Carcinogenicity of Antihypertensive Therapy

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Current Hypertension Reports 2002, **4:**195–201
Current Science Inc. ISSN 1522-6417

Several studies have suggested that antihypertensive treatment may promote cancer through unknown mechanisms. Early retrospective studies implicated reserpine in breast cancer, but data from prospective studies and meta-analysis of several case-controlled studies showed only a weak association between reserpine and breast cancer which, although statistically significant, is of little clinical concern. Data from case-controlled studies and several cohort studies suggested an association between the use of a diuretic and the occurrence of renal cell cancer, particularly in women. A recent study showed an association between the use of a diuretic and the occurrence of colon cancer. Several prospective studies showed that treatment with atenolol may increase mortality from malignancy. However, other studies that analyzed data from several thousand patients could not confirm this association. In three prospective and a few case-controlled studies, angiotensin converting enzyme inhibitors were not associated with increased mortality from malignancy. In addition, a recent retrospective study showed that long-term use of angiotensin converting enzyme inhibitors had a protective effect against malignancy. Data from three large case-controlled studies and the combined data from eight randomized controlled studies and seven longitudinal studies showed a similar risk for malignancy among users and nonusers of calcium antagonists. Until further data from prospective clinical trials are available, we advise caution about long-term diuretic therapy in women. With regard to other antihypertensive drug classes, we suggest continuing the management of hypertension according to current treatment guidelines with little fear of any substantial cancer risk.

Introduction

Treatment of hypertension decreases cardiovascular morbidity and mortality [1–5]. Antihypertensive treatment has, however, been less effective in reducing all cause mortality [1–5]. It is not clear whether this is due to dilution of the above through lack of association between antihypertensive therapy and other causes of mortality, or by a relative increase in mortality from other causes, such as malignancy, in treated hypertensive patients. Several studies raised the possibility that antihypertensive treatment may increase the rate of malignancy. It is possible that antihypertensive therapy prolongs life by decreasing mortality from cardiovascular causes, and in turn exposes patients to increased morbidity and mortality from extracardiovascular causes such as malignancies. Furthermore, patients who are treated for hypertension are under closer medical supervision, which statistically increases the risk of a malignancy being detected when compared with healthy subjects who are under no medical supervision. Hypertension per se may also increase the risk of malignancy. We recently showed that hypertension, mainly systolic, is associated with a 23% increased risk for malignancy [6]. Alternatively, antihypertensive drugs may increase the risk of malignancy. Several antihypertensive agents have been implicated in increasing the incidence and mortality from malignancy [7–24]. A drug may increase the risk of malignancy either by being directly carcinogenic, by eliciting or accelerating other carcinogens, or by impeding defense mechanisms. Many clinical studies tried to determine whether antihypertensive drugs, in general, are carcinogenic [7–15,25].

We recently summarized the available data regarding the relation between antihypertensive treatment and malignancy [26]. In this paper we update our recent review.

Antihypertensive Treatment and Cancer

Many clinical studies have been directed to determine whether antihypertensive drugs, in general, are carcinogenic [7–14,25,27].

Dyer *et al.* [25] and Andersson *et al.* [28] found no association between antihypertensive treatment and malignancy. However, several other studies observed a significant association between antihypertensive treatment and malignancy [7–9,11,12,27]. Whereas two studies [11,12] showed an association between nondiuretic antihypertensive treatment and renal cell carcinoma, others found an increased risk for renal cell carcinoma with antihypertensive treatment in general [8,9,13,27]. One case-controlled study [7] showed an association between multiple drug use and breast cancer. In one 18-year prospective cohort study of

5249 Copenhagen men aged 40 to 59 years, use of antihypertensive medicine was highly significantly associated with risk of colon cancer, with a RR of 3.5 (95% CI, 1.6–7.5). However, in the same study, use of minor tranquilizers or sleeping pills was also related to colon cancer, and the authors could not exclude the possibility that hypertension itself and not the treatment was associated with colon cancer [10]. The association between specific antihypertensive agents and cancer is discussed below.

