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Androgen Receptor Expression and Breast Cancer Survival in Postmenopausal Women

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Abstract

Purpose—Androgen receptor (AR) is commonly expressed in breast cancers. However, the association between tumor AR status and breast cancer survival is uncertain. Hence, we examined the association between AR status and breast cancer survival in the Nurses' Health Study (NHS).

Experimental Design—It was a prospective study of postmenopausal women enrolled in the Nurses' Health Study (NHS) with stage I to III breast cancer diagnosed between 1976 and 1997 and followed from the date of diagnosis until January 1, 2008 or death. Analyses were conducted using Kaplan-Meier methods and Cox proportional hazard models, to determine the association of AR status with survival outcomes adjusting for covariates.

Results—Among 1467 breast cancers, 78.7% were AR-positive (AR+). Among 1,164 estrogen receptor (ER)-positive cases, 88.0% were AR+. AR positivity was associated with a significant reduction in breast cancer mortality (hazard ratio, 0.68; 95 percent confidence interval, 0.47 to 0.99) and overall mortality (hazard ratio, 0.70; 95 percent confidence interval, 0.53 to 0.91) after adjustment for covariates. In contrast, among women with ER-negative tumors (303 cases), 42.9% were AR+. There was a non-significant association between AR status and breast cancer death (hazard ratio, 1.59; 95 percent confidence interval, 0.94 to 2.68).

Conclusions—The association of AR status and breast cancer survival is dependent on ER status. In particular, AR expression was associated with a more favorable prognosis among women with ER-positive tumors. Thus, determination of AR status may provide additional information on prognosis for postmenopausal women with breast cancer, and provide novel opportunities for targeted therapy.

Keywords

breast cancer; androgen receptor; estrogen receptor; survival outcomes and breast cancer mortality

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Introduction

The androgen receptor (AR) is a member of the steroid receptor subfamily with well known biological and therapeutic importance in prostate cancer. There is emerging evidence that the androgen signaling pathway also may play a critical role in normal and malignant breast tissue (1). In particular, AR is expressed in normal breast epithelial cells and in approximately 70–90% of invasive breast carcinomas, a percentage equal to or higher than that of either estrogen receptor (ER) (70–80%) or progesterone receptor (PR) (50–70%) (2). In addition, 25–82% of metastatic breast tumors that are ER-negative and PR-negative express a significant amount of AR (3).

Previous studies have suggested that AR may be both a prognostic factor for survival and a predictive factor for response to endocrine treatment in patients with breast cancer (1,4–12). Of the studies conducted to date, most were small, with only two including more than 350 breast cancer cases. The largest study evaluating the prognostic significance of AR was conducted on 1,181 patients with primary breast cancer. However, in this study, the only prognostic factor that was taken into account in the analysis was ER status (8). In addition, few studies have examined the prognostic value of AR expression according to ER status (1,2,7,8,12) or in triple negative tumors (5).

The purpose of the current study was to evaluate the associations between AR expression and survival outcomes in a large cohort of postmenopausal women with stage I to III breast cancer identified from the Nurses' Health Study (NHS), and to assess this association stratified by ER status as well as in the triple negative subtype of breast cancer.

Materials and Methods

Study population

The NHS is a prospective cohort study established in 1976 when 121,700 female registered nurses from across the United States, aged 30–55 years, completed a mailed questionnaire on factors that influence women's health. Follow-up questionnaires have since been sent out every two years to the NHS participants to update exposure information and ascertain non-fatal incident diseases. Follow-up rate from 1976 through December 2007 is 98.9% in our study.

Incident breast cancer was ascertained by the biennial questionnaire to study participants. For any report of breast cancer, written permission was obtained from participants to review their medical records to confirm the diagnosis and to classify cancers as in situ or invasive, by histological type, size and presence or absence of metastases. Overall, 99% of self-reported breast cancers have been confirmed. To identify breast cancer cases in non-respondents who died, death certificates and medical records for all deceased participants were obtained to ascertain cause of death. This study was approved by the Human Subjects Committee at Brigham and Women's Hospital in Boston, Massachusetts.

Measurement of mortality and breast cancer recurrence

Breast cancer cases were followed from the date of diagnosis until January 1, 2008 or death, whichever came first. Ascertainment of deaths included reporting by next of kin or postal authorities or searching the National Death Index. Approximately 98% of deaths in the NHS have been identified by these methods (14–16). Cause of death was ascertained from death certificates and physician review of medical records.

