Original Investigation

Use of Antihypertensive Medications and Breast Cancer Risk Among Women Aged 55 to 74 Years

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IMPORTANCE Antihypertensive agents are the most commonly prescribed class of medications in the United States. Evidence regarding the relationship between different types of antihypertensives and breast cancer risk is sparse and inconsistent, and prior studies have lacked the capacity to assess impacts of long-term use.

OBJECTIVE To evaluate associations between use of various classes of antihypertensive medications and risks of invasive ductal and invasive lobular breast cancers among postmenopausal women.

DESIGN, SETTING, AND PARTICIPANTS Population-based case-control study in the 3-county Seattle–Puget Sound metropolitan area. Participants were women aged 55 to 74 years, 880 of them with invasive ductal breast cancer, 1027 with invasive lobular breast cancer, and 856 with no cancer serving as controls.

EXPOSURES Recency and duration of use of antihypertensive medications.

MAIN OUTCOMES AND MEASURES Risks of invasive ductal and invasive lobular breast cancers.

RESULTS Current use of calcium-channel blockers for 10 or more years was associated with higher risks of ductal breast cancer (odds ratio [OR], 2.4; 95% CI, 1.2-4.9) (P = .04 for trend) and lobular breast cancer (OR, 2.6; 95% CI, 1.3-5.3) (P = .01 for trend). This relationship did not vary appreciably by type of calcium-channel blocker used (short-acting vs long-acting, dihydropyridines vs non-dihydropyridines). In contrast, use of diuretics, β-blockers, and angiotensin II antagonists were not associated with risk.

CONCLUSIONS AND RELEVANCE While some studies have suggested a positive association between calcium-channel blocker use and breast cancer risk, this is the first study to observe that long-term current use of calcium-channel blockers in particular are associated with breast cancer risk. Additional research is needed to confirm this finding and to evaluate potential underlying biological mechanisms.

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Invited Commentary
page 1637

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Considered together, the major forms of antihypertensive medications are the most commonly prescribed class of drugs in the United States. In 2010, the numbers of millions of filled prescriptions for β-blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, calcium-channel blockers, and angiotensin receptor blockers were 191.5, 168.7, 131.0, 97.9, and 83.7, respectively, together totaling 678.2 million filled prescriptions.

Despite the widespread use of antihypertensive agents, relatively few studies have characterized how use of different classes of antihypertensives are related to breast cancer risk. Of the 12 studies that have evaluated at least 1 class of antihypertensive agent, results are somewhat inconsistent: 4 studies found that use of calcium-channel blockers or diuretics[1-4] is positively associated with breast cancer risk, but 8 studies reported no associations.[5-12] However, in those studies finding no association, few investigated more than 1 class of antihypertensive or duration of use. Drawing inferences across studies is challenging because the studies contain variations in the populations evaluated and use different study designs (ranging from hospital-based studies to cohorts of a specific population to population-based case-control and cohort studies). In addition, most of the 12 studies included relatively few cases, with 5 of them having fewer than 100 cases[1,6,9,10,12] and

another 3 having fewer than 400 cases.[2,5,8] Furthermore, almost all of the women in the 3 largest studies were recruited during the 1990s, and as such these analyses were limited in their abilities to assess more recently introduced forms of antihypertensive drugs and longer durations of use.

The purpose of the present study is to assess the relationships between the major classes of antihypertensive agents and risk of the 2 most common histologic types of breast cancer, invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), in a contemporary population of postmenopausal women who have experienced longer durations of antihypertensive use than those in prior studies. In the United States, an estimated 70% of all invasive breast cancers diagnosed among postmenopausal women are ductal, and approximately 20% are lobular.[13] Consideration of risk by histologic type is relevant because other risk factors, most notably use of menopausal hormone therapy,[14-16] have been shown to be differentially associated with risk of ductal compared with lobular tumors. Since antihypertensive drugs, once prescribed, are often taken for the rest of a woman's life, characterizing their potential associations with risk of developing the most common cancer affecting women, breast cancer, is of both clinical and public health importance, particularly given the increasingly large number of options available to manage hypertension.

Methods

We conducted a large population-based case-control study of the 2 most common histologic subtypes of breast cancer, IDC and ILC. The overall goal of this study was to evaluate similarities and differences in the risk factor profiles of ductal and lobular breast cancers. Potentially eligible case patients were all women aged 55 to 74 years diagnosed as having a primary invasive breast cancer between January 2000 and December 2008 in the 3-county greater Seattle metropolitan area with no prior history of cancer. These patients were identified through the Cancer Surveillance System (CSS), the population-based tumor registry that serves western Washington state and participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. We enrolled 2 groups of case patients, those with ILC and those with IDC. All women diagnosed as having invasive breast cancer with a lobular component, based on *International Classification of Diseases for Oncology* (*ICD-O*) codes 8520, 8522, and 8524 assigned by the CSS, were potentially eligible as ILC case patients. Given the greater frequency of IDC, a sample of about 25% of the total eligible IDC case patients was selected for recruitment among those with an *ICD-O* histology code of 8500. The case patients with IDC were frequency matched with the ILC case group by 5-year age group. The pathology reports in all cases were centrally reviewed to confirm eligibility and recategorize histology groupings as necessary. Of the 2495 eligible case patients identified, 1984 (80%) were interviewed, including 1068 with ILC and 916 with IDC. Seventeen percent of eligible case patients refused to participate, and 3% died before we could interview them. The case sampling strategy used, and the exclusion of breast cancers with histologic characteristics other than ductal or lobular, prohibits the assessment of risks for breast cancer overall.