Reserpine and Breast Cancer

The association between the use of rauwolfia derivatives and breast cancer in women over the age of 50 years was reported originally in 1974 [15,29,30]. Three case-control studies from Boston, Bristol, and Helsinki reported similar results, indicating reserpine caused breast cancer [15,29,30]. The initial reports raised serious concern and stimulated further studies scrutinizing the safety of reserpine as an antihypertensive agent. Three additional studies [7,31,32] confirmed the positive association between breast cancer and the use of rauwolfia derivatives. Our recent analysis of all published case-controlled studies, including a total of 5852 cases of breast cancer and 9776 controls, found a statistically significant association between breast cancer and use of reserpine with an OR of 1.25 (95% CI, 1.09–1.44). Three prospective studies [33–35] failed to confirm excess rate of breast cancer in reserpine users. In the Hypertension Detection and Follow-Up Program (HDFP) a total of 2529 women were followed for 5 years in the stepped care group. Of this group, 1036 received reserpine with an average exposure of 1.97 years. The RR for breast cancer in those who took reserpine compared with those who did not was 1.28 (95% CI, 0.58–2.80) [34]. The clinical meaning of the association between breast cancer and the use of rauwolfia derivatives is unknown since reserpine is no longer used often.

Since reserpine may elevate prolactin levels, it has been suggested that reserpine also might cause prostate cancer [36]. However, at least two studies failed to observe an association between prostate cancer and use of reserpine [36,37]. Reserpine use was also not associated with other types of malignancy [31].

Diuretics

Thirteen observational studies, 10 case-controlled studies, and three cohort studies evaluated the association between the use of diuretics and renal cell carcinoma. The 10 case-controlled studies included a total of 4389 cases of renal cell carcinoma and 6566 controls. In all, the odds were greater for users of diuretics [11,12,17–21,27,38,39], with a pooled OR of 1.54 (95% CI, 1.41–1.68). The OR for renal cell carcinoma among users of diuretics relative to nonusers was 2.03 (95% CI, 1.71–2.40) in women and 1.58 (95% CI, 1.28–1.94) in men, respectively.

The relationship between diuretic use and renal cell carcinoma was further confirmed in three cohort studies comprising a population of 1,226,229 patients [16,40,41]. In these studies, the pooled age-adjusted RR related to diuretic use was 2.00 (95% CI, 1.55–2.59). The use of diuretics was associated with an increase of the age-adjusted risk for fatal renal cell carcinoma in women, where the pooled ratio was 2.43 (95% CI, 2.13–2.78), but not in men (RR, 1.29; 95% CI, 0.42–3.97).

The risk of renal cell carcinoma appeared to be related to the duration of the diuretic use [11,21,27], while the average daily dose of the diuretic seemed to carry a lesser risk [20]. In some studies, the association between diuretic use and renal cell carcinoma became weaker when other risk factors, such as the presence of hypertension, were controlled statistically [11,12,18,27,39]. However, the association remained significant in five of 10 studies [17,19–21,38]. Diuretic use also was associated with renal cell carcinoma in normotensive subjects [19,38]. Studies carried out in animals indicated that the diuretic drugs, hydrochlorothiazide and furosemide, had a possible carcinogenic effect on the kidney [42], as well as on other organs, though the effect was probably of small magnitude. Continuous treatment of rats with hydrochlorothiazide provoked massive degenerative changes in the distal converted module; these cells were reported to look like tumor cells and to express markers for tumor cells [43].

We recently showed that long-term exposure to diuretic therapy is associated with an increased risk for colon cancer [44•,45]. In the Bezafibrate Infarction Prevention (BIP) study, a total of 14,166 patients aged 45 to 74 years with a previous myocardial infarction and/or stable angina were followed for 5.6 years. Of this group, 2153 patients received diuretics and 12,013 patients received no diuretics. The hazard ratio in diuretic users compared with nonusers was 2.0 (95% CI, 1.2–3.2) for colon cancer incidence and 3.7 (95% CI, 1.7–8.3) for colon cancer mortality [44•,45]. The association between diuretic therapy and colon cancer incidence was observed only among nonusers of aspirin and was more pronounced in those who used a combination of hydrochlorothiazide and amiloride.

