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Body mass index, tumor characteristics, and prognosis following diagnosis of early stage breast cancer in a mammographically-screened population

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Abstract

Purpose—Many studies suggest increased body mass index (BMI) is associated with worse breast cancer outcomes, but few account for variability in screening, access to treatment, and tumor differences. We examined the association between BMI and risk of breast cancer recurrence, breast cancer-specific mortality, and all-cause mortality, and evaluated whether tumor characteristics differ by BMI among a mammographically-screened population with access to treatment.

Methods—Using a retrospective cohort study design, we followed 485 women aged ≥40 years diagnosed with stage I/II breast cancer within 24 months of a screening mammogram occurring between 1988 and 1993 for 10-year outcomes. BMI before diagnosis was categorized as normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). Tumor marker expression was assessed via immunohistochemistry using tissue collected before adjuvant treatment. Medical records were abstracted to identify treatment, recurrence, and mortality. We used Cox proportional hazards to separately model the hazard ratios (HR) of our three outcomes by BMI while adjusting for age, stage, and tamoxifen use.

Results—Relative to normal weight women, obese women experienced increased risk of recurrence (HR-2.43; 95%CI-1.34–4.41) and breast cancer death (HR-2.41; 95%CI-1.00–5.81) within 10 years of diagnosis. There was no association between BMI and all-cause mortality. Obese women had significantly faster growing tumors, as measured by Ki-67.

Conclusions—Our findings add to the growing evidence that obesity may contribute to poorer breast cancer outcomes, and also suggest that increased tumor proliferation among obese women is a pathway that explains part of their excess risk of adverse outcomes.

Keywords

breast cancer recurrence; breast cancer specific mortality; tumor characteristics; obesity; body mass index

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Background

Many studies have demonstrated positive associations between body mass index (BMI) and increased breast cancer recurrence and mortality rates in pre-(1–4) and postmenopausal(1, 5, 6) women. These studies have reported risk estimates for higher BMI ranging from 1.1 to 4.2, relative to normal weight women,(1–11) with stronger and more consistent evidence for postmenopausal women.(1, 6) However, other studies have observed no association between body mass and breast cancer prognosis.(12–18)

There has been substantial variation in the design and methods of these prior studies, including age ranges of the study populations, measurement of body mass (weight adjusted for height vs. BMI), BMI cut-points, how and when BMI is measured (self-report vs. measured, and timing relative to diagnosis), length of follow-up, how mortality is defined (overall vs. breast cancer-specific), examination of tumor characteristics, ability to account for treatment differences (primary and adjuvant therapy receipt), and control of other confounding factors. Heterogeneity in these design features could partly account for the observed inconsistencies in reported findings.

Our study examines the relationship between BMI and risk of breast cancer recurrence, breast cancer-specific mortality, and all-cause mortality in a cohort of women aged ≥40 years who were diagnosed with early-stage invasive breast cancer following a screening mammogram, taking into account treatment and multiple potential confounders. We were also able to examine associations between BMI and tumor characteristics (p53, c-erbB-2, bcl-2, Ki-67, p27, cyclin E, and estrogen and progesterone receptor (ER/PR)), to evaluate whether specific attributes might explain any observed differences in prognosis.

Methods

We conducted a retrospective cohort study within Group Health Cooperative (GHC), an integrated health care delivery system in western Washington State with approximately 450,000 members. The population-based Breast Cancer Screening Program (BCSP)(19, 20) was used to identify the cohort. Self-reported breast cancer risk factor data were obtained from women when they joined the BCSP and at each subsequent mammogram.(21) Cancer diagnoses were identified using the western Washington's Surveillance Epidemiology and End Results (SEER) cancer registry.

We studied female GHC members aged ≥40 years (mean: 64.5 years; range: 40–93 years) at the time of their diagnosis of an incident, early-stage (stage I or II(22)), invasive breast cancer. The BCSP collected information about symptoms reported at the time of mammography and also the radiologists' indication for the exam. Women were diagnosed within 24 months of a screening mammogram (per BCSP indication), which took place between January 1, 1988 and December 31, 1993.(23, 24) We excluded women with any prior history of breast cancer, with breast implants, or who disenrolled from the health plan for any reason other than death in the 24-month period following their mammogram.

