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Beta blockers and angiotensin converting enzyme inhibitors' purported benefit on breast cancer survival may be explained by aspirin use

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Abstract

Preclinical and epidemiologic evidence supports a possible role for beta-adrenergic blocking drugs (beta-blockers), and angiotensin converting enzyme inhibitors (ACEIs) in promoting survival after breast cancer. However, these drugs are often used concurrently with aspirin, and there is a growing body of evidence indicating a survival benefit for aspirin. Therefore, we analyzed the use of beta-blockers and ACEIs after a breast cancer diagnosis and their association with breast cancer mortality, both individually, combined with each other, and in combination with aspirin use in the Nurses' Health Study, using updated measures of medication use and Cox proportional hazards models.

There were 4,661 women with stages I-III breast cancer included; 292 breast cancer deaths occurred during median follow-up time of 10.5 years. Modeled individually, the multivariable relative risk and 95% confidence intervals (RR, 95% CI) for breast cancer death were (0.76, 0.54-1.05) for beta blockers, (0.89, 0.60-1.32) for ACEIs, and (0.46, 0.35-0.60) for aspirin. Modeled simultaneously, the multivariable (RR, 95% CI) for breast cancer death were (0.83, 0.60-1.16) for beta blockers, (1.00, 0.68-1.46) for ACEIs, and (0.46, 0.35-0.61) for aspirin.

We did not see a significant association with beta blockers and survival, but there was a suggestion. Our study was limited in that we could not assess type of beta blocker and the number of events among users was still quite low. We found no evidence of a protective effect for ACEIs. The strong protective association with aspirin use confounds the associations with these other drugs and underscores the importance of considering aspirin use in analyses of breast cancer survival

Keywords

Adrenergic beta-antagonists; angiotensin-converting enzyme inhibitors; aspirin; breast neoplasms; survival

INTRODUCTION

Medications developed for one purpose have sometimes been found to have other clinical effects. The process of cancer growth and metastasis involves many pathways, leading to the possibility that non-cancer drugs might influence survival after a cancer diagnosis. We recently reviewed the evidence supporting the potential anti-cancer effects of several commonly used over the counter and prescription medications that have been evaluated among breast cancer survivors in prospective studies, including beta-adrenergic blocking drugs (beta-blockers), and angiotensin converting enzyme inhibitors (ACEIs) and aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). [1]

There is great interest in how stress might affect survival after a cancer diagnosis. Catecholamines produced in the stress response are mediated by beta-adrenergic receptors which are in turn blocked by beta-blockers such as propranolol. A 2006 review examined the neuroendocrine pathways by which stress might particularly affect cancer progression. [2] Catecholamine stimulation has been shown to increase angiogenesis, tumor invasion, metastasis, and inhibit apoptosis in preclinical studies of several types of cancer; in some cases these effects could be inhibited by the use of beta-blockers. [3,4] Human breast cancer cells have beta-adrenergic receptors, [5] and four prospective epidemiologic studies have suggested a survival benefit for women with breast cancer who use beta-blockers. [6-9]

ACEIs and angiotensin type I receptor blockers (ARBs) are commonly used drugs which inhibit the renin-angiotensin-aldosterone-system (RAAS). Because RAAS receptors have been found on human breast cancer cells, [10] this system has the potential to affect breast cancer processes. Increased RAAS activity associated with RAAS gene polymorphisms has been associated with increased risk of breast cancer. [11,12] Stimulation of breast cancer cells via the RAAS has been shown to increase cell proliferation via protein kinase C activation and epidermal growth factor receptor transactivation, and also by activating the P13K-kinase B (AKT) pathway. [13,14] In hormone-receptor negative breast cancer cells, RAAS stimulation increased expression of angiogenesis related genes. [10] However three prospective epidemiologic studies of ACEI or ARB use and recurrence in women with breast cancer showed mixed results, including decreased recurrence, [15] no association, [7] and increased recurrence. [8]