Unlike the association between diuretics and renal cell carcinoma and colon cancer, no association has been found between diuretic use and breast cancer [33,46,47]. Likewise, in a population-based prospective study of more than 20 years, hypertensive men receiving diuretics had no additional increased risk of cancer than nondiuretic users [28]. Moreover, in two randomly controlled trials in elderly patients, those receiving diuretics had a similar rate of malignancies as those not receiving diuretics [4,48].

β-Blockers

Three randomized controlled trials raised concern that atenolol, a cardioselective β blocker, may increase mortality from malignancy [3,49,50]. In the Medical Research

Council's randomized trial of elderly hypertensive patients, men receiving atenolol exhibited an almost twofold higher death rate from lung cancer than those receiving a diuretic or placebo [3]. This was not observed in women receiving atenolol, whose lung cancer mortality was similar to those receiving a diuretic and lower than those receiving placebo. Coope and Warrender [49], in a randomized controlled trial of elderly hypertensive patients in a primary care setting, reported an excess of fatal lung cancers in the group given atenolol compared with the control group (OR, 1.89; 95% CI, 0.88–4.08). In the randomized controlled United Kingdom Prospective Diabetes Study (UKPDS) of diabetic hypertensive patients, those receiving atenolol exhibited a higher death rate from cancer than those receiving captopril (OR, 1.87; 95% CI, 0.83–4.30) [50]. Meta-analysis of these three prospective studies, including 1879 patients receiving atenolol and 3078 patients not receiving atenolol, showed an increase rate of cancer death in those receiving atenolol, with a pooled OR of 1.36 (95% CI, 1.02–1.82). In one case-control study [27], the use of β-blockers was associated with renal cell carcinoma in women (RR, 1.8, 95% CI, 1.0–3.2).

Some laboratory studies have suggested that propranolol, a noncardioselective β-blocker, may be a possible promoter of malignancies at high doses and prolonged administration [51,52]. Propranolol has been shown to increase liver tumor incidence in male rats when administered during treatment with 3'-methyl-4-dimethylminoazobenzene [53] or with diethylnitrosamine [54]. Zavanella *et al.* [51], however, found no evidence that atenolol would promote liver carcinogenesis in rats pretreated with diethylnitrosamine.

In contrast to the above observations, one longitudinal and three case-controlled studies found no association between use of β-blockers and malignancy [14,55–57]. In one of the studies [14], the incidence rate of renal cell carcinoma was increased in those receiving β-blockers, although this could have been related to additional diuretic use in the same patients [58].

This finding notwithstanding, the overall evidence from experimental and clinical studies regarding the association of β-blocker therapy with malignancy is inconclusive but remains of concern.

Calcium Antagonists

Calcium antagonists in high doses have been used to potentiate the antitumor effect of certain antineoplastic drugs [59–64]. In animal models, calcium antagonists may reverse the resistance to antineoplastic drugs [65]. The increase in cytosolic calcium may play an important role in the regulation of cell proliferation [66]. Calcium antagonists have been shown to regulate calcium influx and thereby diminish proliferation of calcium-dependent neoplastic cells. These experimental data notwithstanding, in clinical studies there is some evidence that calcium antagonists may increase the risk of malignancy. In the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT), of 348 patients with coronary artery disease, three patients died of carcinoma, all in the nifedipine group [67]. Recently, few observational studies suggested that use of calcium antagonists could be associated with increased risk of malignancy [22–24]. In one small study of 750 elderly hypertensive patients followed for 4 years [22], the use of short-acting calcium antagonists, as a group, was associated with increased risk for malignancy compared with use of β-blockers (RR, 2.02; 95% CI, 1.16–3.54). These patients represented a part of an observational cohort study of 5052 people, aged 71 years or more, in which the adjusted hazard ratio for cancer associated with calcium antagonists was 1.72 (95% CI, 1.27–2.34) [23]. In the Cardiovascular Health Study, in which the data of 3198 elderly women (aged 65 years or more) were analyzed, an elevated risk of breast carcinoma was observed in users of calcium antagonists (hazard ratio, 2.57; 95% CI, 1.47–4.49) [24]. This association was enhanced when a high dose was used at baseline and when calcium antagonists were combined with estrogen, and persisted when the comparison group was users of other antihypertensive medication.