We assumed that breast cancer had recurred if a woman with a primary breast cancer reported a second cancer in lung, liver, bone or brain cancer, because these are the most

common sites of recurrence. We reviewed medical records to distinguish primary lung cancer from breast cancer metastases to the lung. In addition, women who died from breast cancer were assumed to have recurred 2 years prior to the date of death (17). Because our questionnaire interval is every 2 years, women with breast cancer frequently die before they can tell us about their recurrence. Approximately 92% of recurred cases are calculated this way due to missing information about the sites and time of recurrence.

Breast cancer tissue microarrays and immunohistochemical analysis

Collection of breast cancer tissue blocks and tissue microarray (TMA) construction have been described in detail previously (18). Briefly, we collected archived formalin-fixed paraffin-embedded breast cancer blocks from participants with incident breast cancers over 20 years of follow-up (1976 to 1996). Of the 5,610 women with breast cancer that were eligible for block collection, we obtained pathology samples for 3,752 participants. Hematoxylin and eosin sections from those cases were reviewed to confirm the diagnosis, classify the cancer according to histological type and grade, and circle the area from which the cores for the TMAs would be taken. TMAs were constructed in the Dana Farber Harvard Cancer Center Tissue Microarray Core Facility, Boston, Massachusetts. Three cores 0.6 mm in diameter were obtained from each breast cancer sample and inserted into the recipient TMA blocks. In total, 23 TMA blocks were constructed from 3,093 cancers and positive lymph nodes from 2,897 participants.

We performed immunohistochemical staining for AR, ER, PR, human epidermal growth factor receptor 2 (HER2), cytokeratin 5/6 (CK5/6) and epidermal growth factor receptor (EGFR) on 5 μm paraffin sections cut from the TMA blocks (see Supplementary Table 1 for details). Immunostained TMA sections were reviewed under a microscope and visually scored for each individual tissue core. For AR, nuclear staining for each core was scored as negative, low positive (1–10% of tumor cell nuclei staining) or positive (>10% tumor cell nuclei staining). For this analysis, cases scored as either low positive or positive were considered to be positive for AR. Overall scoring was as follows: if any one core was positive the case was scored as positive, and when all three cores were negative the case was scored as negative. If no tumor or unevaluable staining for all three cores, the status of AR was missing. The concordance of AR status between any 2 of 3 cores per participant included in TMAs was extremely high with a Kappa statistic ranging from 0.86 to 0.88, denoting excellent concordance (19).

Selection criteria for analysis

We included women with invasive breast cancer diagnosed after return of the 1976 baseline questionnaire through August, 1997, whose tumors were included in the TMAs. Women were excluded from analysis if they were diagnosed with positive lymph nodes only (25 cases), rare tumor types including malignant phyllodes tumors, neuroendocrine carcinoma and angiosarcoma (10 cases), an in situ carcinoma (401 cases), stage IV breast cancer (62 cases), metastases at diagnosis or stage III but lacking a complete metastatic work-up (172 cases), premenopausal at diagnosis (449 cases), missing information on AR status (193 cases) or ER status (43 cases), and special tumor types (e.g. microinvasive ductal, microinvasive lobular) without a tumor grade (36 cases). An additional 39 women were excluded due to impossible date of recurrence, when date of recurrence was estimated to occur prior to date of diagnosis. Hence, 1,467 women were eligible for this analysis.

Covariates evaluated in the analysis

Covariate information on the study population was obtained from biennial questionnaires. The following covariate data were obtained from the questionnaire preceding the report of breast cancer diagnosis: age, body mass index (BMI), oral contraceptive use, age at first

birth, parity, postmenopausal hormone use, alcohol intake and smoking status. Information on breast tumor characteristics and treatments was extracted from the medical record and supplemental questionnaire including year of diagnosis, stage, radiation, and chemotherapy and hormonal treatment. Information on histological grade was obtained from centralized pathology review by a single pathologist (YF). Covariates considered in the multivariate model were based on both statistical significance and clinical significance. Variables included in the final multivariate model were ER status, age at diagnosis, year of diagnosis, radiation treatment, chemotherapy and hormonal treatment, grade and stage of breast cancer.

