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Antihypertensive Medication Use and Incident Breast Cancer in Women

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Abstract

Purpose—To evaluate whether antihypertensive medication use, including long-term use, is associated with increased breast cancer incidence in women

Methods—We studied 210,641 U.S. registered nurses participating in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II). Information on antihypertensive medication use was collected on biennial questionnaires in both cohorts, and breast cancer cases were ascertained during this period. Multivariable-adjusted Cox proportional hazard models were used to estimate

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relative risks of invasive breast cancer over follow up (1988–2012 in NHS, 1989–2011 in NHS II) across categories of overall antihypertensive medication use and use of specific classes (diuretics, beta blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors).

Results—During follow up, 10,012 cases of invasive breast cancer developed (6,718 cases in NHS and 3,294 in the NHS II). Overall, current use of any antihypertensive medication was not associated with breast cancer risk compared with past/never use in NHS (multivariable-adjusted relative risk=1.00, 95% CI=0.95 to 1.06) or NHS II (multivariable-adjusted relative risk=0.94, 95% CI=0.86 to 1.03). Furthermore, no specific class of antihypertensive medication was consistently associated with breast cancer risk. Results were similar when we considered hypertensive women only, and when we evaluated consistency and duration of medication use over time.

Conclusions—Overall, antihypertensive medication use was largely unrelated to the risk of invasive breast cancer among women in the NHS cohorts.

Keywords

Antihypertensive medication; breast cancer; cohort study; epidemiology

INTRODUCTION

Hypertension is highly prevalent among adults, especially with advancing age; the lifetime risk of hypertension exceeds 80% in the United States[1]. Consequently, antihypertensive medications are commonly prescribed, and help to limit the risk of cardiovascular-related conditions, including stroke, coronary artery disease, and heart failure[2]. Breast cancer is the most prevalent malignancy and the second leading cause of cancer death among women in the United States[3]. Numerous studies have examined the association of antihypertensive medication use and incident breast cancer; some[4–15], but not all[16–22], studies have reported no association, although previous studies have generally lacked information on long-term use of these medications, which may have contributed to null findings. Still, two recent studies that collected such information reported that long-term use of antihypertensive drugs might be associated with an increased risk of breast cancer[20,22]. One of these studies identified an association with use of any antihypertensive medication (although little information was available on individual classes of medication)[20], and the second study found an association between long-term use of calcium channel blockers among current users (although the study was retrospectively designed, with a very small number of long-term users)[22]. To investigate this association further, we utilized longitudinal data from the Nurses' Health Studies (which, together, include >200,000 women) to prospectively evaluate the association of antihypertensive medication use, including different classes of medication and long-term use, with incident breast cancer in women.

METHODS

Study population

The Nurses' Health Study (NHS) was established in 1976, when 121,701 U.S. female nurses, aged 30–55 years, returned a mailed questionnaire about their health and

lifestyle[23]. In 1989, the Nurses' Health Study II (NHS II) was initiated among a younger generation of 116,434 female nurses aged 25–42 years[24]. Women have updated their information biennially with mailed questionnaires, and follow up is ≥90% in each cohort. Voluntary return of the questionnaires is considered to imply informed consent, and the Institutional Review Board of Brigham and Women's Hospital (Boston, Massachusetts) has approved both studies.

Ascertainment of antihypertensive medication use

Antihypertensive medication use was ascertained on most cohort questionnaires beginning in 1988 in NHS and 1989 in NHS II. In NHS, women were queried about their use of beta blockers, diuretics, calcium channel blockers, and "other" antihypertensive medications in 1988 and 1994, and every two years thereafter; angiotensin-converting enzyme (ACE) inhibitor use was ascertained in 1988, 1996, and every two years thereafter in this cohort. In NHS II, there was more variability in the timing of these queries: "any" antihypertensive use and diuretic use were assessed in 1989, 1993, and every two years thereafter; beta blocker use was queried in 1989, 2001, and every two years thereafter; and calcium channel blocker use and ACE inhibitor use were assessed in 2001 and every two years thereafter.

Ascertainment of incident breast cancer cases

Breast cancer cases were identified during the period of June 1, 1988 to June 1, 2012 in NHS and June 1, 1989 to June 1, 2011 in NHS II. Nurses who reported breast cancer on cohort questionnaires were asked for permission to review their medical records, which was used to confirm breast cancer diagnoses. When medical records were unavailable, breast cancer cases were defined as probable and included in the analysis if corroborated by phone interview or written confirmation from the participant. In some cases, breast cancer was reported during death follow-up, when family members, the postal service, or the National Death Index informed the study of a participant's death. The National Death Index was also reviewed after each questionnaire cycle to determine the status of women who were unresponsive to cohort questionnaires. In both cohorts, self-reported breast cancer was >98% accurate compared to pathology reports[25,26]; thus, although pathology reports were pending for 8% of cases in NHS and 12% cases in NHS II, we based our analyses on the total cases because of this high accuracy.

Ascertainment of possible confounding variables

Covariate information was derived from participants' self reports on biennial questionnaires in both cohorts.