We have previously reported on a strong survival benefit seen among women with breast cancer who use aspirin in the Nurses' Health Study (NHS). [16,17] However, aspirin, beta blockers, and ACEIs are all commonly used in a set of related illnesses such as hypertension, stroke, ischemic heart disease, congestive heart failure, and chronic kidney disease. It is conceivable that concurrent use of any combination of these drugs could confound their effects seen with breast cancer survival. Therefore, we analyzed the use of beta-blockers and ACEIs after a breast cancer diagnosis and their association with breast cancer mortality, both individually, combined with each other, and in combination with aspirin use in the NHS.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston MA. The NHS was established in 1976 when 121,700 female registered United States nurses, aged 30 to 55 years, answered a mailed questionnaire on cancer and cardiovascular risk factors. We have sent questionnaires every 2 years since. As of June 2010, follow-up of the entire cohort's person-years is 95% complete

We included women in the NHS diagnosed with Stages I-III invasive breast cancer between June 1, 1985 and June 1, 2005. Beta-blocker and ACEI use was first asked in 1988 and we

wished to first assess use of these medications (asked over the past 2 years) to avoid the immediate breast cancer treatment period assumed to be one year. We also wanted to have sufficient follow-up time before end of follow-up in 2008. For any report of breast cancer, participants gave written permission for physicians (blinded to exposure information) to review their medical records. Tumor prognostic factors including size, grade, histology, estrogen receptor (ER), progesterone receptor (PR), presence of metastatic lymph nodes and stage were extracted from the medical record. Initial treatment received (radiation, chemotherapy, and hormonal therapy) was self-reported by a supplemental questionnaire. Date and cause of death were determined by physician review of death certificates. Women missing stage or medication use data were excluded from the analysis. A total of 4,661 women remained in the analysis.

Assessment for each of the medications varied somewhat. Beta blocker was first assessed in 1988, then in 1994 and every 2 years thereafter. Because beta blocker use was not assessed in 1990 or 1992, 1988 beta blocker use was carried forward for those cycles. ACEI use was first assessed in 1988, then in 1996 and every 2 years thereafter. Because ACEI use was not assessed in 1990, 1992, or 1994, the 1988 ACEI use was carried forward for those cycles. ARB use was first asked combined with ACEI use beginning in 2006. Aspirin use was assessed in 1988 and every two years afterwards. Medication use was characterized as current use versus never/past use. On each questionnaire, participants were asked if they used a medication regularly over the past 2 years. Because aspirin use can be contraindicated during the period of active breast cancer treatment, and treatment can last for up to one year, the baseline assessment of aspirin use was 3 years after diagnosis. Beta blocker and ACEI use was assessed similarly for consistency. If a participant did not answer her baseline questionnaire, but did answer the questionnaire 2 years previous, that information was carried forward. If that information was not available, she was excluded. Medication use was assessed as current use vs. past/never use, and subsequently updated until death or the end of follow-up.

In statistical analyses, we used Cox proportional hazards regression with time since diagnosis as the underlying time variable and death from breast cancer as the outcome; other causes of death were censored. In a secondary analysis, death from any cause was the outcome. Women were followed from diagnosis until death or June 1, 2008, whichever came first. Simple models were adjusted for time since diagnosis and age at diagnosis. Multivariable models were additionally adjusted for disease stage at diagnosis, treatment, and the other factors shown in the footnote to Table 2.

RESULTS

We followed 4661 women and observed 292 breast cancer deaths and 738 deaths from any cause with median follow-up of 10.5 years. Clinical characteristics of the participants, standardized by age and categorized by medication use are shown in Table 1. Beta blocker and ACEI use was less common than aspirin use. Of the 4,661 participants, 770 (17%) ever used beta-blockers, 478 (10%) ever used ACEIs and 1,922 (41%) ever used aspirin. Beta-blocker and ACEI users tended to be heavier and less physically active than non-users, while aspirin users tended to be more physically active than non-users. Users of all three drugs were more likely to also use post-menopausal hormones at diagnosis than non-users. Disease characteristics such as stage, estrogen receptor positivity, and treatment were similar among users and non-users of all three drugs.