We used the Mitofsky-Waksberg[17] method of random-digit dialing of land-line telephones to identify potential controls from the general population of female residents of King, Pierce, and Snohomish counties. As such, case patients without a land-line telephone were excluded, but these 36 excluded patients represented only 1.2% of our total number of potentially eligible cases. Controls were frequency matched within 5-year age groups to the ILC case patients using 1-step recruitment with the goal of having a 1:1:1 ratio of controls to ILC and IDC cases. Of the 1313 eligible controls identified, 902 (69%) were interviewed, and 411 (31%) declined to participate.

Data Collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects. Case patients and controls were interviewed in person, primarily in their own homes. Through a series of structured questions, detailed histories were obtained of hypertension, heart disease, and all uses of ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium-channel blockers, diuretics, and combination antihypertensive preparations regardless of indication, including beginning and ending dates, drug name, dose, route of administration, pattern of use (number of days per month), and indication. Two primary strategies were used to enhance recall. First since these medications are typically used over a long term, we asked women to show the interviewer all of the bottles of prescription medications they were currently taking so that the interviewer could transcribe information directly from them. Second, for medications used in the past, women were shown photographs of pills of commonly used antihypertensives (organized by category) along with a show card listing the brand and generic names of each of these drugs. High correlation between self-reported antihypertensive use and pharmacy record data using this approach has been previously published (for case patients, 92% sensitivity and 91% specificity; for controls, 92% sensitivity and 93% specificity).[18] All participants were additionally queried about various known or suspected breast cancer risk factors including pertinent aspects of their reproductive, medical, breast cancer screening, and family histories, as well as information about their body size, lifestyle habits, and demographic characteristics (including self-reported race and ethnicity). Our questioning was limited to exposures that occurred before each participant's reference date. The reference date used for each woman with breast cancer was her diagnosis date. Control reference dates were assigned to reflect the expected distribution of reference dates among the case patients. The mean time between reference date and interview date was 18 months for case patients and 20 months for controls, and the median times were 16 months and 19 months, respectively.

Statistical Analysis

Women who never used any type of antihypertensive medication served as the reference category. Our main analysis fo-

cused on recency of antihypertensive medication use where *current users* were those who ever used these medications for 6 months or longer and were currently using them within 6 months of their reference date. *Former users* were patients who ever used these medications for 6 months or longer who last used them more than 6 months prior to their reference date. *Short-term users* were women who used these medications for less than 6 months regardless of their recency of use. We also conducted analyses restricted only to those women who were current users as a means of evaluating potential confounding by indication. In these analyses, current users of a particular class of antihypertensive medication were compared with women who were not using this class of antihypertensive but were current users of other classes of antihypertensives. Additionally, we assessed risks associated with different subclasses of calcium-channel blockers according to whether women used short- vs long-acting calcium-channel blockers and dihydropyridine vs non-dihydropyridines. These groupings were defined as follows: *short-acting* included verapamil, diltiazem, nifedipine, and nicardipine; *long-acting* included verapamil slow release (SR), diltiazem extended release, amlodipine, felodipine, nifedipine SR, and isradipine; *dihydropyridines* included amlodipine, felodipine, nifedipine SR, isradipine, nifedipine, nicardipine; and *non-dihydropyridines* included verapamil, diltiazem, verapamil SR, and diltiazem extended release.

We used polytomous logistic regression to calculate odds ratios (ORs) and their associated 95% CIs to compare IDC and ILC case patients with controls.[19] *P* values for trend were computed across categories of duration of use (5-year categories). Given the design of this study, its frequency-matched sample of IDC case patients based on age, and our exclusion of other histologic subtypes of breast cancer risk, estimates for breast cancer overall could not be calculated. All analyses were conducted using Stata/SE, version 11.2 (StataCorp LP). All models were adjusted for age (5-year categories), reference year (continuous), and county, since controls were matched to case patients on these factors. Several potential confounders and effect modifiers of the relationship between antihypertensive use and breast cancer risk were assessed, those included in **Table 1** as well as other commonly used medications (lipid-lowering, nonsteroidal anti-inflammatory, and antidepressant drugs) and common comorbid conditions (cardiovascular disease, diabetes, hyperlipidemia, and depression). Only recency of alcohol use changed our risk estimates by more than 10% when added to the model, and so only it was added as a covariate to our final statistical models. None of these factors were found to be statistically significant effect modifiers based on likelihood ratio testing (all *P* values for interaction were >.05). Excluded from all analyses were the 11 controls, 11 IDC cases, and 13 ILC cases missing data on either use of antihypertensive medications and/or recency of alcohol use, leaving a final analytic sample size of 891 controls, 905 IDC cases, and 1055 ILC cases. Finally, we conducted analyses stratified according to estrogen receptor (ER) status in 3 groupings: ER-positive IDC (n = 735), ER-negative IDC (n = 156), and ER-positive ILC (n = 996), using our controls as the common comparison group.

