Calcium Channel Blockers and the Risk of Cancer

Lynn Rosenberg, ScD; R. Sowmya Rao, MS; Julie R. Palmer, ScD; Brian L. Strom, MD; Paul D. Stolley, MD; Ann G. Zauber, PhD; M. Ellen Warshauer, MS; Samuel Shapiro, MB

Context.—Recent epidemiologic studies have raised the concern that calcium channel blocker use may increase the risk of cancer overall and of several specific cancers.

Objective.—To assess whether calcium channel blocker use increases the risk of cancer overall and of specific cancers.

Design.—Case-control drug surveillance study based on data collected from 1983 to 1996.


Patients.—A total of 9513 patients aged 40 to 69 years with incident cancer of various sites and 6492 controls aged 40 to 69 years admitted for nonmalignant conditions.

Main Outcome Measures.—Incident cancer overall and 23 specific cancers.

Results.—Calcium channel blocker use was unrelated to the risk of cancer overall (relative risk [RR], 1.1; 95% confidence interval [CI], 0.9-1.3). Use was not significantly associated with increased risks of individual cancers, including those previously implicated, except cancer of the kidney (RR, 1.8; 95% CI, 1.1-2.7). Recent use, use for 5 or more years, and use of individual calcium channel blocker drugs were also not associated with cancer incidence. Use of β-blockers and angiotensin-converting enzyme inhibitors was generally unrelated to cancer overall or individual cancers, but both were associated with kidney cancer (RR, 1.8; 95% CI, 1.3-2.5; and RR, 1.9; 95% CI, 1.2-3.0, respectively).

Conclusions.—The present study suggests that the use of calcium channel blockers is unrelated to an increase in the overall risk of cancer or of individual cancers, except kidney cancer, which has been associated with hypertension or drugs to treat hypertension in previous studies.

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IN 1996, Pahor et al1,2 raised the concern that calcium channel blockers (CCBs) may be carcinogenic. After 3.7 years of follow-up of 5082 people, they found a statistically significant 1.72-fold increase in the overall risk of cancer among persons who used CCBs, based on 47 cancers that occurred among users and 373 among nonusers. Elevations in risk greater than 1.5-fold were observed for cancers of the bladder, ureter, or kidney; breast; colon; prostate; lymphatic or hemopoietic system; stomach; and uterus. Results from subsequent studies have been mixed. A case-control study reported by Jick et al,3 which included 446 cases of cancer and which had more complete data on drug exposure, did not support a material effect of CCB use on cancer risk overall; the relative risk (RR) estimate was 1.27 (95% confidence interval [CI], 0.98-1.63) in CCB users relative to users of β-blockers, and the risk did not increase with increasing duration of use. Relative risk estimates were not elevated for the individual cancers for which risk was elevated in the study of Pahor et al,4 but numbers were small. In a Danish follow-up study of 17,911 patients who had received at least 1 prescription for a CCB, the incidence of cancer was not increased after up to 3 years of follow-up: 412 cancers occurred, whereas 414 were expected on the basis of national incidence rates.4 An association between CCB use and increased risk of breast cancer was reported from a study of 3198 women who had been followed up for up to 5 years.5 Based on 20 cases of breast cancer among women who had used CCBs and 55 cases among women who had not, the hazard ratio was 2.57 (95% CI, 1.47-4.49).

We report here on the relation of CCB use to cancer risk, based on data from a case-control drug surveillance study.6 In addition to assessing all cancers together (9513 cases), numbers of cases were sufficient to assess individual cancers, including those for which risk was elevated in the previous studies.1,2,5-8 As a check for bias, we assessed the relation of cancer risk to the use of β-blockers and angiotensin-converting enzyme (ACE) inhibitors, which were unrelated to cancer risk in the previous studies.1,2,5

METHODS

Data Collection

From 1976 to 1996, specially trained nurse-interviewers stationed in participating hospitals interviewed patients less than 70 years old who had been admitted for first occurrences of cancer or for any of a variety of nonmalignant conditions.7 The vast majority of patients were interviewed in Boston, Mass, New York, NY, Philadelphia, Pa, and Baltimore, Md; 95% of patients approached for an interview participated. Over the course of the study, different diagnoses were given priority for interview. The proportions of patients with particular diagnoses who were enrolled varied, depending on priorities, staffing, and the availability of patients for interview (when they were not undergoing diagnostic tests or treatments or seeing visitors).

