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Use of calcium channel blockers and breast cancer risk in the Women's Health Initiative

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Abstract

Background—Use of calcium channel blockers (CCBs) has been associated with increased risk of breast cancer in some, but not all studies. Differences in reported associations from prior studies may be due, in part, to inadequate control of confounding factors.

Methods—Participants were 28,561 postmenopausal women from the Women's Health Initiative who reported use of either CCBs or other anti-hypertensive medications (AHM) at baseline; 1,402 incident breast cancer cases were diagnosed during 12 years of follow-up. Adjusted Cox

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regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations between CCB use relative to other AHM use and breast cancer risk.

Results—Use of CCBs was not associated with breast cancer risk (HR 1.06, 95% CI: 0.94–1.20) relative to use of other AHM. Associations approximated the null value when CCBs were considered by duration of use, length of action, or drug class.

Conclusions—We provide additional evidence that CCBs do not influence breast cancer risk in postmenopausal women.

Impact—The results from this study, which includes strong control for potential confounding factors, cast doubt on increases in risk with CCBs.

Introduction

The use of calcium channel blockers (CCBs) has been recently been found to be associated with increased risk of breast cancer (1, 2), although inconsistently. The inconsistency may be due to differences inherent in study design, or inadequately controlled confounding, including factors related to prescription for CCBs. Indeed, a number of important risk factors are shared between hypertension and breast cancer, making interpretation of results from studies that do not restrict to hypertensive women challenging. Given the high prevalence of CCB use and their hypothesized potential to disrupt apoptotic pathways, additional high-quality prospective data are needed.

Here we examine the association between CCB use and breast cancer risk in the Women's Health Initiative (WHI), a large cohort of postmenopausal women. To further control for potential confounding, we compared CCB exposure with use of any other anti-hypertensive medication (AHM).

Materials and Methods

Study population

Information about the WHI methods have been published (3). From 1993–1998, 161,808 postmenopausal women, ages 50–79 years, were recruited into an observational study (OS) and one or more clinical trials (CT). Women were followed to 2005 and, via an extension study, to 2010. For the present analysis, we excluded at baseline women who: had prevalent breast cancer (n=5,551); did not self-report a history of hypertension (n=95,530), were non-users of CCBs or other AHM (n=26,840) or who used CCBs in combination with other AHM (n=5,325) or were missing these data (n=1); leaving n=28,561 for analysis.

Data collection

Participants attended baseline screening visits, during which they completed extensive baseline questionnaires. Height and weight were measured by clinical staff. In-person medication inventories were obtained by review of participants' pill containers at baseline and year 3 in the OS and additionally in years 1, 6, and 9 in the CT. CCBs were sub-classified into dihydropyridines or non-dihydropyridines and short-acting or long-acting. Duration of medication use was categorized as <5 years, 5–9.9 years, and ≥10 years. Other

AHM data (including diuretics, ACE inhibitors, adrenergic receptor antagonists, angiotensin II receptor antagonists, renin inhibitors, and vasodilators) were obtained in an identical manner.

Case ascertainment

Incident, first-primary, invasive breast cancers were self-reported annually in the OS and semi-annually in the CT until 2005 and annually thereafter. Cases were confirmed by medical record review by physician-adjudicators. After a median follow-up of 12.7 years, 1,402 invasive breast cancers were identified. Breast cancer subtypes, defined here as joint expressions of ER, PR, and HER2, were abstracted from medical records.

Statistical analyses

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the associations between baseline CCB and breast cancer risk relative to other AHM. Categories of CCB duration were compared to the same categories of other AHM in regression models. Regression models were adjusted *a priori* for breast cancer risk factors thought to potentially confound associations and CT randomization. We performed several sensitivity analyses: 1) in the WHI-CT, CCB and other AHM use were treated as time-varying in regression models; 2) We additionally examined associations of CCB use versus non-use (n=156,255) in the larger WHI cohort (including women *without* hypertension; n=156,255) in order to compare our findings with others that did not account for confounding by shared risk factors.