Results

Control women and IDC and ILC case patients had similar distributions of age and annual household income and histories of hypertension, heart disease, and hypercholesterolemia (Table 1). Compared with control women and IDC case patients, ILC case patients were somewhat less likely to be African American, more likely to be college graduates, and less likely to be obese (BMI ≥30.0 [calculated as weight in kilograms divided by height in meters squared]). Both IDC and ILC case patients were somewhat more likely to have a first-degree family history of breast cancer, to be current alcohol users, and to be current smokers. The proportion of current users of combined estrogen and progestin menopausal hormone therapy was highest among ILC case patients, intermediate among IDC case patients, and lowest among controls.

Overall, current, former, and short-term use of antihypertensives were not associated with risk of either IDC or ILC (**Table 2**). In examining duration effects for current users, we found an increased risk only in relation to use of calcium-channel blockers for 10 years or longer, and an increased risk was observed for both IDC (OR, 2.4; 95% CI, 1.2-4.9) (*P* = .04 for trend) and ILC (OR, 2.6; 95% CI 1.3-5.3) (*P* = .01 for trend). This association with 10 years or longer of current calcium-channel blocker use did not vary appreciably when results were further stratified by ER status (ER-positive IDC: OR, 2.3; 95% CI, 1.1-4.8; ER-negative IDC: OR, 3.1; 95% CI, 1.1-8.8; and ER-positive ILC: OR, 2.6; 95% CI, 1.3-5.2) (data not shown). There was also some indication that current use of ACE inhibitors for 10 years or longer was associated with reduced risks of both IDC (OR, 0.7; 95% CI, 0.5-1.2) and ILC (OR, 0.6; 95% CI, 0.4-1.0), though the risk estimate for IDC was within the limits of chance. Again, this association did not vary according to ER status (ER-positive IDC: OR, 0.7; 95% CI, 0.5-1.2; ER-negative IDC: OR, 0.5; 95% CI, 0.2-1.4; and ER-positive ILC: OR, 0.6; 95% CI, 0.4-0.97). No statistically significant associations were seen for the other drug categories examined. With respect to diuretic use, risks associated with thiazide and non-thiazide diuretic use were also assessed separately, but neither was associated with breast cancer risk (data not shown). These same relationships were observed in analyses restricted to only current users of antihypertensives (**Table 3**).

In evaluating risks according to calcium-channel blocker subclass, there was some indication that risks may be higher among current users of short-acting formulations (**Table 4**). Current users of short-acting calcium-channel blockers had a 3.7-fold increased risk (95% CI, 1.2-11.8) of IDC and a similar 3.6-fold increased risk (95% CI 1.2-11.4) of ILC. However, because of the infrequency of use of short-acting preparations, the effect of duration of use could not be assessed. Overall, current use of long-acting calcium-channel blockers was not related to risk of IDC or ILC, but again, current users for 10 years or longer did have elevated risks (IDC: OR, 2.7; 95% CI, 1.2-5.7; ILC: OR, 2.5; 95% CI, 1.2-5.5). Current use of non-dihydropyridines for any duration

Table 1. Characteristics of Breast Cancer Case Patients and Population-Based Controls