Population for analysis

In NHS, 103,551 women first provided information on antihypertensive medication use in 1988; in NHS II, antihypertensive medication use was assessed at baseline, in 1989, among all 116,343 participants. Of these, we excluded 2,304 women with breast cancer diagnoses (2,098 invasive cases and 206 in situ cases) prior to 1988 in NHS, and five women with such diagnoses (three invasive cases and two in situ cases) in NHS II. We also excluded women with a prior diagnosis of other cancers (except non-melanoma skin cancer) at baseline

(n=5,637 in NHS and n=1,045 in NHS II). Finally, we removed 109 participants in NHS and 239 participants in NHS II because they did not report information on height—an important risk factor for breast cancer in women[27]. After these exclusions, 95,501 women in NHS and 115,140 women in NHS II constituted our baseline population.

Statistical analysis

Follow up began with the initial report of antihypertensive medication use in our cohorts: 1988 in NHS and 1989 in NHS II. Because antihypertensive medications of interest were not assessed on every cohort questionnaire, we carried forward information that had been previously ascertained until the next questionnaire cycle that included new information for a particular medication. We used several approaches to examine the association between antihypertensive medication use and risk of invasive breast cancer in each of the NHS cohorts. First, we examined current use of any antihypertensive medication as well as individual classes of medication (diuretics, beta blockers, calcium channel blockers, and ACE inhibitors), updating this information biennially. Secondly, we restricted our analyses to women with a diagnosis of hypertension (n=61,427 in NHS and n=36,036 in NHS II) to address the possibility of confounding by indication, and eliminate hypertension as the primary reason for any observed associations. Third, we evaluated women according to consistency of antihypertensive medication use: consistent use, inconsistent use, and never use. Women were assigned to “consistent use” if they reported current antihypertensive medication use, either for the first time or after reporting such use on every questionnaire following their initial report of use. Women were assigned to “inconsistent use” if they reported no current antihypertensive medication use after previously reporting antihypertensive use. Women were assigned to “never use” if they reported no current use of antihypertensive medications after never reporting antihypertensive use previously. Finally, we extended our consistency analyses to incorporate duration of medication use among women with “consistent use”. To calculate duration, we assumed two years of medication use every time a participant reported use of antihypertensive medications on a biennial questionnaire, and then added these years together.

In NHS II, the initial report of calcium channel blocker and ACE inhibitor use occurred in 2001; thus, for current use analyses, we imputed 2001 information for questionnaire cycles from 1989 through 1999 to maximize the number of breast cancer cases utilized in our analyses. (Results were very similar using this approach compared to beginning these analyses in 2001, with fewer breast cancer cases). Consistency and duration analyses were begun in 2001, when all classes of antihypertensive medications began to be consistently included on the cohort questionnaires.

We used Cox proportional hazards models to estimate age- and multivariable- adjusted relative risks (RR) of incident breast cancer, with 95% confidence intervals (CI). We used age (in months) as the time scale in our models, and calculated person-time from the return date of the baseline questionnaire through the end of follow-up (June 1, 2012 in NHS and June 1, 2011 in NHS II), date of breast cancer diagnosis, date of death, or loss to follow-up, whichever occurred first. Statistical models were adjusted for the following potential confounding factors: body mass index, height, oral contraceptive use, menopausal status,

age at menopause, postmenopausal hormone use, age at first birth and parity, age at menarche, family history of breast cancer, history of benign breast disease, alcohol intake, physical activity, smoking history, and shift work history. These covariates were determined at baseline and updated at each follow-up cycle; missing indicators were utilized to represent missing data in statistical models. We also considered possible confounding by aspirin use and mutual adjustment for each of the different antihypertensive medications, but neither approach changed our effect estimates; thus, these adjustments were not included in our final models.

In secondary analyses, we stratified our models according to estrogen-receptor (ER) status of breast tumors and aspirin use, testing for heterogeneity using the likelihood ratio test. All p-values were two sided and considered statistically significant if $p<0.05$. We used SAS software, version 9 (SAS Institute, Cary, North Carolina, United States) for all statistical analyses.

RESULTS

There were 10,012 cases of invasive breast cancer (6,718 cases in NHS and 3,294 in NHS II) that developed over follow up. Table 1 describes age and age-adjusted characteristics of 179,021 women participating in the NHS cohorts at the midpoint of follow-up, according to current vs. past/never use of antihypertensive medication. As expected, the majority of women who reported current use of antihypertensive medication had a diagnosis of hypertension (88% in NHS and 69% in NHS II). Most characteristics were similar comparing current vs. past/never antihypertensive users, although current users of these medications tended to be older, with higher body-mass index, lower physical activity levels, and less regular use of aspirin compared with past/never users. Moreover, we observed greater use of antihypertensive medications over time in both cohorts (data not shown).