Table 2 shows the relative risk of dying from breast cancer, according to medication use. In the first 3 rows, each medication is modeled separately, and both simple and multivariable adjusted models are shown. Relative risks and 95% confidence intervals for simple models

were similar to those for multivariable models, indicating that there was little confounding by the factors adjusted for, including stage and treatment. There was a suggestion of a reduced risk of breast cancer death associated with beta-blocker (RR, 95% CI = 0.76, 0.54-1.05) and ACEI (RR, 95% CI = 0.89, 0.60-1.32) use, but neither reached statistical significance. Notably, we again observed a more than 50% reduced risk of breast cancer death associated with aspirin use (RR, 95% CI = 0.46, 0.35-0.60), as we had previously reported. [16]

Rows 4, 5, and 6 of Table 2 represent models where beta-blockers, ACEIs, and aspirin are included in the same model two at a time to determine the independent impact of each medication. The risk estimate for beta-blockers was not attenuated when ACEIs were included in the model, but was attenuated with the inclusion of aspirin. The risk estimate for ACEIs was slightly attenuated beta-blockers were added to the model, and more so with the addition for aspirin. In contrast, the risk estimate for aspirin did not materially change when either beta-blocker or ACEI were included in the model simultaneously.

The final model (row 7 of Table 2) included beta-blockers, ACEIs, and aspirin in the same model. Compared to models where each drug is modeled separately, the risk estimate for beta-blockers is attenuated, the risk estimate for ACEIs is completely null, and the risk estimate for aspirin did not change.

We repeated the analyses in Table 2 using death from any cause as the outcome; the pattern of results was similar to that in Table 2 (data not shown). For example, in a multivariable model simultaneously containing all three drugs, the RR, 95% CI for beta-blockers was 0.85, 0.70-1.04, for ACEIs was 0.97, 0.77-1.23, and for aspirin was 0.66, 0.57-0.77.

We performed analyses of beta blocker and ACEI use stratified by body mass index, and estrogen receptor status (Table 3). Because the results in Table 2 indicated that aspirin use attenuated both the beta-blocker and ACEI results, the multivariable models in Table 3 are additionally adjusted for aspirin use. However, in Table 3, the beta-blocker models are not adjusted for ACEI use, or vice-versa. We additionally performed an analysis of beta blocker and ACEI use stratified by aspirin use. Results are limited by small numbers of deaths, particularly among women with estrogen receptor negative tumors. Although none of the results stratified by BMI or estrogen receptor status reached statistical significance, a beneficial association for beta-blocker use appeared to be stronger among women with estrogen receptor negative tumors (p-value for the interaction =0.09 and also for women of normal compared with overweight body mass index(p-value for interaction =0.11). In the analyses stratified by aspirin use, both beta-blocker and ACEI use appeared beneficial only among those who were also using aspirin, although the p-values for interaction were not statistically significant.

We performed several additional analyses. The multivariate results for women taking only beta blockers (RR=1.01, 95% CI=0.64-1.59), and only ACEI (RR=1.09, 95% CI=0.60-1.98) and only aspirin (RR=0.52, 95% CI=0.39-0.70), were similar to results from row 7 in Table 2, where all three drugs were mutually adjusted for each other (RR=0.83, 95% CI=0.60-1.16 for beta blockers; RR=1.00, 95% CI=0.68-1.48 for ACEI; and RR=0.46, 95% CI=0.35-0.61 for aspirin). Because confounding by indication was a concern, we performed an analysis of thiazide diuretic, an anti-hypertensive for which no survival benefit was hypothesized, and there was no association (multivariate RR=0.94, 95%CI=0.67-1.33). Finally, there was no association for use of either beta blocker or ACEI for at least 5 years (5 year duration, data not shown).

DISCUSSION

Four prospective epidemiological studies have been published which examined the association between intake of beta-blockers and risk of adverse outcomes (either breast cancer mortality or recurrence) among women with breast cancer and all generally found a protective effect. An initial 2010 report among 466 stages I-III breast cancer patients with more than 10 years of follow-up found a marked decrease in breast cancer mortality (RR=0.29, 95% CI, 0.12-0.72) and distant recurrence (RR=0.43, 95% CI, 0.20-0.93) among the 9% who used beta-blockers for hypertension. [6]

Three larger studies were published in 2011. The LACE cohort reported on 1,779 women with stages I-III breast cancer with mean follow-up of 8.2 years and 174 breast cancer deaths and 15% used beta-blockers. Linked pharmacy records were used to determine beta-blocker use. They reported a non-statistically-significant decreased risk of breast cancer death (RR=0.76, 95% CI, 0.44-1.33), and recurrence (distant, loco-regional, or contralateral, RR=0.85, 95% CI, 0.57-1.32), [8]

