Use of antihypertensive medications not associated with risk of contralateral breast cancer among women diagnosed with estrogen-receptor positive invasive breast cancer

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Abstract

Background: Antihypertensive medications are widely used among adults in the U.S. and there is some evidence that certain classes may affect the risk of adverse breast cancer outcomes, but their impact on risk of second primary contralateral breast cancer is unclear.

Methods: We used data from a population-based nested case-control study consisting of 359 women diagnosed with both a first primary breast cancer and a second primary contralateral breast cancer and 691 control women diagnosed with only a single breast cancer and individually matched to cases. Multivariate conditional logistic regression was used to estimate odds ratios and 95% confidence intervals for risks associated with ever, recency and duration of use for various antihypertensive medications.

Results: No class of antihypertensive, including calcium channel blockers, β blockers, ACE inhibitors and diuretics, was associated with risk of second primary contralateral breast cancer. These results did not change materially in a sensitivity analysis restricted to women with a history of hypertension.

Conclusion: Our findings do not support associations between use of various antihypertensives and CBC risk among women with estrogen receptor + breast cancer.

Impact: The present study adds evidence to support the safety of commonly used antihypertensive medications among breast cancer survivors with respect to risk of second primary contralateral breast cancer.

Introduction

Breast cancer survivors have a 2-to-6-fold higher risk of developing second primary contralateral breast cancer (CBC) compared to the risk women in the general population have of being diagnosed with a first breast cancer.(1) Use of adjuvant hormonal therapy lowers this risk by an estimated 50% (2), with some additional evidence that maintaining a healthy weight, quitting smoking, and reducing alcohol consumption may also reduce CBC risk (3,4).

Antihypertensives, the most commonly prescribed category of medications in the U.S., may also affect risks of certain adverse breast cancer outcomes. Specifically, use of β -blockers, a widely used medication to treat hypertension, heart failure, migraines and other conditions, has been associated with 58-81% reductions in risk of breast cancer specific mortality (5,6). However, only one prior study evaluated antihypertensive use in relation to CBC risk and observed that angiotensin-converting enzyme (ACE) inhibitors was associated with a 66% higher risk of CBC, while other classes of antihypertensives did not impact risk (7). To further advance knowledge in this area, we examined the relationship between various antihypertensives and CBC risk among women diagnosed with estrogen positive (ER+) breast cancer.

Materials and Methods

We used data from a population-based nested case-control study designed to evaluate risk factors for CBC. Details regarding this study's design and data collection methods have been previously described (8). Briefly, from an underlying cohort identified through the Cancer Surveillance System (CSS, our local SEER cancer registry) of 17,628 women 40-79 years of age diagnosed in the years 1990-2005 with stage I-IIIA ER+ breast cancer, we enrolled 369 cases, defined as those diagnosed with a subsequent CBC through 2007 and 734 control women never diagnosed with a CBC individually matched 2:1 to cases on age, year of diagnosis, county, race/ethnicity, and cancer stage. Controls also had to be alive for at least the duration between their matched cases' first and CBC diagnoses.

Information on use of various antihypertensive medications between the date of the first breast cancer diagnosis (index date) and reference date (date of CBC diagnosis for cases and date of their matched case's CBC diagnosis for controls) was abstracted from medical records for 359 (97%) cases and 691 (94%) controls. Antihypertensive drugs were grouped into the following categories: calcium-channel blockers, ACE inhibitors, β-blockers and diuretics regardless of indication. Data on potential confounding variables were ascertained from a variety of sources including medical record reviews, telephone interviews conducted with study participants, and data collected by CSS.

Ever use of a given antihypertensive was defined as having used it for ≥6 months between the index and reference dates. Among ever users, current users were defined as those who had last used the medication <6 months prior to the reference date and former users were those whose last use was ≥6 months prior to reference date. A sensitivity analysis restricted to women with a history of hypertension was conducted to assess potential confounding by indication.

We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between use of various antihypertensive medications and CBC risk. All analyses were additionally adjusted for adjuvant hormone therapy, chemotherapy and radiation therapy, therefore women with missing information on these treatment variables were dropped, leaving a final analytic sample of 352 cases and 661 controls. None of the variables listed in Table 1 were identified as confounders or effect modifiers of the risk estimates shown in Table 2.

Results

Cases and controls were similar in most aspects of patients' characteristics examined (Table 1). No antihypertensive type was associated with CBC risk, and this did not vary when evaluating recency or duration of use (Table 2). These results did not change materially in a sensitivity analysis restricted to women with a history of hypertension (data not shown).

Discussion

Our null results with respect to calcium channel blockers, β blockers, and diuretics are consistent with the only previous study to evaluate their association with CBC risk.(7) However, this prior study observed that ACE inhibitor use was associated with a 66% increased risk of CBC while we found no association. No dose response pattern was observed in this prior study and so this may have been a chance result, but warrants further investigation. Key strengths of our study includes the large number of CBCs and the use of medical records review to determine medication eliminating recall bias inherent to self-reported data.