In age- and multivariable- adjusted models, the risk of incident breast cancer was similar among current vs. past/never antihypertensive users (multivariable-adjusted [MV] RR=1.00, 95% CI=0.95 to 1.06 in NHS, and MV RR=0.94, 95% CI=0.86 to 1.03 in NHS II) (Table 2). When examining specific classes of antihypertensive drugs, in age-adjusted models, current use of calcium channel blockers was related to a small increase in breast cancer risk in NHS (RR=1.10, 95% CI=1.01 to 1.19), but not in NHS II (RR=0.94, 95% CI=0.76 to 1.17). This association was attenuated after multivariable adjustment in NHS (MV RR=1.07, 95% CI=0.99 to 1.17), and remained non-significant in NHS II (MV RR=0.97, 95% CI=0.78 to 1.20). Current use of diuretics, beta blockers, and ACE inhibitors was not related to incident breast cancer in NHS in age- or multivariable- adjusted models. In NHS II, ACE inhibitor use was associated with lower risk of breast cancer in age- and multivariable- adjusted models (MV RR=0.74, 95% CI=0.62 to 0.89, comparing current vs. past/never users of ACE inhibitors), whereas use of diuretics and beta blockers was not related to breast cancer risk. Results were similar when we restricted our analyses to hypertensive women only (Table 3).

In addition, consistent use of antihypertensive medications was not related to risk of developing breast cancer in either age- or multivariable- adjusted models; the multivariable-adjusted RR was 0.99 (95% CI=0.93 to 1.05) in NHS and 0.95 (95% CI=0.84 to 1.07) in

NHS II comparing consistent vs. never users of antihypertensive medication (Table 4). When we evaluated individual classes of antihypertensive medications, we found a small, borderline reduction in breast cancer risk among women who reported consistent vs. never use of beta blockers in NHS only (MV RR=0.93, 95% CI=0.86 to 1.00). Furthermore, in NHS II only, consistent users of ACE inhibitors had a lower risk of breast cancer compared to never users of these medications (MV RR=0.76, 95% CI=0.60 to 0.96). All other associations between antihypertensive medications and breast cancer risk were non-significant in analyses that considered consistency of medication use.

Similar results were apparent in analyses that divided consistent users of antihypertensive medications into categories according to duration (Table 5). There were no trends for duration of medication use across the various antihypertensive medications, except that longer, consistent use of ACE inhibitors was related to a decreased risk of breast cancer in NHS II (p-trend=0.01, MV RR=0.57, 95% CI=0.35 to 0.94 comparing consistent users with ≥6 years of ACE inhibitor use vs. never use of these medications). Still, longer duration of ACE inhibitor use was not associated with breast cancer risk in NHS (p-trend=0.06, MV RR=0.90, 95% CI=0.51 to 1.59 comparing ≥16 years of consistent use vs. none), where exposure data was reported consistently over a longer time period, and therefore longer durations could be evaluated.

Finally, in stratified analyses, we found few differences in the associations of antihypertensive medication use and incident breast cancer according to ER tumor status. Beta blocker use was related to a reduced risk of ER- tumors (MV RR=0.77, 95% CI=0.62 to 0.96 comparing current vs. past/never users), but not ER+ tumors (MV RR=1.00, 95% CI=0.92 to 1.09 for the same comparison), in NHS (p-heterogeneity=0.02); however, there was no such difference in NHS II (p-heterogeneity=0.2) (see Online Resources 1 and 2). Calcium channel blocker use was associated with a significantly increased risk of ER- tumors in NHS (MV RR=1.36, 95% CI=1.09 to 1.70 for current vs. past/never users) and a non-significantly elevated risk of ER- tumors in NHS II (MV RR=1.20, 95% CI=0.75 to 1.93 comparing current vs. past/never users), although p-values for heterogeneity were not significant between tumor types. Moreover, analyses stratified by aspirin use were similar to our overall results (results not shown).

DISCUSSION

Overall, we found that antihypertensive medication use was largely not associated with the risk of invasive breast cancer among women participating in the NHS cohorts, in accordance with a previous analysis in NHS, which included six years of follow up[8]. Our results were generally similar across analyses of current antihypertensive medication use, hypertensive women only, and consistency and duration of medication use over two decades of follow up. Thus, in contrast to two recent studies utilizing long-term data on antihypertensive medication use[20,22], and consistent with a recent study from the Swedish National Board of Health and Welfare[15], our findings do not indicate that use of these medications generally, or calcium channel blockers specifically, is associated with an increased risk of developing breast cancer.

Recent studies that reported long-term use of antihypertensive medication was related to an increased breast cancer risk utilized somewhat different study designs compared to our study. The first of these studies, conducted in a cohort of California teachers, was a prospective cohort study with 4,151 incident cases of breast cancer occurring between 1995 and 2006[20]. A baseline questionnaire was used to assess women's history of antihypertensive medication use, but updated information on medication use during follow up was not incorporated into analyses of long-term medication use. The study reported an increase in the risk of breast cancer among women with a longer history of antihypertensive use compared with those with no history of use, but the point estimate was relatively small (RR=1.18, 95% CI=1.04 to 1.34 comparing women with ≥10 years of antihypertensive medication use vs. none), and information on specific antihypertensive medications was limited to diuretic use; thus, interpretability of these results is somewhat limited.

A recent retrospective, case-control study among women in Seattle-Puget Sound provided more specific analyses related to different classes of antihypertensive medication in relation to breast cancer risk[22]. In that study, use of calcium channel blockers for ≥10 years among current users was associated with an increased breast cancer risk that was approximately 2.5 times greater compared to women who never used antihypertensive medications, although confidence intervals for these estimates were wide due to the small number of participants in the longest duration category (n=12 controls, 27 ductal cases, and 31 lobular cases) (RR=2.4, 95% CI=1.2 to 4.9 for invasive ductal cases, and RR=2.6, 95% CI=1.3 to 5.3 for invasive lobular cases). Thus, this finding needs to be interpreted very cautiously, especially given the very small number of controls that comprise the reference group for both of these estimates.