Statistical Analysis

AR-positive and AR-negative tumors were compared according to tumor characteristics and treatment variables by the chi-square test or Wilcoxon rank sum test, as appropriate. Three survival end points were evaluated in this study. In overall survival analysis, death from any cause was the end point; in breast cancer specific survival analysis, death from breast cancer was the end point and deaths from any other causes were censored; in recurrence-free interval analysis, breast cancer recurrence was the end point. Survival curves were estimated by the Kaplan-Meier method with a log-rank test to assess statistical significance. Cox proportional hazard regression models were used to evaluate the association of AR status with survival outcomes after adjusting for covariates. Because approximately 19% of women were missing information on treatment, we considered them as a separate group for our multivariate analysis. We conducted sensitivity analyses excluding women with missing treatment information. All analyses were performed using SAS version 9.1. All statistical tests were two sided and $P<0.05$ was considered statistically significant.

Results

Participants and Breast Tumor Characteristics

Of 1,467 breast cancer cases among postmenopausal women included in this study, 1,154 (78.7%) were AR-positive and 313 (21.3%) were AR-negative. Among women with ER-positive tumors, 88.0% were AR+. It was 42.9% in ER-negative subgroup. The median age at breast cancer diagnosis was 61 years (range: 39–75 years). Participants' characteristics, tumor biomarkers and characteristics according to AR status are summarized in Table 1. Compared with AR-negative tumors, AR-positive tumors were more likely to be ER-positive, PR-positive and HER2-negative, smaller in size (≤2cm), lower histological grade and stage, and treated with hormonal therapy ($P<0.001$). They were also less likely to have nodal involvement and to be treated with chemotherapy ($P<0.001$).

Survival Estimates

The median length of follow-up was 14 years. Overall, there were 595 total deaths, 279 breast cancer deaths and 292 recurrences through the end of the follow-up period. Five-and ten-year survival estimates are shown in Table 2. Women with AR-positive tumors had a longer survival than women with AR-negative tumors. Among women with AR-negative tumors, the estimated 5- and 10-year breast cancer specific survival rates were 88% and 82%, respectively; among women with AR-positive tumors, the rates were 95% and 88%, respectively. The Kaplan-Meier curves show women with AR-positive/ER-positive tumors had the best survival relative to women with the other subtypes ($P=0.0004$), and significantly better breast cancer specific survival in women with AR-positive/ER-positive tumors than in women with AR-negative/ER-positive tumors ($P=0.003$) (Figure 1). In contrast, among women with ER-negative tumors, no significant association was found between AR status and breast cancer specific survival ($P=0.14$) (Figure 1) possibly due to the small number of outcomes (n=70). Kaplan-Meier curves for recurrence-free

(Supplementary Figure 1) and overall survival (data not shown) were similar to breast cancer specific curves.

Multivariate Analysis

In multivariate analysis, there was no overall association between AR status and breast cancer death (hazard ratio, 0.96, 95 percent confidence interval, 0.69 to 1.34) (Table 3). However, the association varied markedly by ER status ($P_{interaction}$=0.0019), hence, a stratified analysis was performed. Among ER-positive tumors (1,164 cases), we found that compared with AR-negative tumors, AR-positive tumors were associated with a 30% reduction in breast cancer mortality (hazard ratio, 0.68; 95 percent confidence interval, 0.47 to 0.99). Similar results were observed for overall mortality and risk of breast cancer recurrence, but not all statistically significant (Table 3).

Although there was no significant difference in the distribution of low (1–10% of tumor cell nuclei staining with ER) and high ER-positive tumors (>10% of tumor cell nuclei staining with ER) across AR status, we conducted secondary analyses restricted to women with high ER-positive tumors only (88% of all ER positive cases). Among women with high ER-positive tumors, we observed a very similar magnitude of association between AR status and breast cancer specific survival to that when all ER-positive tumors were considered (multivariate hazard ratio, 0.71, 95 percent confidence interval, 0.46 to 1.09; P=0.11). At the same time, AR status was also categorized into 3 groups: negative, low positive and high positive. We found that only 8.1% (93/1154) of AR-positive tumors were low AR-positive tumors and the proportion differed by ER status. However, in multivariate models we did not see any differences in breast cancer specific survival by low and high AR positivity.

In contrast, among women with ER-negative tumors (303 cases) we noted a suggestive positive association between AR status and breast cancer mortality (AR positivity compared with AR negativity: hazard ratio, 1.59; 95 percent confidence interval, 0.94 to 2.68; P=0.08), overall mortality, and breast cancer recurrence (Table 3).