In contrast to the above observations, several studies found no association between calcium antagonist use and malignancy [14,48,57,68–85]. Three large case-controlled studies [14,57,78] showed no association between use of calcium antagonists and malignancy. One additional large case-controlled study found no association between long-term calcium antagonist use and breast cancer [79]. Another case-controlled study suggests that calcium antagonists do not increase the risk of prostate cancer [80]. Meta-analysis of seven longitudinal studies, including 11,581 calcium antagonist users and 35,211 nonusers, showed an identical risk for malignancy among calcium antagonist users compared with nonusers (Table 1) (OR, 1.05; 95% CI, 0.94 –1.18).

Meta-analysis of eight randomized controlled studies including 9091 calcium antagonists users and 11,007 nonusers followed for several years showed a similar risk for malignancy among calcium antagonist users compared with nonusers (Table 1) (OR, 0.91; 95% CI, 0.80–1.04).

In addition, Sorensen *et al.* [81•] recently extended their previous observation [76]. They identified 967 cancers among 23,167 individuals who received at least two prescriptions for calcium antagonists between January 1, 1989 and December 31, 1995, and were followed for 3.2 years in Denmark. This number was identical to that expected on the basis of rates from the Danish Cancer registry [81•]. Thus, the existing data make it unlikely that calcium antagonists increase the risk of malignancy.

Angiotensin Converting Enzyme Inhibitors

In several studies it was shown that in vitro captopril can inhibit the growth of neoplastic cells such as pancreatic ductal cancer cells [86], human mammary carcinoma cells [87], and human neuroblastoma cells [88]. In vivo, capto-

Table 1. Longitudinal studies relating calcium antagonists to malignancy

Study	Type of study	CA users cancer yes/no, *n/n*	Nonusers cancer yes/no, *n/n*	OR (95% CI)
Borhani *et al.* [70]	RC	13/429	20/421	0.64 (0.3–1.36)
Packer *et al.* [71]	RC	9/562	10/572	0.92 (0.34–2.46)
Gong *et al.* [72]	RC	2/785	8/738	0.24 (0.03–1.19)
Staessen *et al.* [74]	RC	73/2325	82/2215	0.85 (0.61–1.18)
Liu *et al.* [73]	RC	17/1236	20/1121	0.77 (0.38–1.54)
Lindoholm *et al.* [48]	RC	209/1987	416/4002	1.01 (0.85–1.21)
Kanamasa *et al.* [84]	RC	18/548	13/475	1.20 (0.55–2.62)
Sajadieh *et al.* [85]	RC	57/821	73/821	0.78 (0.54–1.14)
	Pooled	398/8693	642/10365	0.91 (0.80–1.04)
Pahor *et al.* [22]	Longitudinal	27/175	28/396	2.18 (1.21–3.95)
Pahor *et al.* [23]	Longitudinal	47/404	373/4228	1.32 (0.94–1.84)
Jonas *et al.* [68]	Longitudinal	22/504	114/1967	0.75 (0.46–1.23)
Hole *et al.* [69]	Longitudinal	134/2163	194/2716	0.87 (0.69–1.10)
Braun *et al.* [75]	Longitudinal	129/5482	117/5426	1.09 (0.84–1.42)
Cohen *et al.* [82]	Longitudinal	16/117	548/2830	0.71 (0.40–1.23)
Michels *et al.* [83]*	Longitudinal	122/2239	730/15544	1.16 (0.95–1.42)
	Pooled	497/11084	2104/33107	1.05 (0.94–1.18)