In contrast, our current study found no overall association between calcium channel blocker use and breast cancer risk, including among current, long-term users, in analyses of ≥10,000 invasive breast cancer cases and ≥150,000 non-cases across the NHS cohorts (our long duration categories for "consistent users" are current, long-term users by definition). This result is consistent with recent findings from the Swedish National Board of Health and Welfare, which reported that five-year use of calcium channel blockers was not associated with breast cancer risk in a prospective case-control study (MV odds ratio=1.1, 95% CI=0.9 to 1.3); however, data on longer-term medication use were not available in that study[15]. Although we found a small (10%) increase in breast cancer risk among current users of calcium channel blockers in NHS, this association was borderline significant and not present in consistent, long-duration users in this cohort, or among women taking calcium channel blockers in NHS II. There was also some suggestion that current users of calcium channel blockers might have an elevated risk of ER- breast cancer in NHS, and perhaps in NHS II as well. However, there is no prior biologic reason to believe that calcium channel blockers would be associated with ER- tumors specifically; thus, this finding should be interpreted cautiously, and explored in future studies. Taken together, then, our findings do not support an overall association of calcium channel blocker use, including long-term use of these medications, with breast cancer risk in women.

Although there was no overall association between use of antihypertensive medications and breast cancer risk in our study, a potentially intriguing finding is that use of ACE inhibitors

was related to a decreased risk of breast cancer among women participating in NHS II. This finding is similar to results in the Seattle-Puget Sound study, which identified a borderline significant risk reduction for ductal and lobular breast cancers among women using ACE inhibitors over long durations (RR of ductal breast cancer=0.7, 95% CI=0.5 to 1.2, and RR of lobular breast cancer=0.6, 95% CI=0.4–1.0, comparing ≥10 years of ACE inhibitor use vs. never using antihypertensive medications)[22]. However, there is limited biologic evidence to indicate a specific mechanism by which ACE inhibitors would reduce the risk of breast cancer in women, and no evidence that these medications reduce breast cancer survival according to a previous study in this cohort (RR=0.89, 95% CI=0.60 to 1.32 comparing current vs. never/past users)[28]. Thus, the association that we observed should not be over-interpreted in our findings, although future studies should further investigate this association.

We also observed a modestly reduced risk of breast cancer incidence among consistent users of beta blockers in NHS, although it was small (i.e., a 9% risk reduction) and not found in analyses that considered duration of medication use or in analyses of the NHS II cohort. In addition, beta blockers are known to decrease melatonin secretion in the body[29], and lower melatonin levels have been associated with an increased risk of breast cancer in the NHS cohorts[30,31]. Thus, we would have expected any observed association to indicate that consistent use of beta blockers elevated breast cancer risk—further suggesting that the association in NHS is likely due to chance.

Our study has several limitations. First, this is an observational study and therefore we cannot rule out the possibility of residual confounding due to unmeasured or poorly measured factors. We adjust our statistical models for a wide variety of health and lifestyle factors, including multiple risk factors for breast cancer, which produced relatively little change in our effect estimates compared with age-adjusted models. Thus, although we cannot definitively rule out residual confounding as an explanation for our findings, we have minimized this possibility by carefully considering many potential confounding factors. Second, use of antihypertensive medications was self reported by women in the NHS cohorts, and therefore some random exposure misclassification may have occurred in our study. However, our nurse-participants are likely to report their medication use accurately due to their high level of health-related knowledge, and previous validation studies in NHS indicate that the validity of self-reported hypertension and other health information is very high[32]. For questionnaire cycles without information on particular antihypertensive medications, we carried forward women's most recent report, and this assumption may have resulted in some misclassification of our exposure. However, such misclassification is less likely to have influenced our results given the similarity of our main findings to results based on the subgroup of women with hypertension, who are likely to have continued their use of antihypertensive medications. Finally, we only had information on broad classes of antihypertensive medications in our cohorts, and therefore we could not evaluate associations between specific subclasses (e.g., short-acting vs. long-acting, or dihydropyridine vs. non-dihydropyridine calcium channel blockers) and breast cancer incidence. However, results of the Seattle-Puget Sound Study do not suggest that associations differ across these subclasses; thus, we may have captured the most relevant

information by asking women to report their use of antihypertensive medications in broad classes[22].

In conclusion, we found that use of antihypertensive medications, including calcium channel blockers, was not related to breast cancer risk among women participating in the NHS cohorts. Our study evaluated current use and longer-term use of antihypertensive medications, and results were generally consistent across these analyses. Importantly, our study differs from several previous reports utilizing long-term drug information, which had suggested that antihypertensive medications, including calcium channel blockers, may increase the risk of breast cancer in women. Future studies are needed to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Informed consent: Implied informed consent, indicated by voluntary return of the cohort questionnaires, was obtained from all individual participants included in the study.