In a series of 1,413 stages I-III breast cancer patients at the MD Anderson Cancer Center there were 404 relapses and 7% using beta-blockers. The authors hypothesized women with triple-negative (ER, PR, and HER2neu) breast cancer would be particularly sensitive to beta-blockers because of their higher prevalence of abdominal obesity and high expression of beta-adrenergic receptors in triple-negative breast cancer cell lines. They observed a decreased risk of relapse (RR=0.52, 95% CI, 0.32-0.88) for users of beta-blockers among all women with breast cancer that was even more pronounced among 377 women with triple-negative breast cancer (RR=0.30, 95% CI=0.20-0.87). Yet, overall survival was not improved in either group. [7]

Finally, 5,333 women with stages I-IV breast cancer were included in a nested case-control linking the Irish national cancer and pharmacy registries. Beta-blockers users were identified and separated according to type of beta-blocker: Propranolol blocks both beta-1 and beta-2 adrenergic receptors and is considered non-selective. Atenolol blocks only beta-1. The authors cited pre-clinical evidence that beta-2 signaling may be more important for cancer metastasis. Of the 595 beta blocker users, 70 used propranolol and 525 used atenolol; these were matched 1:2 to controls on aspirin and statin use and other factors. There was a large decreased risk of breast cancer mortality (RR=0.19, 95% CI, 0.06-0.60) for propranolol use, but there were only 4 breast cancer deaths among them. No such association was seen for atenolol (number of breast cancer deaths not reported). [9]

We found a modest reduction in risk of breast cancer death among women with breast cancer who used beta-blockers compared to non-users. This reduced risk did not reach statistical significance. The magnitude of our risk estimate was similar to that found in the LACE study when beta blockers were modeled alone but was attenuated when adjusted for aspirin use. In analyses stratified by ER status and BMI, we attempted to test the hypotheses raised in the MD Anderson report. We were not able to look specifically at triple-negative tumors, but only ER negative and still had limited numbers. Our tumor subtype results are in line with those from MD Anderson suggesting that a beneficial effect of beta-blockers on breast cancer death may indeed be more pronounced among women with ER negative tumors. We also examined beta blocker use stratified by body mass index (normal weight versus overweight) as a proxy for abdominal obesity. Contrary to the hypothesis, we found a beneficial effect of beta-blocker use among normal weight rather than overweight women. Finally, the Irish registry study raises the possibility that type of beta blocker used may matter greatly. Historically over time patterns of use have moved from the non-selective to the cardioselective (beta-1) blockers, and this may explain the heterogeneity in results seen,

particularly the marked beneficial effects seen in the earliest report. Unfortunately, we do not have detailed data on the type of beta blocker used in our population.

In terms of the effects of ACEI use, both the LACE and the MD Anderson cohorts which reported on beta blocker use also reported on ACEI/ARB use among women with breast cancer. Contrary to the preclinical, evidence, neither study found decreased recurrence, breast cancer deaths, or total mortality [8,7]. In fact, the LACE cohort reported an elevated risk of recurrence (RR=1.56, 95% CI=1.02-2.39). [8] A third study of 703 Stage II and III breast cancer patients from Albert Einstein Medical Center evaluated ACEI use and reported a reduced risk of breast cancer recurrence (RR=0.49, 95% CI, 0.31-0.76. However, total mortality was not reduced. [15]

Similar to the MD Anderson study, we also did not find a reduced risk of breast cancer death or total mortality among users of ACEI similar to the MD Anderson study. Unlike the LACE study, we did not find an increased risk of adverse breast cancer outcome like the LACE study. We did not observe any differences in the effect of ACEI when participants were stratified by body mass index or ER status. However, the small number of deaths among women with ER negative tumors combined with the low prevalence of ACEI use makes interpretation of the ACEI results stratified by ER status difficult.