In summary, we did not find evidence that use of calcium channel blockers, β blockers, ACE inhibitors or diuretics is associated with CBC risk among women with ER+ breast cancer. Given the widespread use of antihypertensive medications in the U.S., future efforts to confirm the safety of these and other commonly used medications will further inform breast cancer survivors and their health care providers as they consider the risk/benefit profiles of these medications.

References:

1. Chen Y, Thompson W, Semenciw R, Mao Y. Epidemiology of contralateral breast cancer. Cancer Epidemiol Biomarkers Prev. 1999 Oct;8(10):855–61.

2. Early Breast Cancer Trialists' Collaborative Group.Tamoxifen for early breast cancer: an overview of the randomised trials.Lancet. 1998 May 16;351(9114):1451–67.

3. Druesne-Pecollo N, Touvier M, Barrandon E, Chan DSM, Norat T, Zelek L, et al. Excess body weight and second primary cancer risk after breast cancer: a systematic review and meta-analysis of prospective studies. Breast Cancer Res Treat. 2012 Oct;135(3):647–54.

4. Li CI, Daling JR, Porter PL, Tang M-TC, Malone KE. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. J Clin Oncol. 2009 Nov 10;27(32):5312–8.

5. Botteri E, Munzone E, Rotmensz N, Cipolla C, De Giorgi V, Santillo B, et al. Therapeutic effect of β-blockers in triple-negative breast cancer postmenopausal women. Breast Cancer Res Treat. 2013 Aug;140(3):567–75.

6. Barron TI, Connolly RM, Sharp L, Bennett K, Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol. Amer Soc Clinical Oncology; 2011 Jul 1;29(19):2635–44.

7. Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJA, Fujii M, et al. Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. Breast Cancer Res Treat. 2014 Feb 21;

8. Li CI, Daling JR, Porter PL, Tang M-TC, Malone KE. Adjuvant hormonal therapy for breast cancer and risk of hormone receptor-specific subtypes of contralateral breast cancer. Cancer Res. 2009 Sep 1;69(17):6865–70.

Table 1 Characteristics of patients with contralateral breast cancer and control patients*

	Controls n=661 n (%)	Patients with contralateral breast cancer n=352 n (%)
Demographic characteristics		
Age at first breast cancer diagnosis, years		
40-49	120 (18.2)	69 (19.6)
50-59	174 (26.3)	89 (25.3)
60-69	206 (31.2)	108 (30.7)
70-79	161 (24.4)	86 (24.4)
Reference age, years		
40-49	59 (8.9)	33 (9.4)
50-59	129 (19.5)	66 (18.8)
60-69	211 (31.9)	111 (31.5)
70-79	199 (30.1)	103 (29.3)
80-89	63 (9.5)	39 (11.1)
Year of first breast cancer diagnosis		
1990-1993	241 (36.5)	131 (37.2)
1994-1997	220 (33.3)	115 (32.7)
1998-2001	147 (22.2)	79 (22.4)
2002-2005	53 (8.0)	27 (7.7)
Race/ethnicity		
Non-Hispanic white	606 (92.0)	322 (92.0)
Asian/Pacific Islander	16 (2.4)	9 (2.6)
African American	24 (3.6)	11 (3.1)
Native American	10 (1.5)	5 (1.4)
Hispanic white	3 (0.5)	3 (0.9)
Missing	2	2
Education		
High school or less	173 (33.7)	78 (31.5)
High school or some college	169 (32.9)	102 (41.1)
College graduates or higher	172 (33.5)	68 (27.4)
Missing	147	104
Treatments for first breast cancer		
Received radiation therapy		
No	229 (34.6)	127 (36.1)
Yes	432 (65.4)	225 (63.9)
Received chemotherapy		
No	488 (73.8)	264 (75.0)
Yes	173 (26.2)	88 (25.0)
Received hormonal therapy, years		
None	183 (27.7)	130 (36.9)
<1	100 (15.1)	56 (15.9)
1-4	195 (29.5)	87 (24.7)
≥5	183 (27.7)	79 (22.4)
Tumor characteristics of first breast cancer		
AJCC stage		
I	454 (68.7)	231 (65.6)
II/III	207 (31.3)	121 (34.4)
Tumor size, cm		
≤1.0	229 (35.6)	111 (33.0)
1.1-2.0	282 (43.8)	136 (40.5)
>2.0	133 (20.7)	89 (26.5)
Missing	17	16