The interviewers administered standard questionnaires to obtain information.
on demographic data, reproductive and medical history, cigarette smoking, alcohol use, family history of cancer, and other factors. Lifetime histories of medication use before the admission to hospital at which the interview occurred, which focused on regular use, were obtained by asking about 40 indications, among them fluid retention, high blood pressure, heart conditions, and angina pectoris. For each episode of use the name of the drug, the date started, and the duration and frequency of use (eg, daily) were recorded. The number of pills taken daily was not recorded, however. Information about the patient’s diagnosis was extracted, blind to the patient’s exposure status, from discharge summaries and pathology reports.

Use of CCBs was infrequent before the 1980s, and we confined the present analyses to patients interviewed from 1983 to 1996; that exclusion eliminated patients from Boston, most of whom were interviewed before 1983. Use of CCBs was also uncommon in patients younger than 40 years, and the analyses were further restricted to patients aged 40 years or older. A total of 9642 patients admitted for cancer and 8826 patients admitted for nonmalignant disorders were available for study.

Cases

We included as cases all interviewed patients aged 40 to 69 years with a primary cancer of a site for which there were at least 20 patients, whose cancer was first diagnosed within the year before the admission at which the patient was interviewed, and who had no history of previous or concurrent cancer other than nonmelanoma skin cancer (9613 patients). We analyzed the risk of cancer overall and of 23 specific cancers: breast, 2593; colon, 1004; lung, 994; prostate, 823; malignant melanoma, 597; rectum, 490; urinary bladder, 304; pancreas, 349; ovary, 262; kidney, 279; uterus, 264; lymphoma, 217; leukemia, 206; esophagus, 144; stomach, 141; bone and connective tissue, 114; respiratory other than lung, 98; gallbladder, 90; testis 43; vulva, 40; thyroid, 33; liver, 29; and small intestine, 20. The mean age of the cases was 56 years; 41% were male; 84% were white; 20% were current smokers; 27% had a body mass index (weight in kilograms divided by the square of height in meters) of 28 or greater; and 23% reported having received medication for hypertension.

Controls

We selected as controls patients aged 40 to 69 years who had been admitted for nonmalignant conditions judged to be unrelated to the use of antihypertensive drugs. Thus, for example, patients admitted for cardiovascular diseases were not included. However, just as cases admitted for cancer sometimes had secondary diagnoses for which antihypertensives are used (eg, hypertension), so too some control patients admitted for accepted diagnoses had secondary diagnoses for which antihypertensives are used. Patients with a history of cancer other than nonmelanoma skin cancer were excluded. There were 6492 controls, 2075 with conditions of acute onset (acute infections, appendicitis, trauma), 2448 with disorders of the digestive or urinary tracts (eg, cholecystitis, urolithiasis, gastric and duodenal ulcers), and 1969 with a variety of other conditions (eg, orthopedic disorders, benign neoplasms, pelvic inflammatory disease, hernia repair). The mean age of controls was 52 years; 42% were male; 68% were white; 35% had a body mass index of 28 or greater; and 23% reported having received medication for hypertension.

Drug Exposure

We assessed the use of CCBs, \( \beta \)-blockers, and ACE inhibitors separately. Only use that preceded the onset of the cancer is etiologically relevant. We therefore focused on use that had begun at least a year before admission; persons whose only use had begun within the year before admission were evaluated separately.

Use of CCBs that had begun at least a year before admission was similar across the diagnostic categories among the controls. Among male controls, the prevalence, adjusted for age and physician visits its 2 years previously, was 5.5% among controls admitted for acute conditions, 6.1% among controls admitted for digestive and urinary tract conditions, and 6.5% among controls admitted for other conditions; among female controls, the corresponding rates were 6.1%, 4.7%, and 5.8%.