*Women only.
CA—calcium antagonist; RC—randomized controlled.

pril treatment reduces the incidence and growth of radiation-induced cutaneous squamous cell carcinomas [89] and sarcomas, as well as the growth of hepatomas [90]. Despite the ability of angiotensin converting enzyme (ACE) inhibitors to inhibit proliferation of neoplastic cells, there is indirect evidence that use of ACE inhibitors may be associated with increased cancer incidence or mortality. Several case reports described an association between the use of ACE inhibitors and malignancy [91–95]. In two case reports, captopril was associated with Kaposi's sarcoma [93,95], in one case report enalapril was associated with lung cancer [91], and in two case reports captopril and enalapril were associated with mycosis fungoides-like lesions [93,95]. In two randomized controlled trials, ACE inhibitors appeared to be associated with increased mortality from cancer [96,97]. In the Left Ventricular Dysfunction (SOLVD) prospective randomized controlled trial of patients with congestive heart failure followed for an average duration of 41.4 months, those who received enalapril had a slightly higher incidence of malignancy than those who received placebo (OR, 1.59; 95% CI, 0.90–2.82) [96]. In another prospective randomized controlled trial of 583 patients with renal insufficiency followed for 3 years, those who received benazepril exhibited a slightly higher incidence of malignancy than did those who received placebo (OR, 1.52; 95% CI, 0.45–5.42) [97]. In the recent Swedish Trial in Old Patients with Hypertension 2 (STOP 2) randomized controlled trial, the risk of cancer was similar among ACE inhibitor users and nonusers [48]. Meta-analysis of the three studies, including 3574 patients receiving ACE inhibitors and 5567 patients not receiving ACE inhibitors, showed a slight increased incidence of malignancy in those receiving ACE inhibitors, with a pooled OR of 1.11 (95% CI, 0.93–1.31).

In contrast, case-controlled and longitudinal studies showed no relation between use of ACE inhibitors and malignancy [14,18,22,24,57,78]. A recent case-controlled study showed that long-term use of ACE inhibitors does not affect the risk of developing breast cancer [79]. Most provocatively, in a recent longitudinal study, long-term use of ACE inhibitors seemed to exert a protective effect against malignancy [98•]. In this study, the RRs of incidence and fatal cancer among patients receiving ACE inhibitors compared with controls were 0.72 (95% CI, 0.55–0.92) and 0.65 (95% CI, 0.44–0.93), respectively.

Further large randomized controlled trials are required to evaluate the association between ACE inhibitors and malignancy.

Other Antihypertensive Agents and Cancer

In one case report, methyldopa was associated with lymphoproliferative disorders [99]. In one retrospective study [100] of 82 patients with biliary carcinoma, a higher than expected prevalence of methyldopa therapy was found. However, a subsequent study [101] failed to confirm this association. Two case-controlled studies found no relation between methyldopa use and breast cancer [46,47].

In case-controlled studies, no association was found between hydralazine use and either breast cancer [102] or lung and colorectal cancers [103]. One small study of the relationship between the use of α-blockers and renal cell carcinoma showed no association [18].

Conclusions

The relationship between diuretic therapy and renal cell carcinoma is supported by biochemical, experimental, clinical, and epidemiologic data. One study suggested that diuretic therapy may also be associated with colon cancer. The relationship between rauwolfia and breast cancer, although statistically significant, is of little clinical concern because reserpine is no longer extensively used. The relationship between β-blockers and malignancy remains unproven. Recent clinical trials eliminated the proposed excess of cancer incidence among calcium antagonist users; current data do not support an association between ACE inhibitors and malignancy. Given that differences in cardiovascular endpoints among various drug classes have been small and inconsistent, more attention should be paid to the effects of these drugs on extracardiovascular morbidity and mortality, such as malignancy.

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