmann K, Jensen MB et al (2009) Breast density and outcome of mammography screening: a cohort study. Br J Cancer 100:1205–1208
7. Brown AJ (2009) "Mammographically dense breasts found in many older women, too." Reuters Health. Reuters, 27 April. Assessed Nov 2011
8. Chiu SY, Duffy S, Yen AM et al (2010) Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. Cancer Epidemiol Biomarkers Prev 19(5):1219–1228
9. Gierach GL, Ichikawa L, Kerlikowske K et al (2012) Relationship between mammographic density and breast cancer death in the breast cancer surveillance consortium. J Natl Cancer Inst 104:1218–1227
10. American Cancer Society (2012) Cancer facts and figures 2012. American Cancer Society, Atlanta
11. Chu KC, Miller BA, Feuer FJ et al (1994) A method for partitioning cancer mortality trends by factors associated with diagnosis: an application to female breast cancer. J Clin Epidemiol 47:1451–1461
12. Jatoi I, Chen BE, Anderson WF, Rosenberg PS (2007) Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. J Clin Oncol 25:1683–1690
13. Jernal A, Center MM, DeSantis C, Ward EM (2010) Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 19(8):1893–1907
14. Berry DA, Cronin KA, Plevritis SK et al (2005) Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784–1792
15. Berry DA, Inoue L, Shen Y et al (2006) Modeling the impact of treatment and screening on U.S. breast cancer mortality: a Bayesian approach. J Natl Cancer Inst Monogr 36:30–36
16. Schairer C, Mink PJ, Carroll L, Devesa S (2004) Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 96(17):1311–1321
17. Rosenberg MA (2006) Competing risks to breast cancer mortality. J Natl Cancer Inst Monogr 36:15–19
18. Lee S, Zelen M (2006) A stochastic model for predicting the mortality of breast cancer. J Natl Cancer Inst Monogr 36:79–86
19. Fryback DG, Stout NK, Rosenber MA et al (2006) The Wisconsin breast cancer epidemiology simulation model. J Natl Cancer Inst Monogr 36:37–47
20. Carolina Mammography Registry. Available at: http://www.unc.edu/cmr. Accessed 30 June 2010
21. Breast cancer surveillance consortium. Available at: http://breastscreening.cancer.gov. Accessed 30 June 2010
22. ICD-9-CM Code for cause of death. Available at: http://www.ihs.gov/publicinfo/publications/trends96/96trind.pdf. Accessed 30 June 2010
23. ICD-10-CM Code for cause of death. Available at: http://www.cdc.gov/nchs/data/dvs/im9_2002.pdf.pdf. Accessed 30 June 2010
24. American College of Radiology (2003) Breast imaging reporting and data system atlas (BI-RADS Atlas). American College of Radiology, Reston
25. Minkin MJ, Wright CV (1997) What every woman needs to know about menopause: the years before, during, and after. Yale University Press, New Haven and London
26. International planned parenthood federation. Women near menopause. Available at: http://www.ippf.org/en/Resources/Guides-toolkits/Women+near+menopause.htm. Accessed Nov 2011
27. Lunn M, McNeil D (1995) Applying Cox regression to competing risks. Biometrics 51:524–532
28. Kalbfleisch JD, Prentice RL (1980) The statistical analysis of failure time data. Wiley, New York
29. Prentice RL, Kalbfleisch JD (1978) The analysis of failure times in the presence of competing risks. Biometrics 34:541–554
30. Pepe MS, Mori M (1993) Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med 12:737–751
31. Gooley TA, Leisenring W, Crowley J, Storer BE (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 18:695–706
32. Marubini E, Valsecchi MG (1995) Analysing survival data from clinical trial and observational studies. Wiley, Chichester
33. Choudhury JB (2002) Non-parametric confidence interval estimation for competing risks analysis: application to contraceptive data. Stat Med 21:1129–1140
34. Zhang S (2011) Modeling the complexity of breast cancer under conditions of uncertainty. Ph.D. Dissertation, Edward P. Fitts Department of Industrial and Systems Engineering, North Carolina State University, Raleigh