Self-reported height and weight were collected at the time of the screening mammogram (mean time between questionnaire and diagnosis: 144 days [standard deviation: 196 days]) and were used to calculate BMI. Women with missing height and weight measurements (n=17) were excluded. BMI was categorized into: normal weight (<25 kg/m^2; n=246), overweight (25–<30 kg/m^2; n=149) and obese (≥30 kg/m^2; n=90).(25) There were insufficient numbers in the extreme weight categories to separately examine underweight (<18.5 kg/m^2; n=9) or extremely obese (≥40 kg/m^2; n=10) women. The questionnaire also collected demographic and breast cancer risk factor data.

Final mammographic evaluations were recorded according to the American College of Radiology Breast Imaging Reporting and Data System(26) (BI-RADS) guidelines and used to classify mode of detection. Interval cancers were those diagnosed following a negative screening mammogram (BI-RADS negative or benign finding). Screen-detected cancers were those diagnosed after a positive mammogram (BI-RADS probably benign finding—short interval follow-up suggested; suspicious for malignancy; highly suggestive of malignancy). Mammographic density ratings were determined by expert radiologist review and grouped into BI-RADS breast composition categories: 1) almost entirely fat, 2) scattered fibroglandular densities, 3) heterogeneously dense, and 4) extremely dense, which we further grouped into fatty (BI-RADS 1/2) and dense (BI-RADS 3/4).(27)

Breast tissue in paraffin blocks was collected before receipt of any adjuvant therapy; 56 women did not have available blocks and 9 had insufficient material, leaving 420 blocks suitable for assay. In some instances, tumor tissue was depleted before all antibodies could be run, resulting in slightly different numbers of tumors tested for each antibody.(24) The study pathologist (PLP) histologically examined and assessed selected protein expression by immunohistochemistry (p53, c-erb B-2, bcl-2, Ki-67, p27, cyclin E, and ER/PR).(24) Fluorescence in situ hybridization (FISH) assays for intermediate values were not routinely performed at the time so we excluded these values (n=38) for analysis of c-erb B-2. Differentiation, nuclear grade, mitotic index, lymphatic or vascular invasion, levels of tumor necrosis, stromal and lymphocyte response, and percent *in situ* component were also measured. Other tumor characteristics were available from the SEER registry including histology, lymph node involvement, and tumor size, site, and extension.

We abstracted medical records for up to 10 years after diagnosis to identify treatment received and subsequent breast cancer diagnoses; date and cause of death were identified from a combination of state death files and medical record review. Primary surgery was separated into breast conserving surgery, with or without radiation treatment, or mastectomy.(28–30) We determined whether women received any chemotherapy, whether they completed their recommended chemotherapy and/or radiation therapy series, and whether they received tamoxifen.(28–30) We defined breast cancer recurrence as any breast cancer in the ipsilateral breast or regional and distant sites >120 days following completion of the initial course of therapy.(29) We recorded all second primary cancers that occurred in the contralateral breast (n=21). We classified women as having died of breast cancer if their death certificate indicated that breast cancer was the primary cause of death.(30)

All statistical tests were two-sided (alpha ≤0.05). We estimated age-adjusted relative risks (RR) for tumor characteristics associated with overweight and obese women relative to normal weight women using multinomial logistic regression for categorical outcomes and a modified Poisson regression approach using generalized linear models with a log link and robust sandwich variance estimators for binary outcomes.(31) Cox proportional hazards models were used to estimate the hazard ratios (HR) between BMI and 10-year risk of breast cancer recurrence, breast cancer mortality, or all-cause mortality. For the mortality analyses, women contributed person-time from their date of initial breast cancer diagnosis to the first of the following: 1) date of death from all-cause or breast cancer-specific mortality) (failure time); 2) GHC disenrollment, defined as a lapse in membership of ≥60 days(23) (censored); or 3) 10-years post-diagnosis (censored). For our recurrence analyses, women contributed person-time as described above with two notable modifications; recurrence diagnosis date was considered the failure time and women were censored on their date of death date (all-cause) or second primary breast cancer diagnosis. All proportional hazards models were adjusted for age, cancer stage, and tamoxifen use. Other factors potentially related to both BMI and breast cancer, including ER/PR status, breast density, family history, and chemotherapy were not confounders in our study and were not included in final

multivariable models. As an exploratory analysis, we further adjusted models for Ki-67 to determine whether this tumor marker might mediate any association between BMI and prognosis. As sensitivity analyses we excluded underweight and extremely obese women, and we refit all Cox models using age instead of time-since-diagnosis as the time metric. This study was approved by GHC's Institutional Review Board.