Characteristic	Study Participants, No. (%)		
	Controls (n = 891)	Ductal Cases (n = 905)	Lobular Cases (n = 1055)
Age, y[a]			
55-59	258 (29)	261 (29)	311 (30)
60-64	233 (26)	248 (27)	302 (29)
65-69	222 (25)	217 (24)	24 (723)
70-74	178 (20)	179 (20)	195 (19)
Race/ethnicity			
Non-Hispanic white	729 (89)	817 (90)	973 (92)
African American	28 (3)	22 (2)	15 (1)
Asian/Pacific Islander	17 (2)	37 (4)	22 (2)
Native American	24 (3)	16 (2)	23 (2)
Hispanic white	30 (3)	13 (1)	22 (2)
Education			
<High school	37 (4)	48 (5)	60 (6)
High school graduate	213 (24)	212 (23)	223 (21)
Some college/technical school	350 (39)	338 (37)	377 (36)
College graduate	291 (33)	307 (34)	395 (37)
Annual household income, $US			
<20 000	83 (11)	101 (13)	105 (11)
20 000-34 999	140 (180)	137 (17)	172 (19)
35 000-69 999	294 (38)	277 (35)	304 (33)
70 000-89 999	89 (11)	101 (13)	136 (15)
≥90 000	176 (23)	188 (23)	209 (23)
Missing data	109	101	129
Alcohol use at reference, drink/d			
None	448 (50)	434 (48)	491 (47)
<1	306 (34)	316 (35)	357 (34)
≥1	136 (15)	154 (17)	207 (20)
Missing data	1	1	0
Recency of alcohol use			
None	322 (36)	311 (34)	364 (35)
Former	126 (14)	123 (14)	127 (12)
Current	443 (50)	471 (52)	564 (54)
Smoking status			
Never	451 (51)	451 (50)	513 (49)
Former	352 (40)	352 (39)	414 (39)
Current	88 (10)	102 (11)	128 (12)
Recency of menopausal hormone therapy use			
Never	254 (29)	322 (36)	266 (25)
Former	308 (35)	249 (28)	260 (25)
Current unopposed estrogen	202 (23)	163 (18)	223 (21)
Current estrogen and progestin	121 (14)	166 (18)	303 (29)
Missing data	6	5	3
First-degree family history of breast cancer			
No	710 (82)	666 (77)	790 (77)
Yes	152 (18)	202 (23)	235 (23)
Missing data	29	37	30
Parity			
Nulliparous	90 (10)	138 (15)	131 (12)
Parous	801 (90)	767 (85)	924 (88)

(continued)

Table 1. Characteristics of Breast Cancer Case Patients and Population-Based Controls (continued)

Characteristic	Study Participants, No. (%)		
	Controls (n = 891)	Ductal Cases (n = 905)	Lobular Cases (n = 1055)
Age at first live birth among parous women, y			
<20	176 (22)	167 (22)	181 (20)
20-24	382 (48)	330 (43)	411 (45)
25-29	171 (21)	189 (25)	213 (23)
30-34	53 (7)	64 (8)	87 (9)
≥35	19 (2)	17 (2)	31 (3)
Missing data	0	0	1
History of hypertension			
No	499 (56)	508 (56)	590 (56)
Yes	391 (44)	396 (44)	464 (44)
Missing data	1	1	1
History of hypercholestorolemia			
No	601 (68)	607 (67)	709 (67)
Yes	288 (32)	298 (33)	344 (33)
Missing data	2	0	2
History of heart disease			
No	388 (44)	401 (45)	476 (45)
Yes	501 (56)	501 (56)	577 (55)
Missing data	2	3	2
BMI			
<25.0	269 (30)	287 (32)	373 (35)
25.0-29.9	302 (34)	290 (32)	345 (33)
≥30.0	314 (36)	328 (36)	335 (32)
Missing data	6	0	2
Screening mammography in 2 years prior to reference date			
No	106 (12)	99 (11)	93 (9)
Yes	783 (88)	805 (89)	962 (91)
Missing data	2	1	0

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Controls were age-matched with case patients.

was associated with a 60% increased risk of both IDC and ILC (though the risk estimate for IDC was within the limits of chance), but only current use of dihyrdropyridines for 10 years or longer was associated with elevated risks of IDC and ILC (IDC: OR, 3.0; 95% CI, 1.0-8.9; ILC: OR, 3.4; 95% CI, 1.1-9.9).

Discussion

This contemporary study of postmenopausal breast cancer adds to evidence that most commonly used forms of antihypertensive agents are not related to breast cancer risk even if used for long durations. However, our results do suggest that long-term current use of calcium-channel blockers is associated with an increased risk of both IDC and ILC and that these associations do not vary according to ER status. Confounding by indication is unlikely to explain these relationships in that findings were similar in analyses limited to only women with hypertension who were currently using antihypertensive medications. Direct comparisons of these results with those of other studies is challenging owing to differences in study design and exposure characteristics. In particular, most prior studies had substantially smaller sample sizes and limited ability to assess risks according to duration of recent use.

In the first of the 3 largest studies on the association between antihypertensive agents and breast cancer risk, our research group[4] conducted an earlier Seattle-Puget Sound population-based case-control study (completely separate from the present study) and found that current use of thiazide and potassium-sparing diuretics were associated with 40% and 60% increases in risk of breast cancer, respectively (duration of use among current users was not assessed). An analysis of the California Teachers Study (CTS) cohort[3] found that diuretic use for 10 years or longer was associated with a 16% increased risk, while use of calcium-channel blockers and ACE inhibitors was not (recency of use in the full cohort could not be assessed). And a case-control analysis derived from the United Kingdom–based General Practice Research Database[7] found no disease associations with ever use of ACE inhibitors, calcium-channel blockers, or β-blockers for 5 or more years (results specific to current users were not presented). So there is considerable variabil-

Table 2. Recency and Duration of Antihypertensive Medication Use and Risk of Invasive Ductal and Invasive Lobular Breast Cancer

