

# Angiotensin-Converting Enzyme Inhibitors, Calcium Channel Blockers, and Breast Cancer

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**Background:** The use of angiotensin-converting enzyme (ACE) inhibitors has been linked to a decreased risk of developing cancer, and longer-term use of calcium channel blockers (CCBs) has been associated with an increased risk of developing cancer in general and breast cancer in particular.

**Methods:** Using data from the General Practice Research Database, we conducted a large case-control analysis. Previous exposure to ACE inhibitors, CCBs, and  $\beta$ -blockers was compared between 3706 postmenopausal women who were diagnosed with incident breast cancer between 1992 and 1997 and 14 155 matched-control women.

**Results:** Compared with nonusers of antihypertensive drugs, women who used ACE inhibitors (odds ratio [OR], 1.0; 95% confidence interval [CI], 0.7-1.5), CCBs (OR,

0.9; 95% CI, 0.7-1.2), or  $\beta$ -blockers (OR, 1.0; 95% CI, 0.8-1.2) for 5 or more years were not at an increased or decreased risk of developing breast cancer (adjusted for smoking and body mass index [calculated as weight in kilograms divided by the square of height in meters]). The risk of breast cancer did not differ between users of different ACE inhibitors or different CCBs (dihydropyridines, diltiazem hydrochloride, and verapamil hydrochloride) or between users of short-acting (OR, 1.0; 95% CI, 0.7-1.4) or sustained-release (OR, 1.0; 95% CI, 0.8-1.3) nifedipine preparations.

**Conclusion:** The findings of this large case-control analysis do not support the hypothesis that longer-term use of ACE inhibitors or CCBs affects the risk of developing breast cancer.

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**T**HE FINDINGS of a recent observational study<sup>1</sup> raised the question of whether longer-term use of angiotensin-converting enzyme (ACE) inhibitors may prevent cancer in humans. Subjects from west Scotland who attended a blood pressure clinic in Glasgow were categorized according to the use of antihypertensive drug treatment (ACE inhibitors, calcium channel blockers [CCBs],  $\beta$ -blockers, or diuretics) and were followed up for several years. The subjects who used ACE inhibitors were at lower risk of developing incident cancer (relative risk [RR], 0.72; 95% confidence interval [CI], 0.55-0.92) or fatal cancer (RR, 0.65; 95% CI, 0.44-0.93) compared with expected cancer rates from 2 comparison populations in west Scotland. No suggestion of an increased cancer risk for users of CCBs was indicated in this recent investigation, which the authors characterized as a hypothesis-generating study.

The use of CCBs has been associated with an increased risk of developing

cancer in 3 follow-up analyses.<sup>2-4</sup> In contrast, several subsequent observational studies,<sup>5-8</sup> long-term controlled clinical trials,<sup>9-11</sup> and preclinical toxicological studies<sup>12</sup> showed no evidence supporting the hypothesis that CCBs may be carcinogenic.

An approximately 2-fold increased risk of developing cancer in association with use of CCBs was first reported by Pahor et al,<sup>2</sup> who analyzed exposure to various antihypertensive drugs in a cohort of 750 elderly subjects with hypertension. An extended reanalysis of the same cohort with different inclusion criteria yielded a 1.7-fold increased risk of developing cancer for CCB users compared with nonusers.<sup>3</sup> The RR of developing breast cancer in this particular cohort was 1.65 (95% CI, 0.49-5.55).<sup>3</sup> In another study<sup>4</sup> of approximately 3000 postmenopausal women, 75 cases of incident breast cancer were detected during follow-up. Users of CCBs were reported to have an approximately 2.6-fold increased risk of breast cancer compared with nonusers. A higher RR was

## METHODS

### STUDY DESIGN

This case-control analysis was based on information derived from the large UK-based General Practice Research Database (GPRD), London. General practitioners from approximately 350 general practices record medical information on more than 3 million patients who are currently actively registered with a physician, using standard procedure and supplied anonymously, to provide data for research purposes. The computer records contain patient demographics, characteristics (ie, height, weight, and smoking status), symptoms and diagnoses (using Oxford Medical Information System [OXMIS] codes,<sup>13</sup> which are mapped onto International Classification of Diseases<sup>14</sup> codes,) referrals, number of hospitalizations, and all drug prescriptions in chronologic order. The computerized recording of patient information was started by many general practitioners in the late 1980s, and it replaced the handwritten records used previously. On request, copies of hospital discharge and referral letters without patient identification were available for review to validate the diagnoses recorded in the computer. The accuracy and comprehensiveness of diagnoses and drug prescriptions have been validated and documented,<sup>15-17</sup> and other studies<sup>5,18</sup> involving patients diagnosed with cancer used the GPRD to gather patient information.