Similar results were found after additional adjustment for BMI at diagnosis, smoking status and physical activity in all analyses above. Sensitivity analyses restricted to only participants with known information on chemotherapy, radiation or hormone treatment yielded similar results as those treating them as a separate group. Further, we conducted a secondary analysis restricted to ER-positive hormone treated cases (718 cases). Among women with ER-positive hormone treated cancer, women with AR-positive tumors had a non-significant 32% reduced risk of breast cancer specific mortality (multivariate hazard ratio (model 3), 0.68; 95 percent confidence interval, 0.39 to 1.19; P=0.18). This magnitude of association is very similar to that observed among all ER-positive cases. However, we were underpowered to evaluate the association between AR status and survival outcomes according to other treatment subgroups. In addition, we also conducted an analysis limited to women with triple-negative (ER-/PR-/HER2-negative) tumors. Among those with triple-negative breast cancer (211 cases), women with AR-positive tumors had an 83% increase in overall mortality compared with those with AR-negative tumors (multivariate hazard ratio (model 3), 1.83; 95 percent confidence interval, 1.11 to 3.01; P=0.02).

Discussion

We conducted the largest study to date examining the role of AR in breast cancer outcomes, with the longest median follow-up time. Among women with ER-positive tumors, AR expression was associated with a 30% reduction in breast cancer mortality. In contrast, among postmenopausal women with ER-negative tumors, AR expression was not associated with a reduction in breast cancer mortality.

Only a few studies have examined the association between AR expression and breast cancer survival, with some indicating improved survival among women with AR-positive tumors (2,4–6,8,10,20–22). However, when adjusted for tumor characteristics, as we have shown, there is no association between AR expression and improved disease-free survival (6,20). The few studies which have stratified by ER status do suggest that AR expression is associated with improved survival among women with ER-positive tumors (1,8,12). Bryan and colleagues reported that in postmenopausal women (n=649), patients with AR-negative tumors had a shorter overall survival than AR-positive cancers. Further analyses taking into account five levels of ER-positivity, suggested that AR remained a significant predictor of survival, but their analyses did not take into account other prognostic factors (8). A recent retrospective study with 6.8 years of median follow-up time also reported that AR expression is an independent prognostic factor of better outcome in patients with ER-positive breast cancers (n=938) (12). Peters et al. recently reported that among 157 women with ER-positive invasive ductal breast cancer, patients with lower than the median percent (75%) of AR positivity in tumor cells, had a 3.0-fold increased risk of relapse and a 4.6-fold increased risk of cancer-related death in multivariate analysis. In functional analyses using breast cancer cell lines, Peters et al demonstrated that AR and ER-α interact with one another and that AR can inhibit ER-α mediated growth of breast cancer cells (1). Thus, the AR is able to bind to estrogen responsive elements in ER-α and prevent activation of growth stimulatory effects.

The role of AR in ER- and triple negative breast cancer is not clear, with some studies reporting improved survival and others worse survival. Peters et al found that among 58 women with ER-negative breast cancer, no association between AR status and overall survival was observed (1). Similarly, Agoff et al. also found that AR expression in ER-negative breast cancer (n=69) was not significantly associated with breast cancer survival in multivariate analyses, but this was attributed to the small sample size (7). Rakha et al. reported that in triple-negative tumors (n=282), especially those which were lymph node-positive, absence of AR expression was associated with higher nuclear grade and increased development of recurrence and distant metastasis (24). Luo et al. also found that the expression of AR was associated with higher 5-year disease-free survival in 137 triple negative breast cancer cases (25). Another study of 97 women with triple negative breast tumors found that AR levels were not a significant prognostic factor for recurrence-free interval (5). In contrast, among women with ER- and triple negative tumors in our study, AR expression was associated with increased mortality. While there are some data to support an adverse role of AR in ER-negative breast cancer, these results could also be due to chance. Based on microarray data, a subclass of tumors termed ‘molecular apocrine’ have been identified that are ER−/AR+ and have increased androgen signaling (26). Using publicly available Sorlie and van’t Veer microarray data sets, Farmer et al reported that the molecular apocrine profile was associated with poor survival. There are studies in cell lines suggesting that androgens may induce proliferative effects in ER-negative cells that are dependent on AR (27). Thus, we may be capturing this subset of molecular apocrine tumors when examining the ER−/AR+ tumors.