	Controls (n = 891)	Ductal Cases (n = 905)			Lobular Cases (n = 1055)		
Medication Use	No. (%)	No. (%)	OR[a] (95% CI)	*P* Value for Trend	No. (%)	OR[a] (95% CI)	*P* Value for Trend
Never	456 (51.2)	477 (52.7)	1 [Ref]	NA	556 (52.7)	1 [Ref]	NA
Short-term (<6 mo)	27 (3.0)	20 (2.2)	0.7 (0.4-1.3)	NA	34 (3.2)	1.1 (0.6-1.8)	NA
Former	27 (3.0)	31 (3.5)	1.1 (0.7-1.9)	NA	32 (3.1)	1.0 (0.6-1.8)	NA
Current	406 (45.7)	396 (43.8)	0.9 (0.8-1.2)		466 (44.2)	1.0 (0.8-1.2)	
<5 y	131 (14.9)	126 (14.2)	0.9 (0.7-1.2)		151 (14.6)	1.0 (0.7-1.3)	
5-9.9 y	90 (10.3)	76 (8.5)	0.8 (0.6-1.2)	.51	104 (10.0)	1.0 (0.7-1.4)	.91
≥10 y	174 (19.8)	180 (20.2)	1.0 (0.8-1.3)		193 (18.6)	1.0 (0.8-1.3)	
Current diuretic use	216 (31.1)	196 (28.4)	0.9 (0.7-1.2)		236 (29.1)	1.0 (0.8-1.2)	
<5 y	79 (11.4)	77 (11.2)	1.0 (0.7-1.4)		97 (12.1)	1.1 (0.8-1.5)	
5-9.9 y	48 (7.0)	37 (5.4)	0.8 (0.5-1.2)	.92	48 (6.0)	0.9 (0.6-1.3)	.20
≥10 y	84 (12.2)	77 (11.2)	0.9 (0.7-1.3)		81 (10.1)	0.9 (0.6-1.3)	
Current β-blocker use	145 (23.1)	145 (22.2)	0.9 (0.7-1.2)		188 (24.1)	1.1 (0.9-1.5)	
<5 y	66 (10.6)	59 (9.1)	0.9 (0.6-1.2)		78 (10.1)	1.0 (0.7-1.4)	
5-9.9 y	36 (5.8)	33 (5.1)	0.9 (0.5-1.4)	.29	46 (6.0)	1.2 (0.7-1.9)	.18
≥10 y	39 (6.2)	48 (7.4)	1.1 (0.7-1.8)		57 (7.4)	1.3 (0.9-2.1)	
Current calcium-channel blocker use	74 (13.2)	94 (15.7)	1.3 (0.9-1.8)		102 (14.9)	1.3 (0.9-1.8)	
<5 y	35 (6.3)	36 (6.1)	0.9 (0.6-1.5)		34 (5.0)	0.8 (0.5-1.3)	
5-9.9 y	23 (4.1)	26 (4.4)	1.2 (0.7-2.2)	.04	32 (4.7)	1.3 (0.8-2.4)	.01
≥10 y	12 (2.2)	27 (4.5)	2.4 (1.2-4.9)[b]		31 (4.6)	2.6 (1.3-5.3)[b]	
Current ACE inhibitor use	135 (21.7)	130 (20.4)	0.9 (0.7-1.2)		158 (21.2)	1.0 (0.8-1.3)	
<5 y	53 (8.6)	58 (9.2)	1.0 (0.7-1.6)		77 (10.4)	1.2 (0.9-1.8)	
5-9.9 y	35 (5.7)	28 (4.5)	0.8 (0.5-1.3)	.20	43 (5.8)	1.1 (0.7-1.8)	.03
≥10 y	45 (7.3)	36 (5.7)	0.7 (0.5-1.2)		32 (4.3)	0.6 (0.4-1.0)[b]	
Current angiotensin II antagonist use	48 (9.4)	53 (9.9)	1.1 (0.7-1.6)		71 (11.2)	1.4 (0.9-2.1)	
<5 y	24 (4.7)	30 (5.6)	1.2 (0.7-2.2)		37 (5.9)	1.4 (0.8-2.5)	
5-9.9 y	9 (1.8)	10 (1.9)	1.1 (0.4-2.8)	.12	17 (2.7)	1.8 (0.8-4.3)	.49
≥10 y	13 (2.6)	11 (2.1)	0.8 (0.3-1.8)		13 (2.1)	1.0 (0.4-2.2)	

Abbreviations: ACE, angiotensin-converting enzyme; NA, not applicable; Ref, referent.

[a] All models are adjusted for age, reference year, county, race/ethnicity, and recency of alcohol use.