Results

A majority of the 485 women included in our study were diagnosed with AJCC stage I (n=365) and nearly half were either overweight (30.7%) or obese (18.6%) at the time of their screening mammogram (Table 1). Obese women were most likely to report a family history of breast cancer (42.2% vs. 39.4% of normal weight and 26.9% of overweight), and most of their breast cancers were screen-detected (77.8% vs. 61.8% of normal weight and 68.5% of overweight). A larger proportion of normal weight women were current users of hormone therapy (29.7% vs. 20.1% of overweight and 15.6% of obese) and had dense breasts (43.4% vs. 19.6% of overweight and 12.8% of obese). There was no difference in receipt of any chemotherapy by BMI; however, among women who did receive chemotherapy, a higher proportion of obese women completed their recommended chemotherapy series (100% vs. 88.4% of normal weight and 89.7% of overweight). We observed no differences in surgery type, tamoxifen use, ER/PR status, time since last screening mammogram, age at diagnosis, and stage at diagnosis by BMI.

We observed an increased age-adjusted risk (RR, 95%CI) of a higher Ki-67 ratio (≥25% vs. <25%) in the tumors of obese (1.22, 1.04–1.43) women compared to normal weight women (Table 2, p_{trend}=0.013). There were no notable differences in other tumor characteristics by BMI. We observed no appreciable differences in results when we excluded underweight and extremely overweight women (n=19) from the analyses.

In 10-years of follow-up, 12.2% of women experienced a recurrence and 6.9% died from their breast cancer. 20.9% of the cohort died from any cause within 10-years of their initial breast cancer diagnosis (Table 3). Obese women experienced the highest rates of all outcomes compared to overweight and normal weight women. In multivariable models adjusting for age, stage, and tamoxifen use, there was no difference in 10-year recurrence risk (HR, 95%CI) among overweight women relative to normal weight women. However, recurrence risk (2.43, 1.34–4.41) was increased for obese women relative to normal weight women. A nonsignificant elevation in breast cancer mortality risk (2.41, 1.00–5.81) was observed for obese women relative to normal weight women, but not for overweight women. There was no association between BMI and all-cause mortality in the 10 years following diagnosis. Adding Ki-67 to the multivariable models attenuated the risks of both recurrence and breast cancer mortality for obese women (recurrence: 1.79, 0.91–3.53). Excluding women in the extreme weight categories or using age as the time scale, to better control for increasing comorbidity with age, did not alter our results.

Discussion

We observed higher rates of breast cancer recurrence and mortality among obese women diagnosed with early stage breast cancer in a study with no meaningful differences in a number of factors related to prognosis: recent screening, screen detection, breast density, access to treatment, or treatment differences. Tumor characteristics, including hormone receptor status, did not differ by BMI in this population of mammographically-screened women, with one notable exception—overweight and obese women had faster growing tumors, as measured by Ki-67. Our findings add to the growing evidence that obesity may contribute to poorer breast cancer outcomes among women with early stage breast cancers,

and also suggest that increased tumor proliferation among obese women is a pathway that explains part of the excess risk of adverse outcomes among obese women.

Our results mirror those recently reported in a large Danish study, which examined the association between BMI at diagnosis and breast cancer outcomes in women treated for early stage breast cancer over a 30-year follow-up period.(7) They reported just over a 40% increased risk of distant metastasis for overweight and obese women within 5–10 years following diagnosis, and around a 30% corresponding increase in the risk of breast cancer mortality compared to normal weight women. An important limitation of this study was that information on BMI was only available on one-third (n=18,967) of the cohort and was selectively available by initial treatment received (primarily women receiving chemotherapy).

To contrast, a major treatment trial(14) found no association between obesity and breast cancer recurrence among lymph-node negative, ER-positive women, but observed higher contralateral breast cancer rates. Results from these studies(7, 14) together suggest the influence of obesity on prognosis could, in part, be related to surveillance of the unaffected breast following initial diagnosis and potentially related to adequacy of primary therapy, since surveillance and primary therapy would have been tightly controlled in the treatment trial(14), but not the observational study(7). In the 10 years following their initial breast cancer diagnosis, 4.3% (n=21) of the women in our cohort experienced a contralateral breast cancer.