### CASE DEFINITION AND VALIDATION

We identified all women who had a first-time diagnosis of incident breast cancer between January 1, 1992, and September

30, 1997. The study was restricted to women who were 50 years of age or older at the date of the breast cancer diagnosis (index date) and who had a drug prescription history in the GPRD of 3 years or more. Potential cases of a diagnosis of any kind of malignancy (except nonmelanoma skin cancer) prior to the breast cancer diagnosis were excluded.

Patient records of potential cases of a diagnosis of breast cancer (code 174.0) were reviewed, with all exposure information of interest (ie, use of antihypertensive drugs and estrogen replacement therapy) suppressed. Based on the available information in the computer records of patient profiles, we categorized potential cases into 1 of 3 groups: (1) uncertain, subjects whose index date was unclear (prevalent or incident cancer?) or for whom there was weak evidence for the diagnosis (no confirmation recorded and no action taken) or the diagnosis was a chance finding at autopsy; (2) probable, subjects who were hospitalized at first-time diagnosis of breast cancer and for whom some treatment information was recorded (eg, a new therapy with tamoxifen citrate) but the patient record lacked further evidence of final confirmation of the diagnosis; and (3) definite, subjects who underwent mastectomy, radiotherapy, and/or chemotherapy or whose details were noted with regard to staging, localization, or histological analysis of the cancer after diagnosis of incident breast cancer. We included definite cases without further validation, since previous validation procedures on a large number of cases documented a high reliability of cancer diagnoses in the GPRD.<sup>5</sup> However, we requested hospital discharge letters for a random sample of 30 probable cases. The computer-recorded breast cancer diagnoses were confirmed by copies of hospital discharge letters (eg, histological results and surgery reports) for all 30 cases; therefore, we decided to include all probable cases in the final analysis. Uncertain cases were eliminated from further analysis.

found for women who had exposure to both CCBs and estrogen replacement therapy (hazard ratio, 4.48; 95% CI, 1.58-12.75; based on 4 exposed cases).<sup>4</sup>

Two case-control analyses, 1 using data from the United Kingdom (UK)<sup>5</sup> and 1 from the United States,<sup>6</sup> compared the risk of developing cancer among patients with hypertension who used CCBs,  $\beta$ -blockers, or ACE inhibitors. The RR estimates for users of CCBs or ACE inhibitors compared with the reference group of users of  $\beta$ -blockers were 1.27 (95% CI, 0.98-1.63) and 0.79 (95% CI, 0.58-1.06), respectively, in the UK study and 0.9 (95% CI, 0.8-1.1) and 1.0 (95% CI, 0.8-1.2), respectively, in the US study. In these 2 large case-control studies (446<sup>5</sup> and 9513<sup>6</sup> incident cancer cases), the RR estimates of developing breast cancer, in particular for users of CCBs, were 1.32 (95% CI, 0.72-2.41) for the UK study and 1.1 (95% CI, 0.8-1.4) for the US study. There was no consistent evidence for an increased risk of cancer with increasing duration of exposure in either of these 2 case-control analyses, which was interpreted as being incompatible with the hypothesis that the use of CCBs may be causally related to an elevated risk of cancer.

To further explore whether long-term use of ACE inhibitors, CCBs, or  $\beta$ -blockers may be associated with a decreased or increased risk of breast cancer, we conducted a large case-control analysis.

## RESULTS

We analyzed 3706 incident breast cancer cases and 14 155 controls. Thirty-two percent of cases and age-matched controls were 50 to 59 years of age at the index date, 26% were between 60 and 69 years, and approximately 42% were 70 years or older. The distribution of body mass index, smoking status, and additional covariates and their independent relation to the risk of developing breast cancer are displayed in **Table 1**. The mean duration of medical history recorded in the GPRD prior to the index date was 5.3 years (range, 3-14 years). For more than 75% of both case and control groups, it was 5 or more years.