Taken together, there is not much consistency with respect to survival outcomes associated with AR status among ER- and triple negative cases. These differences may be attributable to small sample sizes, and differences in length of follow-up. The current study is one of the largest to evaluate the role of AR in this subset, with over 31 years of follow-up. In addition, the frequency of AR-positive cases among triple negative tumors in our study was 37% (78/211). This is similar to what has been observed in other studies, where the proportion of AR-positive tumors ranges from 28% to 43% (23,25,28). Also similar to other retrospective studies, we observed that AR was significantly associated with HER2 overexpression (P=0.004) in ER-negative tumors (7,23). However, we also saw a significant association in

ER-positive tumors, which is not consistent with the results published by Park et al. (23). Given these differences we did include HER2 status in our multivariable models and found no differences in our survival results.

Currently, there are no available targeted therapies for women with triple negative disease. However, there are therapeutic targets of AR. Given that the triple negative subtype has the worst overall and disease free survival compared with other breast cancer subtypes (13), and more than one third of triple negative breast cancers are AR-positive, this represents a potential opportunity for novel targeted treatment for these women. Bicalutamide is a nonsteroidal antiandrogen therapy used to treat metastatic prostate cancer. A phase II trial of bicalutamide is currently enrolling women with ER−/PR−/AR+ breast cancers (ClinicalTrials.gov Identifier NCT00468715). Although there are no published studies of AR targeted therapy and breast cancer survival, taken together these data suggest that AR status may have a clinically important role in terms of prognosis and treatment for women with triple negative breast cancer.

Our study has a number of strengths including the large study size, long follow-up time, standardized uniform staining and scoring of molecular markers, and the prospectively collected information about lifestyle and prognostic factors. We found that other than AR status, disease grade and stage were the only other independent prognostic factors for breast cancer specific survival. Additional adjustment for treatment methods (radiation, chemotherapy and hormonal treatment), PR status, and personal characteristics (smoking status, BMI and physical activity) did not affect the results.

The current study was limited to women for whom we were able to obtain a breast cancer tissue specimen. The women from whom we were able to obtain tissue specimens were very similar with respect to demographics and tumor characteristics to those for whom we were unable to obtain tissue (18). The pathologist scoring the TMA slides was blind to the survival outcomes of the participants. Thus, any misclassification of AR status is likely to be no differential with respect to survival outcomes and would likely bias the results towards the null.

A potential limitation of the current study is that we did not have detailed information on treatment. Treatment information was abstracted from medical records and from self-report on questionnaires. It is possible that there could be residual confounding by treatment. However, because AR status is not routinely assessed in clinical practice it is unlikely that differences in treatment would be associated with AR status. Because hormone receptor expression is known to vary by menopausal status (28) and the majority of cases in the Nurses' Health Study are postmenopausal, we have focused the current analyses on this group.

In conclusion, we found that the association of AR status and breast cancer survival is dependent on ER expression. Among women with ER-positive tumors, AR expression was associated with significantly improved survival. Thus, immunohistochemical determination of AR status may provide additional information on prognosis in breast cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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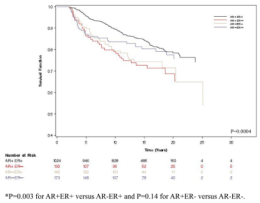

*P=0.003 for AR+ER+ versus AR-ER+ and P=0.14 for AR+ER- versus AR-ER-.

Figure 1.
Kaplan-Meier analysis of the probability of breast cancer specific survival in postmenopausal women with stage I to III breast cancer by androgen and estrogen receptor status, Nurses' Health Study (1976–1997). The P value was calculated with use of the log-rank test.

Table 1

Means and frequencies of participants' characteristics by androgen receptor status (N=1467), Nurses' Health Study (1976–1997)