Prior research has indicated that inadequate chemotherapy dosing contributes to worse outcomes for obese women.(32, 33) This could also explain the discordant findings since the Danish study consisted primarily of women receiving chemotherapy, whereas most of the node-negative, ER-positive women with early stage disease included in the treatment trial would not be recommended to receive chemotherapy. We were able to determine that the obese women in our study were more likely to complete their recommended chemotherapy; however, information on dose was not available so adequacy of chemotherapy dosing could not be assessed.

While relatively few studies have examined tumor characteristics in relation to BMI, and reports focused on premenopausal women have been inconsistent with respect to the relationship between BMI and ER/PR status,(34–38) in a study of women <45 years, Daling and colleagues(4) reported that tumors of women in the highest quartile of BMI were more likely to be larger and have markers of high cellular proliferation (measured by high Ki-67 expression ratio, mitotic cell count, and S-phase fraction). Our results on Ki-67 and obesity lend further support to the hypothesis that heavier women may have faster growing tumors, which may be one of the pathways leading to poorer outcomes. Additional research exploring how tumor markers may differ by BMI will be interesting because it will enhance our understanding of body mass as a prognostic factor and may enable the identification of subgroups of breast cancer patients whose prognosis might be improved through weight loss.

Our study had several strengths. Prior studies have demonstrated different rates of screening by BMI with obese women less likely to receive mammographic screening.(39–42) The fact that all women in this study were diagnosed within 24 months of a screening mammogram equilibrates screening exposure by BMI. The integrated health plan setting greatly enhanced completeness of outcome information and allowed for long-term follow-up on a cohort of women with access to health care; further equalizing an important prognostic factor. Like many other studies, our measures of height and weight were self-reported, but all were taken

before diagnosis and receipt of any treatment. Additionally, all tumor makers were evaluated by one pathologist using a standard protocol with quality control measures in place.(24)

The size of our study was modest and we were unable to adjust for some potential confounders, including clear surgical margins and comorbidities. Weight change during and after treatment may be an important factor associated with prognosis,(43) and we plan to examine this in a subsequent analysis. There is evidence that suggests insulin resistance and diabetes may play a role in breast cancer prognosis,(44–46) but we were unable to evaluate these factors in our study. In the years since this study was initiated, breast cancer therapy has evolved to include the dissemination of selective estrogen-receptor modulators (SERMs), and later aromatase inhibitors (AIs).(47) Although we are unable to address the impact AI use may have on the association between BMI and prognosis, we were able to consider tamoxifen use, which is still used by a large proportion of women with early stage cancer today.(48) There are currently no clinical practice guidelines that tailor recommendations for hormone therapy by BMI.(47)

Obesity is a well-established risk factor for breast cancer in postmenopausal women. Our findings add to the growing evidence that high BMI is associated with worse long-term outcomes among women diagnosed with breast cancer. As the percentage of obese adults rises, increasing health promotion efforts towards decreasing body mass may well be a vital component of both breast cancer prevention strategies and survivorship care.

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Table 1

Characteristics of study population by body mass index (BMI) at screening mammogram before diagnosis of early-stage breast cancer.

Characteristic	BMI (kg/m^2) <25 (n=246) n(%)	25 – <30 (n=149) n(%)	≥30 (n=90) n(%)
Race			
White	227 (94.6)	137 (97.2)	79 (94.1)
Non-white	13 (5.4)	4 (2.8)	5 (6.0)
1st and/or 2nd degree family history of breast cancer			
No	149 (60.6)	109 (73.2)	52 (57.8)
Yes	97 (39.4)	40 (26.9)	38 (42.2)
Hormone therapy use			
Current	73 (29.7)	30 (20.1)	14 (15.6)
Former	71 (28.9)	54 (36.2)	29 (32.2)
Never	102 (41.5)	65 (43.6)	47 (52.2)
Time from current screen to prior screening mammogram			
0–36 months	79 (32.1)	47 (31.5)	32 (35.6)
37+ months	62 (25.2)	35 (23.5)	15 (16.7)
No previous mammogram	105 (42.7)	67 (45.0)	43 (47.8)
Age at diagnosis (years)			
<50	34 (13.8)	10 (6.7)	10 (11.1)
50–59	65 (26.4)	25 (16.8)	16 (17.8)
60–69	69 (28.1)	44 (29.5)	38 (42.2)
≥70	78 (31.7)	70 (47.0)	26 (28.9)
Stage at diagnosis(22)			
I	192 (78.1)	103 (69.1)	70 (77.8)
IIA/IIB	54 (22.0)	46 (30.9)	20 (22.2)
Mode of diagnosis†			
Screen-detected	152 (61.8)	102 (68.5)	70 (77.8)
Interval cancer	94 (38.2)	47 (31.5)	20 (22.2)
Mammographic breast density‡			
Fatty	133 (56.6)	115 (80.4)	75 (87.2)
Dense	102 (43.4)	28 (19.6)	11 (12.8)
Chemotherapy			
No	197 (82.1)	119 (80.4)	73 (83.0)
Yes	43 (17.9)	29 (19.6)	15 (17.1)
Chemotherapy series completed	38 (88.4)	26 (89.7)	15 (100.0)
Surgery type			
Breast conserving surgery with RT	140 (57.1)	97 (65.1)	56 (62.2)
Breast conserving surgery without RT	5 (2.0)	1 (0.7)	0 (0.0)
Mastectomy (with or without RT)	100 (40.8)	51 (34.2)	34 (37.8)