Data Analysis

Unconditional multiple logistic regression analysis was used to estimate RRs (odds ratios) for categories of drug use controlling for multiple factors.\(^3\) Cancers that affected both men and women were compared with all controls, male cancers (eg, prostate) with male controls, and female cancers (eg, breast) with female controls. Indicator terms were included for correlates of antihypertensive drug use and for risk factors for the cancers. Use of CCBs differed among the 3 study centers, was greater in men than women, and increased with increasing age, interview year, body mass index, and annual visits to a physician 2 years before admission. (The latter factor was controlled because hypertension is more commonly diagnosed and treated in persons who regularly visit physicians than in those who do not.) Terms for these factors and for race and years of education, which are risk factors for several specific cancers, were included in the regressions. Age was controlled in 5-year categories; when it was controlled as a continuous variable, the results were unchanged. We included additional terms in the logistic regressions as follows: regressions for all cancers combined, lung cancer, nonlung respiratory cancers, urinary bladder cancer, and esophageal cancer included pack-years of cigarette smoking; regressions for breast cancer included breast cancer in a mother or sister, benign breast disease, age at menarche, age at first birth, parity, age at menopause, alcohol consumption, duration of oral contraceptive use, and duration of estrogen supplement use; regressions for prostate cancer included prostate cancer in a father or brother; regressions for ovarian cancer included duration of oral contraceptive use and parity; and regressions for uterine cancer included duration of oral contraceptive use and duration of estrogen supplement use. In the analyses of ovarian cancer, controls who did not have at least 1 ovary were excluded. In the analyses of uterine cancer, controls who had previously undergone hysterectomy were excluded.

### RESULTS

In Table 1, the use of CCBs, \( \beta \)-blockers, and ACE inhibitors is shown among all cases of cancer and the controls. For CCB use that had begun at least a year before admission, the mean duration of use was...
3.8 years among case users and 3.7 years among control users; the RR estimate for cancer overall was 1.1. The RR estimates for β-blocker and ACE inhibitor use were also 1.1. None of the estimates differed significantly from 1.0, and the upper 95% confidence limit for each estimate was 1.3. The estimates were virtually unchanged when terms for all 3 classes of antihypertensive drugs were included simultaneously in the logistic regression. Use that began within the year before admission was unrelated to risk. Such use is not of etiologic interest because the cancer may have been present before the drug use began. Persons whose only use of CCBs, β-blockers, or ACE inhibitors began in the year before admission were therefore excluded from the analyses that follow.

In an analysis confined to users of CCBs, β-blockers, or ACE inhibitors, we compared use of CCBs or ACE inhibitors with use of β-blockers (ie, β-blockers were the reference category), as in the analyses of Pahor et al, Jick et al, and Fitzpatrick et al. For CCB use that began at least a year before admission relative to β-blocker use that began at least a year before admission, the RR estimate for cancer overall was 0.9 (95% CI, 0.9-1.1); the corresponding estimate for ACE inhibitor use was 1.0 (95% CI, 0.8-1.2). In separate analyses using each of the 3 major diagnostic groups among the controls as the comparison group, the RR estimate for CCB use was 1.1 (95% CI, 0.8-1.5) using controls admitted for acute conditions, 0.8 (95% CI, 0.6-1.1) using controls with digestive or urinary tract conditions, and 0.8 (95% CI, 0.6-1.1) using controls with other conditions; the corresponding estimates for ACE inhibitor use were 1.2, 1.0, and 0.8, and all were compatible with 1.0.

Among persons who had used CCBs, β-blockers, or ACE inhibitors, we identified those who had used 1 drug class exclusively. For CCB use (126 cases, 113 controls) relative to no CCB use, the RR estimate for cancer overall was 0.9 (95% CI, 0.6-1.1); for β-blocker use (371 cases, 210 controls) relative to no use of β-blockers, the estimate was 1.1 (95% CI, 0.9-1.3); and for ACE inhibitor use (80 cases, 62 controls) relative to no ACE inhibitor use, the estimate was 1.1 (95% CI, 0.8-1.6).