ABBREVIATIONS

ACE	Angiotension-converting enzyme
CI	Confidence interval
ER	Estrogen receptor
MV	Multivariable
NHS	Nurses' Health Study
NHS II	Nurses' Health Study II
RR	Relative risk4

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Table 1

Age and age-adjusted characteristics of women in the Nurses' Health Studies at the midpoint of follow up (1998 in NHS and 1999 in NHS II), according to antihypertensive medication use (n=179,021)

	NHS (n=79,404)		NHS II (n=99,617)	
	Past/never use (n=52,282)	Current use (n=27,122)	Past/never use (n=86,374)	Current use (n=13,243)
Mean age, in years (SD)	63.6 (7.1)	65.9 (6.9)	44.5 (4.6)	46.7 (4.2)
Mean body-mass index, in kg/m^2 (SD)	26.0 (5.0)	28.2 (5.9)	26.0 (5.8)	30.6 (7.8)
History of hypertension, %	24	88	6	69
Mean height, in inches (SD)	64.5 (2.4)	64.5 (2.5)	64.9 (2.6)	64.9 (2.7)
Oral contraceptive use, % ever	49	50	88	88
Menopausal status, % postmenopausal	97	97	16	22
Age at menopause, in years, %[a]				
<45 years	10	12	39	44
45–49 years	25	24	38	33
50–52 years	44	44	22	22
≥53 years	21	20	1	1
Postmenopausal hormone use, %[a]				
Never	26	23	29	22
Past	22	22	12	13
Current	52	55	59	65
Regular aspirin use, %[b]	28	36	14	27
Parity and age at first birth, %				
Nulliparous	6	5	18	21
1–2 children and <25 years old	14	15	15	21
1–2 children and 25–29 years old	15	15	21	22
1–2 children and ≥30 years old	6	6	17	13
≥3 children and <25 years old	35	36	13	13
≥3 children and ≥25 years old	24	23	16	10
Age at menarche, % ≥14 years old	21	18	18	14
Family history of breast cancer, %	20	20	25	25
History of benign breast disease, %	16	20	18	18
Mammography screening, %	92	97	84	88
Mean alcohol intake, in grams/day (SD)	5.1 (9.0)	4.7 (9.3)	4.0 (7.1)	3.4 (7.6)
Mean physical activity level, in MET-hours/week (SD)	18.6 (22.2)	15.1 (19.5)	18.8 (23.0)	15.5 (21.0)
Smoking status, %				
Current	52	55	59	65
Never or past	88	91	91	90
Current and <25 cigarettes/day	10	8	8	8
Current and ≥25 cigarettes/day	2	1	1	2

	NHS (n=79,404)		NHS II (n=99,617)	
	Past/never use (n=52,282)	Current use (n=27,122)	Past/never use (n=86,374)	Current use (n=13,243)
Shift work history				
None	41	40	30	29
1–9 years	48	48	63	63
≥10 years	11	12	7	8

[a] Among postmenopausal women only.

[b] Regular aspirin use was defined as currently taking ≥3 tablets per week in NHS, and currently taking aspirin ≥2 times per week in NHS II.

Table 2

Relative risks of incident breast cancer over the follow-up period in the Nurses' Health Studies (1988–2012 in NHS and 1989–2011 in NHS II), according to current use of antihypertensive medication (n=210,641)

	NHS (n=95,501)		NHS II (n=115,140)	
	Past/never use	**Current use**	**Past/never use**	**Current use**
Any antihypertensive medication				
Cases/Person-years	4,179/1,159,086	2,539/620,212	2,690/1,771,464	604/316,944
Age-adjusted RR (95% CI)	1.00 (ref)	1.05 (1.00 to 1.11)	1.00 (ref)	0.91 (0.83 to 1.00)
Multivariable-adjusted RR (95% CI)[a]	1.00 (ref)	1.00 (0.95 to 1.06)	1.00 (ref)	0.94 (0.86 to 1.03)
Diuretics				
Cases/Person-years	5,614/1,510,215	1,103/268,933	3,082/1,980,583	209/104,401
Age-adjusted RR (95% CI)	1.00 (ref)	1.05 (0.98 to 1.12)	1.00 (ref)	0.90 (0.78 to 1.04)
Multivariable-adjusted RR (95% CI)[a]	1.00 (ref)	1.00 (0.94 to 1.07)	1.00 (ref)	0.93 (0.80 to 1.08)
Beta blockers				
Cases/Person-years	5,767/1,540,824	950/238,324	3,079/1,993,088	215/95,320
Age-adjusted RR (95% CI)	1.00 (ref)	1.00 (0.93 to 1.07)	1.00 (ref)	1.06 (0.92 to 1.22)
Multivariable-adjusted RR (95% CI)[a]	1.00 (ref)	0.97 (0.90 to 1.04)	1.00 (ref)	1.09 (0.95 to 1.26)
Calcium channel blockers				
Cases/Person-years	6,077/1,634,906	640/144,242	3,025/1,925,448	87/47,431
Age-adjusted RR (95% CI)	1.00 (ref)	1.10 (1.01 to 1.19)	1.00 (ref)	0.94 (0.76 to 1.17)
Multivariable-adjusted RR (95% CI)[a]	1.00 (ref)	1.07 (0.99 to 1.17)	1.00 (ref)	0.97 (0.78 to 1.20)
ACE inhibitors				
Cases/Person-years	6,170/1,639,888	548/139,410	2,991/1,886,834	121/86,045
Age-adjusted RR (95% CI)	1.00 (ref)	0.96 (0.88 to 1.05)	1.00 (ref)	0.72 (0.60 to 0.87)
Multivariable-adjusted RR (95% CI)[a]	1.00 (ref)	0.94 (0.86 to 1.03)	1.00 (ref)	0.74 (0.62 to 0.89)