Characteristic	BMI (kg/m^2) <25 (n=246) n(%)	25 – <30 (n=149) n(%)	≥30 (n=90) n(%)
Radiation therapy series completed	144 (97.3)	101 (99.0)	58 (100)
Tamoxifen use			
No	132 (53.7)	80 (53.7)	43 (47.8)
Yes	114 (46.3)	69 (46.3)	47 (52.2)
ER/PR status			
ER+/PR+	145 (69.4)	92 (70.2)	57 (76.0)
ER+/PR−	34 (16.3)	18 (13.7)	8 (10.7)
ER−/PR+	8 (3.8)	6 (4.6)	0 (0.0)
ER−/PR−	22 (10.5)	15 (11.5)	10 (13.3)
Time in months between BMI measure and diagnosis, mean (sd)	5.1 (6.6)	4.5 (6.4)	3.9 (6.1)

†Screen-detected defined as diagnosis following a positive mammogram; interval cancers are those diagnosed following a negative mammogram.

‡Fatty defined as entirely fat or scattered fibroglandular; dense defined as heterogeneously dense or extremely dense.

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Table 2

Association between body mass index (BMI) and tumor markers among women with a diagnosis of early stage breast cancer.

				Age-adjusted RR* (95% CI)	
	BMI (kg/m^2)			BMI (kg/m^2)	
Tumor marker/characteristic**	**<25 (n=246)**	**25 – 29.9 (n=149)**	**≥30 (n=90)**	**25 – 29.9**	**≥30**
	n(%)	**n(%)**	**n(%)**		
ER/PR status (n=415)					
Either positive	187 (89.5)	116 (88.6)	65 (86.7)		
Both negative	22 (10.5)	15 (11.5)	10 (13.3)	1.17 (0.62, 2.23)	1.30 (0.64, 2.63)
BCL-2 (n=415)					
High	106 (50.7)	62 (47.3)	42 (56.0)		
Low	103 (49.3)	69 (52.7)	33 (44.0)	1.04 (0.84, 1.29)	0.89 (0.66, 1.18)
Cyclin E (n=414)					
Low	198 (94.7)	120 (92.3)	70 (93.3)		
High	11 (5.3)	10 (7.7)	5 (6.7)	1.65 (0.72, 3.76)	1.33 (0.48, 3.68)
P27 (n=415)					
Intermediate/high	102 (48.8)	77 (58.8)	36 (48.0)		
Low	107 (51.2)	54 (41.2)	39 (52.0)	0.83 (0.65, 1.06)	1.03 (0.80, 1.32)
P53 (n=410)					
Negative	178 (86.4)	114 (88.4)	66 (88.0)		
Positive	28 (13.6)	15 (11.6)	9 (12.0)	0.91 (0.51, 1.65)	0.90 (0.45, 1.82)
Ki-67 ratio (%) (n=412)					
0–24	76 (36.5)	39 (30.0)	17 (23.0)		
25–100	132 (63.5)	91 (70.0)	57 (77.0)	1.13 (0.97, 1.31)§	1.22 (1.04, 1.43)§
c-erb B-2† (n=376)					
Negative	176 (92.6)	108 (92.3)	64 (92.8)		
Positive	14 (7.4)	9 (7.7)	5 (7.2)	1.20 (0.55, 2.63)	1.05 (0.39, 2.80)
Histologic grade (n=388)					
Low	80 (41.9)	49 (38.6)	26 (37.1)		
Intermediate	71 (37.2)	52 (40.9)	29 (41.4)	1.15 (0.69, 1.91)	1.24 (0.67, 2.30)
High	40 (20.9)	26 (20.5)	15 (21.4)	1.27 (0.68, 2.38)	1.27 (0.60, 2.69)