As we have previously reported, [16,17] we found an approximate 50% decreased risk of breast cancer death among women with breast cancer who use aspirin. This association was not affected by adjustment for beta blocker or ACEI use. This is consistent with results in three other observational studies, [18-20] and a pooled analysis of randomized trials of aspirin for cardiovascular disease in the UK. [21] Furthermore, in a linked meta-analysis the risk of breast cancer with distant metastases pooled from observational studies, (RR=0.58, 95% CI=0.20-1.71) was similar to that found in randomized trials, although it did not reach statistical significance. [20]

In our study, the strong beneficial association with aspirin use did appear to attenuate the associations seen with beta blocker and ACEI when those drugs were modeled individually. Simultaneous adjustment for aspirin use attenuated the risk estimates for beta blockers and ACEIs. ACEI and beta blocker appear to decrease breast cancer mortality only among aspirin users. Although power was more limited to look at each drug among women who used only that drug, the null results for beta blocker and ACEI, and the continued survival association with aspirin, similar to results seen when all 3 drugs are mutually adjusted for each other, seems to indicate that associations seen with beta blocker and ACEI could be confounded by simultaneous aspirin use. Therefore, aspirin use should be considered in analyses where there may be a high prevalence for concurrent use.

The strong beneficial association seen with aspirin use could be due to confounding by indication if women with breast cancer who are approaching death stop taking aspirin as unnecessary or detrimental. In our earlier report, we used marginal structural models to appropriately adjust for this type of time-dependent confounding and did not find a bias in favor of aspirin. [16] One might expect that women approaching death from breast cancer might also stop taking medications such as beta-blocker, ACEI, and thiazides as well as aspirin. The fact that we found little to no benefit associated with use of these drugs after accounting for aspirin use also argues against confounding by indication as an explanation for the aspirin results.

Strengths of our study include its prospective nature, repeated measurement of medication use, and its size which is larger than other reports except for the Irish registry nested case-control study of beta blockers. Our length of follow-up exceeds that of most other reported studies. Prevalence of beta-blocker and ACEI use was similar to other reported studies.

Limitations of our study include the fact that medication use was self-reported and did not distinguish between types of beta blocker. Despite the size and length of follow-up of our cohort, we do not have enough triple negative cases to examine them separately. Since beta-blockers may affect survival via pathways involving stress, it is unfortunate that we were not able to measure stress and stratify analyses on that factor.

In conclusion, in our study of 4,661 women with breast cancer, we found a suggestion that beta blocker use might be associated with a lower risk of breast cancer death. Consistent with a prior hypothesis, this effect may be stronger in women with ER negative tumors; but contrary to hypotheses, the effect appeared to be stronger among normal weight compared with overweight women. We were limited in that we could not distinguish between types of beta blockers, as those having beta-2 agonist blocking ability (non cardioselective) may be more active in cancer progression than those having only beta-1 agonist blocking ability (cardioselective). We found no association of ACEI use with breast cancer death. The strong protective association with aspirin was confirmed. Importantly, aspirin use appears to confound the associations seen with beta blockers and ACEIs, and may potentially confound the associations with other drugs which may frequently be taken together for cardiovascular or other indications, such as statins. Future studies of these and other drugs likely to be used simultaneously with aspirin should account for aspirin use.

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Human Subjects: This work was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston MA, and complies with all U.S. laws regarding human subjects.

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Table 1

Age-Standardized* Clinical Characteristics of 4,661 women with Breast Cancer by Baseline Medication Use After Diagnosis

Characteristic	Beta Blocker		ACEI		Aspirin	
	No	Yes	No	Yes	No	Yes
Number of breast cancer deaths Number of women (% of women using drug)	247 3891 (83%)	45 770 (17%)	261 4183 (90%)	31 478 (10%)	213 2739 (59%)	79 1922 (41%)
Mean age at diagnosis, years	62.7	65.8	62.8	66.3	61.7	65.3
Mean body mass index at diagnosis, kg/m ²	26.2	27.3	26.2	27.8	26.2	26.6
Mean total energy intake after treatment, kcal/d	1702	1723	1706	1713	1704	1714
Mean protein intake after treatment, g/d	73.7	74.3	73.6	74.6	73.6	73.8
Mean physical activity after treatment, MET- hours/week	17.3	14.9	17.1	14.7	16.6	17.3
Mean parity, number of children	2.9	2.8	2.9	2.9	2.9	2.9
Current smoker at diagnosis, %	12	10	12	10	11	12
Ever used oral contraceptives, %	46	48	45	52	46	46
Current users of postmenopausal hormones, %	42	45	42	46	40	44
Disease stage, % Stage I Stage II Stage III	63 32 5	66 29 5	63 32 5	62 32 7	63 32 5	65 32 4
Estrogen receptor positive, %	83	83	83	85	83	82
Treatment, % Radiation Chemotherapy Tamoxifen or aromatase inhibitor	55 35 70	58 34 70	55 35 70	59 39 75	54 35 71	57 34 71
Gained weight after treatment (>0.5 kg/m ²)	42	42	42	42	43	42