[a]These models are adjusted for age and body-mass index (<20, 20–21.9, 22–24.9, 25–29.9, ≥30 kg/m^2), height (inches), oral contraceptive use (never, ever), menopausal status (premenopausal, postmenopausal), age at menopause (<45, 45–49, 50–52, ≥53 years), postmenopausal hormone use (among postmenopausal women only: never, past, current), parity and age at first birth (nulliparous, 1–2 children and <25 years old, 1–2 children and 25–29 years old, 1–2 children and ≥30 years old, ≥3 children and <25 years old, ≥3 children and ≥25 years old), age at menarche (<12, 12, 13, ≥14 years old), family history of breast cancer (yes, no), history of benign breast disease (yes, no), alcohol intake (none, 1–7.49, 7.5–14.99, 15–29.9, ≥30 grams/day), physical activity level (quintiles of MET-hours/week), smoking status (never or past, current and <25 cigarettes/day, current and ≥25 cigarettes/day), and shift work history (none, 1–9, ≥10 years).

Table 3

Relative risks of incident breast cancer over the follow-up period among women with hypertension in the Nurses' Health Studies (1988–2012 in NHS and 1989–2011 in NHS II), according to current use of antihypertensive medication (n=97,463)

	NHS (n=61,427)		NHS II (n=36,036)	
	Past/never use	**Current use**	**Past/never use**	**Current use**
Any antihypertensive medication				
Cases/Person-years	1,018/267,198	2,245/545,596	216/111,156	459/220,193
Age-adjusted RR (95% CI)	1.00 (ref)	1.05 (0.98 to 1.14)	1.00 (ref)	0.91 (0.77 to 1.07)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	1.01 (0.93 to 1.10)	1.00 (ref)	0.89 (0.75 to 1.06)
Diuretics				
Cases/Person-years	2,280/570,949	982/241,696	504/249,295	171/80,579
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.94 to 1.09)	1.00 (ref)	0.92 (0.77 to 1.10)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.98 (0.91 to 1.06)	1.00 (ref)	0.91 (0.76 to 1.09)
Beta blockers				
Cases/Person-years	2,464/610,430	798/202,215	528/271,702	147/59,647
Age-adjusted RR (95% CI)	1.00 (ref)	0.96 (0.89 to 1.05)	1.00 (ref)	1.14 (0.95 to 1.38)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.94 (0.87 to 1.02)	1.00 (ref)	1.14 (0.94 to 1.38)
Calcium channel blockers				
Cases/Person-years	2,678/682,711	584/129,934	590/288,980	64/30,427
Age-adjusted RR (95% CI)	1.00 (ref)	1.11 (1.01 to 1.21)	1.00 (ref)	0.99 (0.76 to 1.29)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	1.10 (1.00 to 1.20)	1.00 (ref)	0.99 (0.76 to 1.30)
ACE inhibitors				
Cases/Person-years	2,724/676,998	539/135,796	552/256,025	102/63,382
Age-adjusted RR (95% CI)	1.00 (ref)	0.95 (0.87 to 1.05)	1.00 (ref)	0.73 (0.59 to 0.91)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.95 (0.86 to 1.04)	1.00 (ref)	0.72 (0.58 to 0.90)

[a] These models are adjusted for age and body-mass index (<20, 20–21.9, 22–24.9, 25–29.9, ≥30 kg/m^2), height (inches), oral contraceptive use (never, ever), menopausal status (premenopausal, postmenopausal), age at menopause (<45, 45–49, 50–52, ≥53 years), postmenopausal hormone use (among postmenopausal women only: never, past, current), parity and age at first birth (nulliparous, 1–2 children and <25 years old, 1–2 children and 25–29 years old, 1–2 children and ≥30 years old, ≥3 children and <25 years old, ≥3 children and ≥25 years old), age at menarche (<12, 12, 13, ≥14 years old), family history of breast cancer (yes, no), history of benign breast disease (yes, no), alcohol intake (none, 1–7.49, 7.5–14.99, 15–29.9, ≥30 grams/day), physical activity level (quintiles of MET-hours/week), smoking status (never or past, current and <25 cigarettes/day, current and ≥25 cigarettes/day), and shift work history (none, 1–9, ≥10 years).