As shown in Table 2, for CCB use that began at least 1 year before admission, the RR estimates for cancer overall were close to 1.0 among both men and women and among persons younger than 65 years and older persons. In addition, the estimates for 5 or more years of use of any CCB and for any use and 5 or more years of use of diltiazem, nifedipine, and verapamil were all compatible with 1.0.

In Table 3, data on CCB, β-blocker, and ACE inhibitor use are given for in-
individual cancers. Among 48 RR estimates based on 5 or more case users, 5 were statistically significant, of which 3 were for renal cancer: 1.8 among CCB users, 1.8 among β-blocker users, and 1.9 among ACE inhibitor users. Kidney cancer has been associated with hypertension, or drugs used to treat hypertension, in previous studies.8,15 The other two statistically significant estimates were 2.4 for nonlung respiratory cancer among β-blocker users, and 2.1 for uterine cancer among ACE inhibitor users.

Table 4 gives data on 5 or more years of use of CCBs, β-blockers, or ACE inhibitors. The RR estimate for colon cancer among CCB users, 1.7, was of borderline statistical significance (95% CI, 1.0-2.8), and the estimates for kidney cancer (1.7) and nonlung respiratory cancer (2.6) among β-blocker users were significantly elevated; all other estimates were compatible with 1.0.

Fitzpatrick et al17 reported a statistically significant hazard ratio of 4.48 for breast cancer among women who had used both CCBs and postmenopausal estrogen supplements. In the present study, based on 16 cases and 32 control women who had used CCBs and estrogen supplements, the RR estimate was 1.1 (95% CI, 0.6-2.0). In 2 further analyses of CCB use, those who had used supplements for at least 5 years and those who had used them within the 5 years before admission, the RR estimates were 0.8 and 1.5, respectively; both estimates were compatible with 1.0.

**COMMENT**

The present study provides evidence against the hypothesis that CCBs increase overall cancer risk. For cancer at all sites combined, the RR estimate for CCB users was compatible with 1.0, and an increase in risk of 30% could be ruled out with 95% confidence. The results were unchanged when the use of CCBs was compared with β-blocker use, as was done in the studies in which CCB use was associated with increased cancer risk.2,5 In addition, the overall risk of cancer was not associated with the use of individual CCBs or long durations of CCB use.

Our results for individual cancers were also largely null. Based on larger numbers than previous studies, the RRs for the specific cancers under suspicion, excluding renal cancer, ranged from 0.4 to 1.3 for CCB use overall and from 0.7 to 1.7 for 5 or more years of CCB use; none of the estimates was statistically significant. For renal cancer, the RR estimate was 1.1 for CCB use overall, as well as for 5 or more years of use. The risk of renal cancer was increased among CCB users, but it was also increased among users of β-blockers and ACE inhibitors.

This cancer has been associated with hypertension, or drugs used to treat hypertension, in earlier studies.8,15 There were a few statistically significant associations of increased risk of other specific cancers with the use of β-blockers or ACE inhibitors, but when multiple comparisons are made, it can be expected that some significant associations will arise by chance.

It has been suggested that antiestrogens induce apoptosis in hormone-dependent tissues such as the breast.26 If so, exogenous estrogens might interfere with apoptosis. In the study of Fitzpatrick et al,2 the hazard ratio was 4.48 (95% CI, 1.88-12.75) based on 4 cases of breast cancer among women who had used both CCBs and postmenopausal hormones. In the present study, the joint use of these medications was not materially related to breast cancer risk.