[b] $P < .05$.

ity in findings across these studies. With respect to diuretics, we did not observe an increased risk of breast cancer associated with diuretic use, though the elevations observed in 2 prior studies were quite modest and fall within the 95% CIs of our risk estimates.[3,4] However, none of these 3 studies found that calcium-channel blockers were associated with an increased risk, though both our group's prior study[4] and the UK study[7] were limited to evaluating only use for 5 years or longer, and herein we report an increase in risk only among users for 10 years or longer. Of note though, in our group's prior study,[4] we did find that ever use of short-acting calcium-channel blockers was associated with a 40% increased risk of breast cancer that was statistically significant. With respect to the CTS study,[3] while it collected data on different durations of diuretic use, it did not collect duration information for other forms of antihypertensives, including calcium-channel blockers, limiting comparisons with our results.

Biological mechanisms through which calcium-channel blockers could influence breast cancer risk are unknown. These medications have a broad spectrum of physiologic effects, and some researchers have hypothesized that they may inhibit apoptosis through increasing intracellular calcium levels,[1,10,20] though evidence supporting this effect is lacking.[21] The suggestion that risk may be higher with short-acting calcium-channel blockers, and that an increased risk associated with long-acting formulations is only observed among long-term users, may help inform studies aimed at elucidating potential biological mechanisms. However, these results require confirmation; the present study is the first to our knowledge to report the impact of long-term use of calcium-channel blockers on breast cancer risk.

Herein we also report a reduction in breast cancer risk associated with long-term use of ACE inhibitors. We know of no prior studies evaluating ACE inihibitors that have

Table 3. Recency and Duration of Antihypertensive Medication Use and Risk of Ductal and Lobular Breast Cancer Among Women With Hypertension Who Were Currently Using Antihypertensive Medication

Current Antihypertensive Medication Use	Controls (n = 360)	Ductal Cases (n = 353)			Lobular Cases (n = 416)		
	No. (%)	No. (%)	OR[a] (95% CI)	*P* Value for Trend	No. (%)	OR[a] (95% CI)	*P* Value for Trend
Not currently using a diuretic	168 (46.7)	178 (50.4)	1 [Ref]	NA	195 (47)	1 [Ref]	NA
Current diuretic use	192 (53.3)	175 (49.6)	0.9 (0.7-1.2)		220 (53)	1.1 (0.8-1.4)	
<5 y	68 (19.2)	70 (20.1)	1 (0.7-1.5)		94 (23.2)	1.3 (0.9-1.9)	
5-9.9 y	44 (12.4)	32 (9.2)	0.7 (0.4-1.1)	.753	40 (9.9)	0.8 (0.5-1.3)	.110
≥10 y	75 (21.1)	68 (19.5)	0.9 (0.6-1.4)		76 (18.8)	0.9 (0.6-1.4)	
Not currently using a β-blocker	234 (65)	222 (62.9)	1 [Ref]	NA	253 (61)	1 [Ref]	NA
Current β-blocker use	126 (35)	131 (37.1)	1.1 (0.8-1.5)		162 (39)	1.2 (0.9-1.6)	
<5 y	55 (15.4)	53 (15.2)	1 (0.7-1.6)		63 (15.4)	1 (0.7-1.5)	
5-9.9 y	33 (9.3)	27 (7.8)	0.9 (0.5-1.5)	.36	42 (10.3)	1.2 (0.7-2.0)	.21
≥10 y	34 (9.6)	46 (13.2)	1.4 (0.9-2.3)		50 (12.3)	1.4 (0.9-2.2)	
Not currently using a calcium-channel blocker	290 (80.6)	268 (75.9)	1 [Ref]	NA	325 (78.1)	1 [Ref]	NA
Current calcium-channel blocker use	70 (19.4)	85 (24.1)	1.4 (0.9-2.0)		91 (21.9)	1.2 (0.8-1.6)	
<5 y	33 (9.3)	32 (9.2)	1 (0.6-1.8)		31 (7.5)	0.8 (0.5-1.4)	
5-9.9 y	22 (6.2)	23 (6.6)	1.2 (0.7-2.3)	.03	29 (7.1)	1.2 (0.7-2.1)	.01
≥10 y	11 (3.1)	25 (7.2)	2.6 (1.2-5.4)[b]		26 (6.3)	2.2 (1.0-4.5)[b]	
Not currently using an ACE inhibitor	232 (64.4)	225 (63.7)	1 [Ref]	NA	261 (62.9)	1 [Ref]	NA
Current ACE inhibitor use	128 (35.6)	128 (36.3)	1 (0.7-1.4)		154 (37.1)	1 (0.8-1.4)	
<5 y	48 (13.4)	57 (16.5)	1.2 (0.8-1.9)		74 (18.1)	1.3 (0.9-2.0)	
5-9.9 y	34 (9.5)	28 (8.1)	0.8 (0.5-1.4)	.10	42 (10.3)	1.1 (0.7-1.8)	.02
≥10 y	44 (12.3)	35 (10.1)	0.7 (0.5-1.2)		32 (7.8)	0.6 (0.4-0.98)[b]	
Not currently using an angiotensin II antagonist	314 (87.2)	303 (86.1)	1 [Ref]	NA	347 (83.6)	1 [Ref]	NA
Current angiotensin II antagonist use	46 (12.8)	49 (13.9)	1.1 (0.7-1.7)		68 (16.4)	1.4 (0.9-2.1)	
<5 y	22 (6.1)	28 (8)	1.3 (0.7-2.4)		35 (8.5)	1.4 (0.8-2.5)	
5-9.9 y	9 (2.5)	9 (2.6)	1.1 (0.4-2.8)	.11	17 (4.1)	1.9 (0.8-4.4)	.50
≥10 y	13 (3.6)	11 (3.1)	0.9 (0.4-2.0)		13 (3.2)	1 (0.4-2.2)	