The results of the analyses on the association between the use of antihypertensive drugs and the risk of developing breast cancer are shown in **Table 2**. Compared with nonusers of antihypertensive drugs, the RR estimates (odds ratios [ORs]) for having ever used ACE inhibitors, CCBs,  $\beta$ -blockers, or a combination of the above (mixed users) were 1.0 (95% CI, 0.9-1.2), 1.0 (95% CI, 0.8-1.1), 1.0 (95% CI, 0.9-1.1), and 0.9 (95% CI, 0.8-1.0), respectively, adjusted for smoking status and body mass index. Approximately 80% of study drug users across all drug groups were current users of antihypertensive drugs at the index date; the risk of developing breast cancer did not differ between current and

## CONTROL GROUP

We randomly selected 4 control women for each subject in the definite and probable incident breast cancer case groups, matched by age (same year of birth), physician practice, calendar date (the same index date), and number of years of medical history recorded in the GPRD. The same exclusion criteria (ie, a history of any malignancy except nonmelanoma skin cancer or a history of less than 3 years prior to the index date in the GPRD) were applied to subjects in the control group as to those in the case group.

## EXPOSURE ASSESSMENT

Exposure to ACE inhibitors, CCBs, and  $\beta$ -blockers was assessed from the computer records. Subjects were classified as users of ACE inhibitors only, users of CCBs only, users of  $\beta$ -blockers only, mixed users if they used multiple drugs (eg, CCBs and  $\beta$ -blockers), or nonusers if they had no exposure to antihypertensive drugs of interest prior to the index date. As in previous studies<sup>2-7</sup> on the association between the use of antihypertensive drugs and the risk of cancer, we assessed the use of ACE inhibitors, CCBs, or  $\beta$ -blockers regardless of any concurrent use of diuretics.

We further stratified users of antihypertensive drugs by duration of treatment and by recency of use. Users of these drugs were classified according to the number of years exposed: 2 or less, 3 to 4, 5 or more, or unknown duration. A subject was categorized as a user of unknown duration if the computer record indicated that she used antihypertensive drugs but the total duration of exposure was not known since she was already taking the drug before the general practitioner initially recorded prescriptions on

the computer. If the start date of the treatment was not known but the computer-recorded exposure exceeded 5 years, the subject was categorized in the 5 or more years group.

Users of antihypertensive drugs were classified as current users if they received a prescription for a study drug within a year prior to the index date and as past users if the last prescription for an antihypertensive drug preceded the index date by more than 1 year.

Furthermore, users of CCBs were stratified by pharmacological class (nifedipine, other dihydropyridines, diltiazem hydrochloride, and verapamil hydrochloride) and nifedipine users, in particular, by drug action (fast-acting vs sustained-release nifedipine). Also, we assessed from the GPRD whether CCB users received postmenopausal estrogen replacement therapy, and, if yes, for how long.

## ANALYSIS

We conducted the statistical analysis using SAS statistical software (release 6.12; SAS Institute Inc, Cary, NC). Conditional logistic regression models were used to analyze the risk of developing breast cancer in relation to previous use of antihypertensive drugs of various duration and to adjust for potential confounders. The independent effect of a number of covariates on the risk of developing breast cancer was evaluated for the following potential confounders: smoking status (current smokers, former smokers, nonsmokers, or unknown), body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters; <25.0, 25.0-29.9,  $\geq$  30.0, or unknown), a history of alcohol abuse (yes or no), previous hysterectomy (yes or no), and a history of benign breast disease (defined as a diagnosis of breast lump at 1 year or more prior to the index date).

past users. Therefore, we combined current and past users of antihypertensive drugs for subsequent analyses.

We further evaluated the effect of duration of exposure on the risk of developing breast cancer (Table 2). Compared with nonusers of antihypertensive drugs, the adjusted RR estimates for users of ACE inhibitors, CCBs, or  $\beta$ -blockers of less than 2 years, 3 to 4 years, or 5 or more years were all equal or close to 1. A direct comparison of longer-term users of ACE inhibitors or CCBs with  $\beta$ -blockers, as reported in previous studies,<sup>2,5</sup> did not yield a decreased risk for users of ACE inhibitors (adjusted OR, 1.0; 95% CI, 0.6-1.6) or an increased risk for users of CCBs (adjusted OR, 0.9; 95% CI, 0.6-1.3).

We also stratified users of CCBs according to pharmacological class. Compared with nonusers of antihypertensive drugs, the adjusted ORs for longer-term users (5 or more years) of nifedipine, diltiazem, or verapamil were 1.0 (95% CI, 0.7-1.4), 0.8 (95% CI, 0.2-3.6), and 1.0 (95% CI, 0.4-2.4), respectively (**Table 3**).