Table 4

Relative risks of incident breast cancer over the follow-up period in the Nurses' Health Studies (1988–2012 in NHS and 2001–2011 in NHS II), according to consistency of antihypertensive medication use over time (n=191,221)

	NHS (n=95,501)			NHS II (n=95,720)		
	Never use	**Inconsistent use**	**Consistent use**	**Never use**	**Inconsistent use**	**Consistent use**
Any antihypertensive medication						
Cases/Person-years	3,621/1,014,173	1,001/251,637	2,096/513,489	1,287/593,620	133/57,023	373/162,765
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.94 to 1.09)	1.04 (0.98 to 1.10)	1.00 (ref)	0.92 (0.76 to 1.11)	0.93 (0.83 to 1.05)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	1.00 (0.92 to 1.08)	0.99 (0.93 to 1.05)	1.00 (ref)	0.96 (0.79 to 1.17)	0.95 (0.84 to 1.07)
Diuretics						
Cases/Person-years	4,911/1,335,053	968/238,823	838/205,272	1,562/708,199	84/43,489	147/61,720
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.94 to 1.09)	1.06 (0.98 to 1.14)	1.00 (ref)	0.75 (0.60 to 0.94)	0.95 (0.80 to 1.13)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.99 (0.92 to 1.07)	1.00 (0.93 to 1.08)	1.00 (ref)	0.78 (0.62 to 0.98)	0.97 (0.82 to 1.16)
Beta blockers						
Cases/Person-years	5,196/1,391,990	756/189,025	765/198,133	1,554/715,982	84/39,603	155/57,823
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.93 to 1.10)	0.96 (0.89 to 1.04)	1.00 (ref)	0.87 (0.69 to 1.08)	1.11 (0.94 to 1.31)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	1.01 (0.93 to 1.10)	0.93 (0.86 to 1.00)	1.00 (ref)	0.90 (0.71 to 1.13)	1.12 (0.94 to 1.32)
Calcium channel blockers						
Cases/Person-years	5,618/1,509,700	570/150,822	529/118,625	1,697/765,222	50/27,214	46/20,971
Age-adjusted RR (95% CI)	1.00 (ref)	0.95 (0.87 to 1.04)	1.08 (0.99 to 1.19)	1.00 (ref)	0.73 (0.55 to 0.97)	0.90 (0.67 to 1.21)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.95 (0.87 to 1.04)	1.06 (0.97 to 1.16)	1.00 (ref)	0.75 (0.56 to 1.01)	0.92 (0.69 to 1.24)
ACE inhibitors						
Cases/Person-years	5,721/1,520,937	543/141,015	454/117,347	1,637/738,583	83/35,562	73/39,262
Age-adjusted RR (95% CI)	1.00 (ref)	0.98 (0.89 to 1.08)	0.94 (0.85 to 1.03)	1.00 (ref)	0.92 (0.73 to 1.15)	0.75 (0.59 to 0.95)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.98 (0.89 to 1.08)	0.91 (0.83 to 1.00)	1.00 (ref)	0.98 (0.77 to 1.23)	0.76 (0.60 to 0.96)

[a] These models are adjusted for age and body-mass index (<20, 20–21.9, 22–24.9, 25–29.9, ≥30 kg/m^2), height (inches), oral contraceptive use (never, ever), menopausal status (premenopausal, postmenopausal), age at menopause (<45, 45–49, 50–52, ≥53 years), postmenopausal hormone use (among postmenopausal women only: never, past, current), parity and age at first birth (nulliparous, 1–2 children and <25 years old, 1–2 children and 25–29 years old, 1–2 children and ≥30 years old, ≥3 children and <25 years old, ≥3 children and ≥25 years old), age at menarche (<12, 12, 13, ≥14 years old), family history of breast cancer (yes, no), history of benign breast disease (yes, no), alcohol intake (none, 1–7.49, 7.5–14.99, 15–29.9, ≥30 grams/day), physical activity level (quintiles of MET-hours/week), smoking status (never or past, current and <25 cigarettes/day, current and ≥25 cigarettes/day), and shift work history (none, 1–9, ≥10 years).

Table 5

Relative risks of incident breast cancer over the follow-up period in the Nurses' Health Studies (1988–2012 in NHS and 2001–2011 in NHS II), according to consistency and duration of antihypertensive medication use over time (n=191,221)