Results

Despite their statistical significance, differences by medication for participants' baseline characteristics were small (Table 1). Compared to other AHM use, CCB use was not associated with breast cancer risk (HR 1.06, 95% CI: 0.94–1.20) (Table 2). No associations were observed when CCB use was stratified by length of action or drug class. When cancers were stratified on molecular subtype defined by ER, PR, and HER-2, CCB use was associated with elevated risk of triple-negative breast cancers (HR 1.60, 95% CI: 1.04–2.48). In the sensitivity analysis, time-varying CCB use was also not associated with breast cancer risk (HR 0.99, 95% CI: 0.78–1.26). When CCB use was contrasted against non-use (thus, insufficiently controlling for shared hypertension/breast cancer risk factors; n=156,255), associations were elevated (HR 1.30, 95% CI: 0.84–2.02). When we restricted the comparison to women who reported prevalent hypertension (n=60,726; HR 1.08, 95% CI: 0.98–1.18) and who used ≥1 AHM (n=33,886; HR 1.08, 95% CI: 0.98–1.20) the association was attenuated.

Discussion

We observed no association between CCB use and breast cancer risk in the WHI. Although these results contrast with recent case-control analyses (1, 2) and an early (4) (but not later (5)) report from a prospective study, our findings of no association are compatible with recent data from several prospective cohorts (6–8). Although a recent case-control study

among Spanish women reported higher postmenopausal breast cancer risk associated with CCB use (OR 1.72, 95% 1.05–2.80) (1), it was neither restricted to hypertensive women nor were CCBs compared to users of other anti-hypertensive medications, leaving a strong possibility for confounding. A >2-fold higher risk reported by Li et al. (2) persisted after restriction of the analysis to hypertensive women; however the referent group included women with untreated hypertension. No study has examined associations with breast cancers characterized by molecular subtypes; the elevated association observed here may be due to chance but warrants consideration.

The advantages of this study include its comprehensive collection of medication use, and its strong control of confounding by restriction of the analysis to women with hypertension and comparing CCB use to that of other AHM. Further, attrition bias was minimized with near-complete follow-up in the WHI.

We provide here additional evidence that CCBs do not broadly influence breast cancer risk in postmenopausal women.

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Table 1

Distribution of selected baseline characteristics of WHI participants by baseline CCB use, as compared with other AHM use, in the Women's Health Initiative Observational Study and Clinical Trials, n=28,561.

Characteristic	Other AHM Use (n=20,510), *n* (%)	CCB Use (n=8,051), *n* (%)
Demographics and Anthropometrics		
Age, mean (SD)	64.97 (6.94)	65.36 (7.00)
Education		
≤ High school graduate	5,359 (26.32)	2,217 (27.72)
Some college	8,133 (39.94)	3,111 (38.90)
College or advanced degree	6,870 (33.74)	2,670 (33.38)
Race/Ethnicity		
White	16,527 (80.58)	5,679 (70.54)
Black	2,436 (11.88)	1,517 (18.84)
Hispanic	611 (2.98)	314 (3.90)
Asian/Pacific Islander	510 (2.49)	357 (4.43)
Other	426 (2.08)	184 (2.29)
Body mass index, kg/m^2		
<25	4,606 (22.66)	1,887 (23.64)
25–29.9	6,857 (33.73)	2,776 (34.77)
≥30	8,867 (43.62)	3,320 (41.59)
Lifestyle Characteristics		
Physical activity, MET-hrs/week		
Inactive	3,706 (18.45%)	1,510 (19.17)
>0–6.7	6,422 (31.96%)	2,494 (31.66)
6.8–16.6	5,327 (26.51%)	2,094 (26.58)
≥16.6	4,637 (23.08%)	1,780 (22.59)
Smoking, pack-years		
Never smoker	10,654 (53.75)	4,041 (52.03)
>0–7.4	3,008 (15.18)	1,170 (15.06)
7.5–23.0	2,829 (14.27)	1,126 (14.50)
≥23.1	3,329 (16.80)	1,430 (18.41)
Alcohol consumption, servings/week		
0	9,792 (47.90)	4,116 (51.25)
0.2–0.8	3,951 (19.33)	1,500 (18.68)
0.9–3.7	3,238 (15.84)	1,137 (14.16)
≥3.8	3,463 (16.94)	1,278 (15.91)
Medical History and Reproductive Health		
Number of 1^{st} degree relatives with breast cancer		
None	16,177 (85.20)	6,428 (85.31)
1	2,506 (13.20)	995 (13.21)
≥2	304 (1.60)	112 (1.49)
Breast cancer screening		