Abbreviations: ACE, angiotensin-converting enzyme; NA, not applicable; Ref, referent.

[a] All models are adjusted for age, reference year, county, race/ethnicity, and recency of alcohol use.

[b] $P < .05$.

reported this relationship. Consequently this observation needs to be interpreted cautiously, and it requires replication in studies with sufficient numbers of long-term users of ACE inhibitors.

Recall bias is a potential limitation of this case-control study. However, misclassification of exposure was reduced by focusing analyses on current use and using a protocol where study interviewers reviewed the prescription bottles of study participants and recorded detailed data directly from them.[18] Furthermore, the differences seen according to class of antihypertensive medication are very unlikely to be affected by recall bias. Such bias would require one to assume that patients with breast cancer recalled exposures only to calcium-channel blockers and ACE inhibitors, but not to other types of antihypertensives, differently than did control women. Two factors enhance the generalizability of this study: one is its population-based design and the other is its high overall response rates from both case patients and controls. There is some potential for selection bias given the somewhat lower response rate among controls compared with case patients. However, for this to impact our results, controls who were users of calcium-channel blockers but not of other types of antihypertensives must have selectively refused study participation, which is unlikely. Other major strengths of this study are its substantial sample size and that it was conducted in a contemporary population and time period in which long-term antihypertensive use is common. Specifically, 45% of our population-based controls were current antihypertensive users and 20% were current users for 10 years or longer.

In summary, this study provides evidence that long-term recent use of calcium-channel blockers may be associated with an increased risk of breast cancer. Further efforts to confirm this association are needed and are of public health importance, given that antihypertensive drugs are the most commonly prescribed class of medication in the

Table 4. Recency and Duration of Use of Different Classes of Calcium-Channel Blocker and Risk of Ductal and Lobular Breast Cancer

Type of Calcium-Channel Blocker Use	Controls (n = 891) No. (%)	Ductal Cases (n = 905) No. (%)	Ductal Cases (n = 905) OR[a] (95% CI)	Ductal Cases (n = 905) *P* Value for Trend	Lobular Cases (n = 1055) No. (%)	Lobular Cases (n = 1055) OR[a] (95% CI)	Lobular Cases (n = 1055) *P* Value for Trend
Never used antihypertensives	456 (51.2)	477 (52.7)	1 [Ref]	NA	556 (52.7)	1 [Ref]	NA
Short-acting calcium-channel blockers							
Former use	19 (4.0)	26 (5.0)	1.3 (0.7-2.4)	NA	23 (3.9)	1.1 (0.6-2.1)	NA
Current use	4 (0.8)	14 (2.7)	3.7 (1.2-11.8)[b]	NA	14 (2.4)	3.6 (1.2-11.4)[b]	NA
Long-acting calcium-channel blockers							
Former use	20 (3.7)	17 (3.0)	0.9 (0.4-1.7)	NA	14 (2.1)	0.6 (0.3-1.2)	NA
Current use	71 (13.0)	80 (13.9)	1.1 (0.8-1.6)		89 (13.5)	1.1 (0.8-1.6)	
<5 y	35 (6.5)	32 (5.6)	0.8 (0.5-1.4)		32 (4.9)	0.8 (0.5-1.3)	
5-9.9 y	21 (3.9)	20 (3.5)	1.0 (0.5-1.9)	.01	26 (4.0)	1.2 (0.6-2.2)	.01
≥10 y	10 (1.8)	25 (4.4)	2.7 (1.2-5.7)[b]		26 (4.0)	2.5 (1.2-5.5)[b]	
Dihydropyridine calcium-channel blockers							
Former use	19 (3.6)	22 (4.0)	1.1 (0.6-2.2)	NA	17 (2.7)	0.8 (0.4-1.6)	NA
Current use	48 (9.2)	51 (9.3)	1.1 (0.7-1.7)		54 (8.6)	1.1 (0.7-1.7)	
<5 y	27 (5.2)	27 (4.9)	0.9 (0.5-1.6)		23 (3.7)	0.7 (0.4-1.3)	
5-9.9 y	14 (2.7)	11 (2.0)	0.9 (0.4-2.0)	.13	16 (2.6)	1.2 (0.5-2.5)	.01
≥10 y	5 (1.0)	12 (2.2)	3.0 (0.99-8.9)		14 (2.2)	3.4 (1.1-9.9)[b]	
Non-dihydropyridine calcium-channel blockers							
Former use	21 (4.2)	18 (3.3)	0.9 (0.4-1.7)	NA	22 (3.5)	0.9 (0.5-1.7)	NA
Current use	27 (5.4)	44 (8.2)	1.6 (1.0-2.7)		50 (8.0)	1.6 (1.0-2.7)[b]	
<5 y	10 (2.0)	14 (2.6)	1.3 (0.6-3.0)		15 (2.4)	1.2 (0.5-2.7)	
5-9.9 y	9 (1.8)	14 (2.6)	1.6 (0.7-3.8)	.08	16 (2.6)	1.7 (0.7-3.9)	.11
≥10 y	6 (1.2)	14 (2.6)	2.4 (0.9-6.3)		16 (2.6)	2.5 (1.0-6.6)	