	NHS (n=95,501)						NHS II (n=95,720)			
	Never use	**Inconsistent Use**	**Consistent use (2–4 years)**	**Consistent use (6–8 years)**	**Consistent use (10–14 years)**	**Consistent use (≥16 years)**	**Never use**	**Inconsistent use**	**Consistent use (2–4 years)**	**Consistent use (≥6 years)**
Any antihypertensive medication										
Cases/Person-years	3,621/1,014,173	1,001/251,637	823/206,140	541/131,721	472/110,440	260/65,187	1,287/593,620	133/57,023	245/105,381	128/57,383
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.94 to 1.09)	1.06 (0.98 to 1.14)	1.04 (0.95 to 1.15)	0.99 (0.90 to 1.10)	1.06 (0.92 to 1.21)	1.00 (ref)	0.91 (0.76 to 1.10)	1.00 (0.87 to 1.14)	0.82 (0.68 to 0.99)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.99 (0.92 to 1.07)	1.02 (0.94 to 1.10)	0.99 (0.90 to 1.09)	0.94 (0.84 to 1.04)	1.00 (0.87 to 1.15)	1.00 (ref)	0.95 (0.79 to 1.16)	1.01 (0.87 to 1.16)	0.84 (0.69 to 1.02)
Diuretics										
Cases/Person-years	4,911/1,335,053	968/238,823	470/115,663	210/54,258	124/25,170	34/10,181	1,562/708,199	84/43,489	120/46,515	27/15,205
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.94 to 1.09)	1.07 (0.97 to 1.18)	1.01 (0.87 to 1.16)	1.15 (0.96 to 1.38)	0.88 (0.63 to 1.24)	1.00 (ref)	0.75 (0.59 to 0.93)	1.06 (0.88 to 1.28)	0.65 (0.44 to 0.96)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.99 (0.92 to 1.06)	1.03 (0.93 to 1.13)	0.95 (0.82 to 1.09)	1.08 (0.90 to 1.29)	0.83 (0.59 to 1.17)	1.00 (ref)	0.77 (0.61 to 0.97)	1.08 (0.89 to 1.30)	0.67 (0.45 to 0.98)
Beta blockers										
Cases/Person-years	5,196/1,391,990	756/189,025	389/99,657	189/49,315	125/32,924	62/16,237	1,554/715,982	84/39,603	115/40,961	40/16,862
Age-adjusted RR (95% CI)	1.00 (ref)	1.01 (0.93 to 1.10)	0.99 (0.89 to 1.10)	0.96 (0.83 to 1.12)	0.87 (0.72 to 1.04)	0.99 (0.77 to 1.28)	1.00 (ref)	0.86 (0.69 to 1.08)	1.20 (0.99 to 1.45)	0.91 (0.66 to 1.24)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	1.01 (0.93 to 1.10)	0.96 (0.87 to 1.07)	0.93 (0.80 to 1.07)	0.83 (0.69 to 0.99)	0.95 (0.73 to 1.22)	1.00 (ref)	0.90 (0.71 to 1.13)	1.21 (1.00 to 1.46)	0.92 (0.67 to 1.26)
Calcium channel blockers										
Cases/Person-years	5,618/1,509,700	570/150,822	320/70,207	133/27,813	62/15,936	14/4,669	1,697/765,222	50/27,214	35/16,405	11/4,567
Age-adjusted RR (95% CI)	1.00 (ref)	0.95 (0.86 to 1.03)	1.12 (1.00 to 1.26)	1.13 (0.95 to 1.34)	0.92 (0.71 to 1.18)	0.79 (0.46 to 1.34)	1.00 (ref)	0.73 (0.55 to 0.97)	0.90 (0.64 to 1.25)	0.94 (0.52 to 1.70)
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.95 (0.87 to 1.04)	1.10 (0.98 to 1.23)	1.09 (0.92 to 1.30)	0.89 (0.69 to 1.15)	0.79 (0.46 to 1.33)	1.00 (ref)	0.75 (0.56 to 1.01)	0.92 (0.65 to 1.28)	0.95 (0.52 to 1.73)
ACE inhibitors										
Cases/Person-years	5,721/1,520,937	543/141,015	288/71,126	96/27,554	58/15,057	12/3,609	1,637/738,583	83/35,562	57/29,267	16/9,995
Age-adjusted RR (95% CI)	1.00 (ref)	0.98 (0.89 to 1.08)	0.97 (0.86 to 1.09)	0.88 (0.71 to 1.07)	0.92 (0.71 to 1.19)	0.91 (0.52 to 1.61)	1.00 (ref)	0.92 (0.73 to 1.15)	0.82 (0.63 to 1.06)	0.57 (0.35 to 0.94)

	NHS (n=95,501)						NHS II (n=95,720)			
	Never use	**Inconsistent Use**	**Consistent use (2–4 years)**	**Consistent use (6–8 years)**	**Consistent use (10–14 years)**	**Consistent use (≥16 years)**	**Never use**	**Inconsistent use**	**Consistent use (2–4 years)**	**Consistent use (≥6 years)**
Multivariable-adjusted RR (95% CI) [a]	1.00 (ref)	0.98 (0.89 to 1.08)	0.94 (0.83 to 1.06)	0.85 (0.69 to 1.04)	0.90 (0.69 to 1.16)	0.90 (0.51 to 1.59)	1.00 (ref)	0.97 (0.77 to 1.23)	0.83 (0.63 to 1.08)	0.57 (0.35 to 0.94)

[a] These models are adjusted for age and body-mass index (<20, 20–21.9, 22–24.9, 25–29.9, ≥30 kg/m^2), height (inches), oral contraceptive use (never, ever), menopausal status (premenopausal, postmenopausal), age at menopause (<45, 45–49, 50–52, ≥53 years), postmenopausal hormone use (among postmenopausal women only: never, past, current), parity and age at first birth (nulliparous, 1–2 children and <25 years old, 1–2 children and 25–29 years old, 1–2 children and ≥30 years old, ≥3 children and <25 years old, ≥3 children and ≥25 years old), age at menarche (<12, 12, 13, ≥14 years old), family history of breast cancer (yes, no), history of benign breast disease (yes, no), alcohol intake (none, 1–7.49, 7.5–14.99, 15–29.9, ≥30 grams/day), physical activity level (quintiles of MET-hours/week), smoking status (never or past, current and <25 cigarettes/day, current and ≥25 cigarettes/day), and shift work history (none, 1–9, ≥10 years).