Based on small numbers of exposed cases, the hazard ratio for cancer overall increased significantly with increasing CCB dose in the study of Pahor et al,1 and the hazard ratio for breast cancer was greater for women who had been exposed to greater than the modal dose of CCBs in the study of Fitzpatrick et al.17 Neither study gave data on the duration of use. In the study of Jick et al,16 the point estimate for cancer risk associated with high doses was greater than that for lower doses, but there was no association with the duration of use. The absence of information on dose is a limitation of the present study; as already noted, we found no evidence of a duration effect.

In the previous positive studies,2,5 point estimates of risk were higher for immediate release than for sustained release CCBs. We could not assess the type of CCB. However, while immediate or sustained release is relevant for the occurrence of acute cardiovascular events, there is no reason to suspect that it is of relevance for carcinogenesis.

The present study was confined to patients younger than 70 years, whereas the patients in the positive studies of Pahor et al12 and Fitzpatrick et al16 were elderly. However, there has been little evidence of a carcinogenic effect in other studies that included elderly patients.3,4

The observation that the use of β-blockers or ACE inhibitors was generally not associated with the risk of cancer in the present study constitutes strong evidence against bias. Biased reporting of drug use was unlikely because the hypothesis concerning CCBs was unknown when the data were collected. Random misclassification of CCB use would have biased RR estimates toward 1.0. However, it is unlikely that associations of the magnitude previously reported12,25 would have been missed. The associations of kidney cancer with the use of CCBs and

<table>
<thead>
<tr>
<th>Cancer Site and Controls</th>
<th>CCBs</th>
<th>β-Blockers</th>
<th>ACE Inhibitors</th>
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<tbody>
<tr>
<td><strong>Cases</strong></td>
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<tr>
<td>Breast</td>
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<td>1.2 (0.8-1.7)</td>
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<td>Malignant melanoma</td>
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<td>1.7</td>
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<td>Rectum</td>
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<td>1.2 (0.5-3.0)</td>
<td>1.1 (0.7-1.9)</td>
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<tr>
<td>Bladder</td>
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<td>1.1 (0.5-2.7)</td>
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<tr>
<td>Pancreas</td>
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<tr>
<td>Ovary</td>
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<td>0.7</td>
<td>1.2 (0.7-2.2)</td>
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<tr>
<td>Kidney</td>
<td>12</td>
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<td>1.7 (1.1-2.8)</td>
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<tr>
<td>Uterus</td>
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<td>Lymphoma</td>
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<td>2.6 (1.2-5.7)</td>
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<tr>
<td>Gallbladder</td>
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<td>0.5</td>
<td>1.1 (0.5-2.9)</td>
</tr>
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</table>

**Controls**

| All                      | 97   | 0.9 (0.5-1.7) | 1.0 (0.7-1.5) |
| Men                     | 44   | 1.2 (0.7-2.5) | 1.4 (0.9-2.2) |
| Women                   | 53   | 1.7 (1.1-2.5) | 1.2 (0.8-1.8) |

*Specific cancers are not included unless at least 5 cases used at least one of the drug classes for 5 or more years.
†Multivariate relative risk (RR) estimate with 95% confidence interval (CI); the CI is not given if there were fewer than 5 exposed cases. Reference category is never use of the particular drug class. Ellipses indicate data not applicable.
other antihypertensives were of the magnitude seen in earlier studies. Moreover, the mean duration of CCB use was long, almost all use occurred less than a decade previously, and 5 or more years of use, a category that is likely to be well remembered, was assessed. There is evidence to suggest that selection bias was absent: Rates of CCB use did not vary materially across the major diagnostic categories among the controls (which suggests that the objective of selecting controls who had been admitted for conditions unrelated to the use of antihypertensives was achieved), and the findings were similar regardless of which diagnostic category was used in the comparisons.

In sum, the present results suggest that CCB use is unrelated to the overall risk of cancer or of specific cancers. Compelling biological evidence to support a carcinogenic effect of CCBs is also lacking. It has been suggested that CCB use may influence cancer risk by interfering with apoptosis, However, we know of no evidence of a tumorigenic effect, and, indeed, some evidence suggests that CCBs, albeit at doses toxic in humans, might inhibit carcinogenesis.

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References