Nifedipine users were further stratified according to drug action. Compared with the reference group of nonusers of antihypertensive drugs, there was no difference in the risk of developing breast cancer for users of fast-acting (OR, 1.0; 95% CI, 0.7-1.4) and slow-release (OR, 1.0; 95% CI, 0.8-1.3) forms of nifedipine.

Further adjusting the multivariate conditional logistic regression models for additional covariates (Table 1)

did not materially change the association between use of antihypertensive drugs and the risk of breast cancer. We also adjusted the analyses for the total number of practice visits (1-9, 10-19, 20-29, and 30 or more) prior to the index date; it had no effect on the results.

Furthermore, we evaluated whether combined exposure to CCBs and estrogen replacement therapy was associated with an increased risk of developing breast cancer. We identified those subjects who used both CCBs and estrogen replacement therapy for 3 or more years, and we compared these subjects with the reference group of nonusers of CCBs (regardless of whether they used  $\beta$ -blockers or ACE inhibitors or did not use any antihypertensive drugs). There were 5 case subjects and 27 control subjects who used both CCBs and estrogen replacement therapy for 3 or more years (OR, 0.8; 95% CI, 0.3-2.0).

## COMMENT

The findings of this large case-control analysis of more than 3700 incident breast cancer cases and more than 14 000 controls do not support the recently generated hypothesis that ACE inhibitors reduce the risk of developing cancer in general and breast cancer in particular,<sup>1</sup> nor do they provide evidence that CCBs increase the risk for breast cancer in postmenopausal women. The risk of developing breast cancer was independent of the use of any

**Table 1. Distribution of Characteristics and Their Independent Unadjusted Effect on the Risk of Developing Breast Cancer\***

Subject Characteristics	Case Subjects (n = 3706)	Control Subjects (n = 14 155)	Odds Ratio (95% Confidence Interval)
Body mass index, kg/m <sup>2</sup>			
>25.0	1124	4385	1.00 (Reference)
25.0-29.9	883	3319	1.04 (0.94-1.15)
≥30.0	500	1779	1.12 (1.00-1.26)
Unknown	1199	4672	0.98 (0.89-1.09)
Smoking status			
Nonsmoker	2188	8008	1.00 (Reference)
Current smoker	532	2224	0.88 (0.79-0.98)
Former smoker	300	1090	1.02 (0.89-1.17)
Unknown	686	2833	0.86 (0.77-0.96)
Alcoholism			
No	3668	14 052	1.00 (Reference)
Yes	38	103	1.30 (0.95-1.80)
Hysterectomy			
No	3040	11 712	1.00 (Reference)
Yes	666	2443	1.07 (0.97-1.18)
Breast lumps			
No	3365	13 375	1.00 (Reference)
Yes	341	780	1.51 (1.35-1.69)

**Table 2. Relative Risk Estimates of Developing Breast Cancer in Relation to Exposure to Angiotensin-Converting Enzyme (ACE) Inhibitors, Calcium Channel Blockers (CCBs), or β-Blockers**

Drug and Duration, y	Case Subjects (n = 3706)	Control Subjects (n = 14 155)	Odds Ratio (95% Confidence Interval)*
None	2567	9745	1.0 (Reference)
ACE inhibitors	112	403	1.0 (0.9-1.2)
1-2	47	188	0.9 (0.7-1.3)
3-4	16	56	1.1 (0.6-1.9)
≥5	28	108	1.0 (0.7-1.5)
Unknown	21	51	1.4 (0.8-2.3)
CCBs	190	735	1.0 (0.8-1.1)
1-2	79	293	1.0 (0.8-1.3)
3-4	19	75	1.0 (0.6-1.6)
≥5	53	226	0.9 (0.7-1.2)
Unknown	39	141	1.0 (0.7-1.5)
β-blockers	498	1888	1.0 (0.9-1.1)
1-2	135	527	1.0 (0.8-1.2)
3-4	73	277	1.0 (0.8-1.3)
≥5	167	633	1.0 (0.8-1.2)
Unknown	123	451	1.0 (0.8-1.3)
Mixed use†	339	1384	0.9 (0.8-1.0)

\*Adjusted for smoking status and body mass index.  
†Subjects used any combination of ACE inhibitors, CCBs, and β-blockers.

antihypertensive drugs, and there was no suggestion that the risk of breast cancer increased or decreased with increasing duration of exposure to any of the drugs of interest.