* except for age at diagnosis

Table 2

Use of medications after breast cancer diagnosis and RR(95% CI) of death from **breast cancer** (N=4,661; total breast cancer deaths = 292)

Row	Model	RR(95% CI) Beta blocker (yes/no)	RR(95% CI) ACEI (yes/no)	RR(95% CI) Aspirin (yes/no)
1	Simple + beta blocker MV + beta blocker	0.75(0.54-1.04) 0.76(0.54-1.05)		
2	Simple + ACEI MV + ACEI		0.85(0.58-1.24) 0.89(0.60-1.32)	
3	Simple + aspirin MV + aspirin			0.41(0.31-0.53) 0.46(0.35-0.60)
4	MV + beta blocker + ACEI	0.76(0.55-1.06)	0.91(0.62-1.35)	
5	MV + beta blocker + aspirin	0.83(0.60-1.16)		0.46(0.35-0.61)
6	MV + ACEI + aspirin		0.99(0.67-1.46)	0.46(0.35-0.60)
7	MV + beta blocker + ACEI + aspirin	0.83(0.60-1.16)	1.00(0.68-1.48)	0.46(0.35-0.61)

Simple model adjusted for time since diagnosis (continuous), age at diagnosis (continuous)

Multivariable (MV) models adjusted for time since diagnosis (continuous), age at diagnosis (continuous)

They are additionally adjusted for the following factors at the time of diagnosis: calendar year, disease stage (I, II, III,) smoking status (never, current, past), body mass index in kg/m² (<21, 21-22.9, 23-24.9, 25-28.9, ≥29), age at first birth and parity (nulliparous, <25 years and 1-2 births, <25 years and ≥3 births, ≥25 years and 1-2 births, ≥25 years and ≥3 births), oral contraceptive use (never, ever), menopausal status and use of hormone replacement (premenopausal, unknown, postmenopausal never-user, postmenopausal past user, postmenopausal current user), radiation treatment (yes/no), systemic treatment with chemotherapy and/or hormonal therapy (chemo no and hormonal no, chemo yes and hormonal no, chemo no and hormonal yes, chemo yes and hormonal yes)

They are additionally adjusted for the following factors after diagnosis and treatment: protein and energy intake (quintiles), physical activity (quintiles), weight change (loss ≥0.5 kg/m², gain ≥0.5 kg/m², maintained weight),

Table 3

Beta Blocker and ACEI use after diagnosis and multivariate RR(95% CI) of death from breast cancer, stratified by BMI

Stratification Factor	N#/deaths	Beta Blocker RR(95% CI)	p- interaction	N#/deaths	ACEI RR(95% CI)	p- interaction
BMI<25kg/m ²	2229/142	0.40(0.20-0.82)	0.11	2229/142	0.83(0.40-1.72)	0.48
BMI 25kg/m ²	2432/150	0.75(0.46-1.21)		2432/150	1.06(0.65-1.75)	
ER positive	3534/221	0.85(0.58-1.24)	0.09	3534/221	0.76(0.46-1.26)	0.86
ER negative	735/42	0.69(0.21-2.24)		735/42	2.04(0.59-7.08)	
Aspirin use=yes	3006/79	0.43(0.21-0.90)	0.17	3006/79	0.57(0.24-1.35)	0.26
Aspirin use=no	3340/213	0.77(0.49-1.22)		3340/213	0.97(0.57-1.65)	

Adjusted for the same factors as Table 2. Additionally adjusted for aspirin use, except for the models stratified by aspirin use.

Because ER status is missing on some participants the N for the strata ER positive and ER negative sum to less than the 4,661 women in the study.

The stratification factors BMI and ER status were assessed only once at the time of breast cancer diagnosis and thus N refers to numbers of women. The stratification factor aspirin use was updated over time; because women could contribute person time to both strata of aspirin use the N for the strata of aspirin use=yes plus aspirin use=no sums to more than the 4,661 in the study.