Characteristic	Other AHM Use (n=20,510), *n* (%)	CCB Use (n=8,051), *n* (%)
Never	541 (2.65)	214 (2.67)
Ever	19,857 (97.35)	7,792 (97.33)
Age at menarche, years		
≤10	1,464 (7.16)	574 (7.15)
11–12	8,845 (43.25)	3,377 (42.08)
13–14	8,249 (40.34)	3,277 (40.83)
≥15	1,891 (9.25)	797 (9.93)
Age at menopause, years		
<47	6,983 (35.87)	2,877 (37.82)
47–51	6,486 (33.31)	2,414 (31.73)
≥52	6,001 (30.82)	2,317 (30.45)
Parity		
Never pregnant	2,239 (10.97)	867 (10.83)
1	1,764 (8.65)	698 (8.72)
2–4	12,932 (63.38)	5,052 (63.11)
≥5	3,468 (17.00)	1,388 (17.34)
Age at first birth, years		
Never pregnant	2,239 (12.16)	867 (12.07)
<20	2,877 (15.62)	1,234 (17.18)
20–29	11,876 (64.48)	4,545 (63.27)
≥30	1,427 (7.75)	537 (7.48)
Duration of unopposed estrogen therapy, years		
<4	14,628 (71.32)	5,823 (72.33)
4–12	2,549 (12.43)	968 (12.02)
≥12	3,333 (16.25)	1,260 (15.65)
Duration of combined hormone therapy, years		
<2.5	17,419 (84.93)	6,992 (86.85)
2.5–7	1,507 (7.35)	514 (6.38)
≥8	1,584 (7.72)	545 (6.77)

AHM, anti-hypertensive medications; CCB, calcium channel blocker

Table 2

Associations of baseline CCB use versus other AHM use with breast cancer risk in the Women's Health Initiative Observational Study and Clinical Trials, n=28,561.

			Baseline duration of CCB use, years[1]		
	AHM Use	**CCB Use**	**>0 to 4.9**	**5.0 to 9.9**	**≥10**
Any calcium-channel blockers					
n cases/*n* non-cases	1,008/19,502	394/7,657	256/5,349	103/1,601	35/707
HR (95% CI)[2]	1.00 reference	1.06 (0.94–1.20)	1.01 (0.87–1.18)	1.33 (1.03–1.71)	1.05 (0.72–1.52)
Action					
Short-acting					
n cases/*n* non-cases	1,008/19,502	112/2,139	72/1,506	32/450	8/192
HR (95% CI)[2]	1.00 reference	1.08 (0.88–1.32)	1.03 (0.80–1.32)	1.35 (0.91–2.02)	0.91 (0.44–1.86)
Long-acting					
n cases/*n* non-cases	1,008/19,502	284/5,548	184/3,878	73/1,159	27/520
HR (95% CI)[2]	1.00 reference	1.06 (0.92–1.22)	0.99 (0.84–1.18)	1.33 (1.00–1.76)	1.08 (0.71–1.63)
Drug Class					
Dihydropyridines					
n cases/*n* non-cases	1,008/19,502	152/3,390	118/2,614	24/564	10/212
HR (95% CI)[2]	1.00 reference	0.96 (0.81–1.15)	1.00 (0.81–1.22)	0.87 (0.56–1.36)	0.92 (0.48–1.78)
Non-dihydropyridines					
n cases/*n* non-cases	1,008/19,502	242/4,300	138/2,765	79/1,039	25/496
HR (95% CI)[2]	1.00 reference	1.13 (0.98–1.31)	1.01 (0.83–1.23)	1.54 (1.17–2.02)	1.09 (0.71–1.66)

AHM, anti-hypertensive medications; CCB, calcium channel blocker

[1] Relative to the same duration of other AHM use; case/non-case frequencies for other AHM users are: 610/12,184 (>0–4.9y), 189/3,654 (5.0–9.9y), and 209/3,664 (≥10y)

[2] Adjusted for baseline age (time variable), WHI-CT intervention assignment, education, race, BMI, physical activity, smoking, alcohol, and breast cancer screening.