Tumor marker/characteristic**	BMI (kg/m^2) <25 (n=246) n(%)	25 – 29.9 (n=149) n(%)	≥30 (n=90) n(%)	Age-adjusted RR* (95% CI) BMI (kg/m^2) 25 – 29.9	≥30
Mitoses≠ (n=419)					
Low	145 (68.4)	87 (65.9)	52 (69.3)		
Intermediate	39 (18.4)	25 (18.9)	12 (16.0)	1.14 (0.64, 2.03)	0.87 (0.42, 1.80)
High	28 (13.2)	20 (15.2)	11 (14.7)	1.56 (0.80, 3.02)	1.22 (0.56, 2.70)
Tumor size (cm) (n=485)					
<2	189 (76.8)	105(70.5)	68 (75.6)		
≥2	57 (23.2)	44 (29.5)	22 (24.4)	1.34 (0.95, 1.88)	1.07 (0.70, 1.64)
Lymph node status (n=413)					
Negative	174 (84.5)	102 (79.1)	66 (84.6)		
Positive	32 (15.5)	27 (20.9)	12 (15.4)	1.49 (0.92, 2.41)	1.03 (0.56, 1.89)

*Risk of tumor marker or characteristic associated with BMI, relative to lowest BMI group (<25 kg/m^2).

**Paraffin blocks for 420 women were suitable for assay. In some instances, tumor tissue was depleted before all antibodies could be run, resulting in slightly different numbers of tumors tested for each antibody.

≠Excludes the indeterminate reads (n=38) as these are the cases that would now undergo fluorescence in situ hybridization (FISH) for more accurate evaluation.

≠Low mitotic rate is <10 mitoses per 10 high power fields (HPF); intermediate mitotic rate is 10–19 mitoses per 10 HPF; and high mitotic rate is >19 mitoses per 10 HPF.

§p=0.013 for trend.

Table 3

Risk of 10-year all-cause mortality, breast cancer mortality and recurrence by BMI category

	BMI (kg/m^2)		
Outcome	**<25**	**25 – 29.9**	**≥30**
All-cause mortality			
Total, No.	235	141	88
Deaths, No.	43	34	20
Person-years, No.	2017	1196	726
Mortality rate per 100,000 person-years	2132	2843	2755
Age-adjusted HR (95% CI)	1.0 (reference)	1.15 (0.73, 1.80)	1.28 (0.76, 2.18)
Multivariable[†] HR (95% CI)	1.0 (reference)	1.09 (0.69, 1.72)	1.31 (0.77, 2.22)
Multivariable[†] + Ki-67 HR (95% CI)	1.0 (reference)	1.15 (0.70, 1.87)	1.36 (0.76, 2.44)
Breast cancer mortality			
Total, No.	231	137	84
Deaths, No.	11	11	9
Person-years, No.	2002	1169	697
Mortality rate per 100,000 person-years	549	941	1291
Age-adjusted HR (95% CI)	1.0 (reference)	1.77 (0.76, 4.13)	2.39 (0.99, 5.77)
Multivariable[†] HR (95% CI)	1.0 (reference)	1.45 (0.62, 3.39)	2.41 (1.00, 5.81)
Multivariable[†] + Ki-67 HR (95% CI)	1.0 (reference)	1.27 (0.51, 3.16)	2.11 (0.83, 5.36)
Recurrence			
Total, No.	246	149	90
Events, No.	24	15	20
Person-years, No.	1995	1196	692
Event rate per 100,000 person-years	1203	1254	2890
Age-adjusted HR (95% CI)	1.0 (reference)	1.10 (0.57, 2.11)	2.43 (1.34, 4.41)
Multivariable[†] HR (95% CI)	1.0 (reference)	0.96 (0.50, 1.85)	2.43 (1.34, 4.41)
Multivariable[†] + Ki-67 HR (95% CI)	1.0 (reference)	0.86 (0.42, 1.77)	1.79 (0.91, 3.53)

[†]Adjusted for age at diagnosis (continuously), stage (I, II), and tamoxifen use (yes, no).