Characteristic	AR−	AR+
N (%)	313 (21.3)	1154 (78.7)
Age at diagnosis, mean (N), yr	59.0 (313)	60.8 (1154)
BMI at diagnosis, mean (N*), kg/m^2	26.6 (280)	26.0 (1041)
Smoking, N* (%)		
Never	138 (44.2)	442 (38.5)
Past	125 (40.1)	482 (42.1)
Current	49 (15.7)	222 (19.4)
ER status, N (%)		
Positive	140 (44.7)	1024 (88.7)
Negative	173 (55.3)	130 (11.3)
PR status, N* (%)		
Positive	114 (36.7)	830 (72.2)
Negative	197 (63.3)	319 (27.8)
HER2 status, N* (%)		
Positive	46 (15.0)	81 (7.1)
Negative	260 (85.0)	1059 (92.9)
Nodal involvement, N (%)		
None	212 (67.7)	883 (76.5)
1 – 3	78 (24.9)	220 (19.1)
4 – 9	16 (5.1)	28 (2.4)
≥ 10	7 (2.3)	23 (2.0)
Tumor size (cm), N (%)		
≤ 2	188 (60.1)	814 (70.5)
> 2	125 (39.9)	340 (29.5)
Histological grade, N (%)		
I (low)	22 (7.0)	302 (26.2)
II (intermediate)	127 (40.6)	692 (60.0)
III (high)	164 (52.4)	160 (13.8)
Stage†, N (%)		
I	154 (49.2)	682 (59.1)
II	126 (40.3)	394 (34.1)
III	33 (10.5)	78 (6.8)
Chemotherapy, N* (%)		
Yes	141 (55.7)	258 (27.4)
No	112 (44.3)	682 (72.6)
Hormone treatment, N* (%)		
Yes	145 (58.2)	672 (71.3)

Characteristic	AR−	AR+
No	104 (41.8)	270 (28.7)
Radiation treatment, N* (%)		
Yes	114 (45.4)	393 (41.6)
No	137 (54.6)	551 (58.4)

*N doesn't add to total because of missing information.

†Stage I=tumor size<=2cm and no nodal involvement;

II=tumor size<=2cm & 1–3 nodes or 2–4cm & 0–3 nodes or 4+cm & 0 nodes;

III=tumor size<=2cm & 4+ nodes or 2–4cm & 4+ nodes or >4cm & 1+ nodes.

Table 2

5- and 10-year survival estimates by androgen receptor status (N=1467)

Group	5-year survival		10-year survival	
	%	95% CI*	%	95% CI*
Breast cancer specific survival				
AR−	88	85–92	82	77–86
AR+	95	93–96	88	86–90
Recurrence-free interval				
AR−	85	81–89	80	75–84
AR+	92	90–94	85	83–87
Overall survival				
AR−	86	82–90	76	71–81
AR+	91	90–93	80	77–82

*CI denotes confidence interval.

Table 3

Multivariate analysis of the survival outcomes by androgen receptor status

Models	N		Hazard Ratio (95% CI*)	
	Cases	Endpoints	AR-negative	AR-positive
Breast cancer specific survival				
All cases:				
Model[1]	1467	275	1.00	0.78 (0.60–1.03)
Model[2]	1467	275	1.00	0.96 (0.69–1.34)
ER-positive cases:				
Model[1]	1164	205	1.00	0.59 (0.41–0.85)
Model[3]	1164	205	1.00	0.68 (0.47–0.99)
ER-negative cases:				
Model[1]	303	70	1.00	1.46 (0.91–2.33)
Model[3]	303	70	1.00	1.59 (0.94–2.68)
Recurrence-free interval				
All cases:				
Model[1]	1467	288	1.00	0.80 (0.62–1.05)
Model[2]	1467	288	1.00	0.99 (0.72–1.36)
ER-positive cases:				
Model[1]	1164	217	1.00	0.62 (0.44–0.89)
Model[3]	1164	217	1.00	0.72 (0.50–1.05)
ER-negative cases:				
Model[1]	303	71	1.00	1.39 (0.87–2.22)
Model[3]	303	71	1.00	1.54 (0.92–2.58)
Overall survival				
All cases:				
Model[1]	1467	576	1.00	0.90 (0.74–1.10)
Model[2]	1467	576	1.00	0.89 (0.71–1.13)
ER-positive cases:				
Model[1]	1164	460	1.00	0.68 (0.52–0.88)
Model[3]	1164	460	1.00	0.70 (0.53–0.91)
ER-negative cases:				
Model[1]	303	116	1.00	1.48 (1.02–2.13)
Model[3]	303	116	1.00	1.42 (0.95–2.13)

* CI denotes confidence interval.

Model[1]: Adjust for age at diagnosis (years).

Model[2]: Adjust for age at diagnosis (years), estrogen receptor status (positive, negative), date of diagnosis (months), disease stage (I, II, III), grade (I, II, III), radiation treatment (yes, no, missing), chemotherapy and hormonal treatment (no/no, yes/no, no/yes, yes/yes, missing).

Model[3]: Adjust for age at diagnosis (years), date of diagnosis (months), disease stage (I, II, III), grade (I, II, III), radiation treatment (yes, no, missing), chemotherapy and hormonal treatment (no/no, yes/no, no/yes, yes/yes, missing).