Established breast cancer risk factors		
First-degree family history of breast cancer		
No	463 (74.3)	227 (70.5)
Yes	160 (25.7)	95 (29.5)
Missing	38	30
No. of full-term pregnancies		
Nulliparous	98 (15.2)	54 (15.9)
1-2	273 (42.5)	149 (44.0)
≥3	272 (42.3)	136 (40.1)
Missing	18	13
Recency of menopausal hormone use at first breast cancer diagnosis		
Never	292 (46.9)	166 (50.9)
Former	71 (11.4)	38 (11.7)
Current estrogen alone user	138 (22.2)	70 (21.5)
Current estrogen + progestin user	122 (19.6)	52 (16.0)
Missing	38	26
Health status and lifestyle factors		
Had a diagnosis of hypertension between first breast cancer and reference date		
No	330 (50.6)	180 (51.9)
Yes	322 (49.4)	167 (48.1)
Missing	9	5
Had a diagnosis of heart disease between first breast cancer and reference date		
No	495 (76.5)	272 (78.8)
Yes	152 (23.5)	73 (21.2)
Missing	14	7
BMI at first breast cancer diagnosis, kg/m^2		
<25	284 (43.8)	125 (36.5)
25-29.9	194 (29.9)	112 (32.7)
≥30	170 (26.2)	105 (30.7)
Missing	13	10
Alcohol consumption between first breast cancer and reference date, drinks/week		
None	241 (47.2)	113 (45.2)
<3	132 (25.8)	71 (28.4)
≥3	138 (27.0)	66 (26.4)
Missing	150	102
Smoking status at reference date		
Never	269 (52.2)	120 (47.6)
Former	49 (9.5)	35 (13.9)
Current	197 (38.3)	97 (38.5)
Missing	146	100

*Cases and controls were individually matched on age, year of diagnosis, county, race/ethnicity, and cancer stage. Controls also had to be alive for at least the duration between their matched cases' first and CBC diagnoses.

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Table 2 Use of antihypertensive medications and risk of second primary contralateral breast cancer*

Use of antihypertensive medications	Controls n=661		Cases n=352		
	n	%	n	%	OR (95% CI)
Use of calcium channel blockers					
Never	557	84	295	84	Reference
Ever (≥ 6 mo)	85	13	47	13.4	1.1 (0.7 ,1.6)
Unknown †	0		1		NA
Recency of use among ever users ‡					
Former	15	2.4	10	3	1.4 (0.6 ,3.5)
Current	60	9.5	33	9.8	1.1 (0.7 ,1.7)
Duration of use among current users					
<2 y	17	2.8	10	3	1.1 (0.5 ,2.6)
2-3 y	15	2.4	3	0.9	0.3 (0.1 ,1.6)
≥3 y	28	4.5	20	6.1	1.4 (0.7 ,2.6)
Use of β blockers					
Never	535	81	289	82.3	Reference
Ever (≥ 6 mo)	97	15	54	15.4	1.0 (0.7 ,1.4)
Unknown †	2		1		NA
Recency of use among ever users					
Former	14	2.2	7	2.1	1.2 (0.4 ,3.2)
Current	75	12	41	12.2	1.0 (0.6 ,1.5)
Duration of use among current users					
<2 y	20	3.3	9	2.7	0.8 (0.3 ,1.9)
2-3 y	12	2	8	2.4	1.3 (0.5 ,3.3)
≥3 y	43	7	24	7.3	0.9 (0.5 ,1.6)
Use of ACE inhibitors					
Never	522	79	271	77.2	Reference
Ever (≥ 6 mo)	114	17	72	20.5	1.2 (0.9 ,1.8)
Unknown †	1		1		
Recency of use among ever users					
Former	20	3.2	11	3.3	1.0 (0.4 ,2.4)
Current	80	13	54	16.1	1.3 (0.8 ,2.0)
Duration of use among current users					
<2 y	31	5.1	21	6.5	1.2 (0.6 ,2.3)
2-3 y	13	2.2	11	3.4	1.7 (0.7 ,4.1)
≥3 y	36	6	22	6.8	1.1 (0.6 ,2.1)
Use of Diuretics					
Never	449	68	238	68.4	Reference
Ever (≥ 6 mo)	177	27	96	27.6	1.0 (0.7 ,1.4)
Unknown †	4		4		
Recency of use among ever users					
Former	31	5.2	15	4.6	1.0 (0.5 ,2.1)
Current	119	20	72	22.2	1.2 (0.8 ,1.7)
Duration of use among current users					
<2 y	35	6.2	29	9.4	1.6 (0.9 ,2.8)
2-3 y	20	3.5	11	3.5	1.2 (0.5 ,3.0)
≥3 y	64	11	32	10.3	1.0 (0.6 ,1.7)

* ORs and 95% Cis were estimated using conditional logistic regression to account for matching factors (age, year of first breast cancer diagnosis, stage of risk breast cancer, county of residence and race/ethnicity). All models were additional adjusted for receipt of adjuvant hormone therapy, radiation therapy and chemotherapy. CI= confidence interval; OR=odds ratio.

† To maximize the utility of data, patients who used multiple drugs of a same class and had missing duration of use for some of these drugs would be classified as ever users if known duration of use was ≥ 6 mo, or unknown users if known duration of use was < 6 mo.

‡ Patients had any incomplete information on duration of use were dropped from analyses on recency and duration.

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