The findings with respect to CCBs are consistent with the results of several previous large observational case-control analyses,<sup>3-8</sup> in which no association between longer-term use of CCBs and cancer risk was observed. However, 3 follow-up analyses<sup>2-4</sup> raised concern about possible

**Table 3. Relative Risk Estimates of Developing Breast Cancer for Users and Nonusers of Calcium Channel Blockers (CCBs)**

Drug and Duration, y	Case Subjects	Control Subjects	Odds Ratio (95% Confidence Interval)*
None	2567	9745	1.0 (Reference)
Nifedipine			
1-2	42	142	1.1 (0.8-1.5)
3-4	12	45	1.0 (0.5-1.9)
≥5	41	159	1.0 (0.7-1.4)
Unknown	23	92	0.9 (0.6-1.5)
Other dihydropyridines			
1-2	17	74	0.8 (0.5-1.4)
3-4	0	1	...
≥5	0	0	...
Unknown	4	14	1.0 (0.3-3.0)
Diltiazem hydrochloride			
1-2	8	37	0.9 (0.4-1.8)
3-4	3	12	1.0 (0.3-3.5)
≥5	2	10	0.8 (0.2-3.6)
Unknown	4	10	1.5 (0.5-4.7)
Verapamil hydrochloride			
1-2	8	19	1.6 (0.7-3.7)
3-4	4	4	4.0 (1.0-16.1)
≥5	7	26	1.0 (0.4-2.4)
Unknown	4	15	1.0 (0.3-3.1)
Mixed CCB use†			
1-2	4	21	0.7 (0.2-2.0)
3-4	0	13	...
≥5	3	31	0.4 (0.1-1.2)
Unknown	4	10	1.6 (0.5-5.0)

\*Adjusted for smoking status and body mass index. Ellipses indicate no data available.

†Subjects used any combination of CCBs.

carcinogenic effects of CCBs. Some of these studies relied on interview-based exposure information that was received at the time of entry into the cohort. Such exposure assessment may not sufficiently account for changes in the antihypertensive treatment pattern over time and may not yield sufficient information on duration of exposure.

There is limited information with regard to combined use of CCBs and estrogen replacement therapy in the current analysis, but the available evidence does not support the hypothesis of a substantially increased risk of developing breast cancer for women who used both CCBs and estrogen replacement therapy for 3 or more years.<sup>4</sup>

A strength of this study is that exposure information was available for at least 3 years (mean, 5.3) for both cases and controls. This information allowed us to stratify subjects into short-term, medium-term, and longer-term users, which was important in detecting potential duration effects. However, despite this considerable amount of information on longer-term use of CCBs, we cannot extrapolate these results to those beyond the available data and infer the risk of developing cancer for users of even longer duration (eg, 10 or more years). Since exposure information was recorded on the computer continuously since the early 1990s by general practitioners and not obtained through patient interviews, there was no recall bias. Another strength of the study was the considerable sample size; to our knowledge, it is the largest group of women

with incident breast cancer that has been studied to date in relation to previous exposure to antihypertensive drugs.

In this study, a number of potential confounders of the association between drug exposure and the risk of breast cancer were assessed, and their independent association with the risk of developing breast cancer was analyzed. None of these parameters substantially confounded the association between antihypertensive drug use and the risk of breast cancer. However, the independent effects of some of these parameters were consistent with previous knowledge on factors that slightly increase the risk for breast cancer: increasing body mass index,<sup>19</sup> a history of increasing alcohol intake,<sup>20,21</sup> and a history of benign breast lumps.<sup>22</sup>

The total number of subjects' visits to the general practitioner prior to the index date was not related to case-control status or to antihypertensive drug use. Thus, differential medical attention as a possible bias is an unlikely alternative explanation for our findings.

We were not able to control for parameters that are not routinely recorded in the GPRD, such as ethnic origin, socioeconomic status, physical activity, or diet. Although some of these parameters might be independently related to some degree to the risk of developing breast cancer, substantial confounding due to a strong relationship between these factors and the use of particular antihypertensive drugs seems unlikely.

In conclusion, our findings neither suggest that ACE inhibitors reduce the risk of developing breast cancer nor provide evidence that the use of CCBs is associated with an increased risk of developing breast cancer.

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