Abbreviations: NA, not applicable; Ref, referent.

[a] All models are adjusted for age, reference year, county, race/ethnicity, and recency of alcohol use.

[b] $P < .05$.

United States. Quantification of the potential relationships between use of these medications and breast cancer risk has the potential to aid clinical decision making regarding selection of antihypertensive agents for patients with hypertension, as the benefits and risks of potential medications are weighed.

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Invited Commentary

Calcium-Channel Blockers and Breast Cancer
A Hypothesis Revived

Patricia F. Coogan, ScD

In this issue of *JAMA Internal Medicine*, a report by Li et al[1] from a large population-based case-control study suggests that long-term use of calcium-channel blockers (CCBs) is associated with a greater than 2-fold increase in the risk of breast cancer in postmenopausal women. This is not the first time that the specter of CCB-associated cancer has arisen: in 1996, Pahor et al[2] reported a statistically significant 72% increase in risk of all cancers among CCB users in an elderly cohort, including a nonsignificant 65% increased risk of breast cancer. This was followed in 1997 by a report from another elderly cohort of a statistically significant relative risk (RR) for breast cancer of 2.6 among ever users of CCBs.[3] Both studies were based on small numbers. Subsequent larger case-control and cohort studies failed to confirm the CCB-cancer association for all cancers[4] or for breast cancer,[5] nor did excess cancers occur in up to 5 years of follow-up in 3 randomized clinical trials of CCBs.[6-8] The CCB-cancer hypothesis went into hibernation.

Related article page 1629

The present study by Li et al[1] revives the hypothesis and focuses it on breast cancer and on long-term CCB use, specifically use of at least 10 years' duration among current users (ie, case patients who reported use within 6 months of their diagnosis date or, for controls, their reference date). In the previous studies that have examined CCB use and breast cancer,[5] the longest duration of use that could be observed among current users was 5 years or longer. None of them found an increase in risk for that category. In the present study, the numbers in the category of 10 or more years were adequate if not huge: 12 controls, 27 invasive ductal cancers, and 31 invasive lobular cancers. Statistically significant RRs of 2.4 (95% CI, 1.2-4.9) and 2.6 (95% CI, 1.3-5.3) were observed for ductal and lobular cancers, respectively. While there were significant trends over duration, the RRs in the category of 5 to 9.9 years of use were not markedly increased (RR for ductal cancer, 1.2; 95% CI, 0.7-2.2 and RR for lobular cancer, 1.3; 95%, CI 0.8-2.4). The RRs for former use (subjects who last used CCBs more than 6 months prior to diagnosis or reference date) were all compatible with 1.0, although there were too few former users to assess duration. The findings were consistent for estrogen receptor–positive and estrogen receptor–negative cancer, for dihydropyridine and non-dihydropyridine CCBs, and for long-acting and short-acting CCBs (although there were too few users of the short-acting CCBs for analysis by duration).

Given these results, should the use of CCBs be discontinued once a patient has taken them for 9.9 years? The answer is no, because these data are from an observational study, which cannot prove causality and by itself cannot make a case for change in clinical practice. Should the results be dismissed as random noise emanating from an observational study? The answer is no, because the data make a convincing case that the hypothesis that long-term CCB use increases the risk of breast cancer is worthy of being pursued. The data are persuasive because this was a first-rate study: it was population-based, large (1900 case patients and 856 controls), identified cases from the Seattle-area SEER surveillance system, had a high (80%) case response rate, and used best practices in ascertaining medication use from study participants. While the control selection method (random-digit dial) and control response rate (69%) are vulnerable to criticism—always true in case-control studies—controls and cases were similar enough on demographic and health-related characteristics to deem the control group valid.

The study particularly excels in the careful analytic efforts used to identify alternate explanations for the findings. An important potential source of bias in observational studies of medication use and cancer risk is confounding by indication. In the present study, confounding by indication would