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EDITORIAL

New data on antihypertensive drugs and risk of cancer: should we worry?

Cardiovascular disease (CVD) and cancer are the two leading causes of mortality worldwide. Over the last four decades, there has been a trend towards a decrease in age-standardized deaths due to both CVD and cancer [1]. However, today, the numbers of deaths due to CVD and cancers are showing opposite trends: deaths attributed to CVD are continuing to decline, whereas cancer deaths are remaining stable or increasing due, in part, to the aging of populations [1,2]. Thus, for the first time ever, cancer deaths exceeded the number of fatalities due to CVD in several American states [1] and European countries [3]. Healthier population lifestyles, earlier diagnoses, more effective treatments and improved management of CVD risk factors may account for the global reduction in CVD mortality.

Lowering blood pressure (BP) with antihypertensive drugs reduces CVD morbidity and mortality without increasing non-CVD mortality [4]. However, as soon as the first BP lowering compounds appeared on the market, concerns were raised that they might increase the risk of developing cancers and hence, cancer deaths. This was the case of reserpine and risk of breast cancer, diuretics and risk of renal cell carcinoma, and also calcium channel blockers (CCB), beta-blockers, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) and risk of various cancers [5–7]. These early observations have generated fear and anxiety among patients, frustration and concern among prescribing physicians and many debates within the scientific community.

The associations between antihypertensive drug classes and risk of cancer observed in early retrospective observational studies were often negated later on, using data from meta-analyses of prospective randomized trials [8,9] or from larger population-based cohort studies using electronic healthcare databases [10]. Further, protective rather than detrimental effects of renin-angiotensin system blockers on cancer risk were even suggested [11]. In general, reported associations were weak and the absolute risk relatively low in comparison to the CV benefits afforded by these drugs. Hence, health authorities have generally considered that the risk/benefit ratio was strongly in favor of use of antihypertensive drug classes for the management of CVD. When assessing associations between antihypertensive drugs and cancer, it is very difficult to rule out the effects of competing risks such as smoking, obesity or toxic exposure. It is particularly difficult to disentangle the role of hypertension per se from that of antihypertensive therapies [12]. Hypertension has been found to be a risk factor for cancer [13] and cancer and hypertension share several common pathogenic mechanisms and risk factors, including inflammation, oxidative stress, and growth factors, which may explain the association between the two clinical entities [14,15].

Recently, three new studies have examined the relationship between antihypertensive drug use and cancer. The first examined the association between the use of hydrochlorothiazide (HCTZ) and the risk of basal cell (BCC) and squamous cell (SCC) carcinoma in a case-control study using data from the Danish Cancer Registry and the Danish Prescription Registry [16]. In this analysis, the use of high cumulative doses of HCTZ (>50 g) was associated with a dose-dependent increase in the risk of BCC (odds ratio 1.29, 95% CI: 1.23–1.35) and SCC (odds ratio 3.84, 95% CI: 3.68–4.31). The proportion of skin cancers attributable to HCTZ use was 0.6% for BCC and 9.0% for SCC. The risk was higher in women than men and in patients <50 years old. This increased risk was not observed with chlorthalidone or indapamide. The mechanism hypothesized is the photosensitizing effect of HCTZ, a property not described with other diuretics. A major limitation of this analysis is the absence of information on sun habits and ultraviolet exposure, a major risk factor for SCC. Moreover, the Danish population, i.e., a white population with fair skin and blond hair, is known to be at high risk of skin cancers. Whether the same level of risk exists in other populations needs to be investigated. In a second analysis using the same databases, the same authors reported an increase in the risk of nodular melanoma with the use of HCTZ [17]. The risks of both BCC and nodular melanoma were relatively low. Of note, in a recent review of the literature and meta-analysis of skin cancer and use of antihypertensive drugs, CCBs were associated with an increased skin cancer risk (OR 1.14, 95% CI 1.07–1.21), and β-blockers were associated with cutaneous melanoma (OR 1.21, 95% CI 1.05–1.40) [18]. In contrast to the Danish studies mentioned above, there was no association between thiazide diuretics, ACEi or ARB use and skin cancer risk.

The third recent publication assessed whether use of ACEIs, compared with ARBs, is associated with an increased risk of lung cancer [19]. This was a population

based cohort study of patients who received ACEIs or ARBs between 1995 and 2015, with a mean follow-up of 6.4 years. ACEI users had a 14% greater risk of developing lung cancer than ARB users. As acknowledged by the authors, "*the magnitudes of the observed estimates are modest*". These results were criticized in many letters to the editor on a number of grounds: (1) The association between ACEI use and risk of lung cancer did not vary by smoking status. Surprisingly, complemental analyses showed that there was no increased risk in non-smokers who used ACEIs or ARBs. (2) There was no information on the intensity of smoking among smokers. (3) Several biases, including residual confounders (socio-economic status, other medications, smoking, and a detection bias due to cough), could have contributed to the association. (4) The role attributed to bradykinin as potential mediator of the increased risk of lung cancer in ACEI users is considered to have low plausibility. (5) Several previous meta-analyses have reported either no effect or a protective effect of ACEIs against lung cancer in prospective randomized controlled trials as well as observational studies [8,20]. Thus, the British observation may well be a chance finding. Therefore, this publication should not dissuade us from prescribing ACEIs for patients with hypertension and related CVD.

As millions of hypertensive patients are receiving HCTZ alone or in combination, the question is: How should this information be integrated into hypertension management? Today, neither the authors of the publications nor the health authorities recommend stopping HCTZ because the risk/benefit is strongly in favor of the CV benefits of HCTZ. Patients who are using HCTZ should be informed about the potential risk and should be encouraged to examine their skin regularly and to avoid over-exposure to UV as recommended by dermatologists for the prevention of skin cancers in all persons. Physicians should examine their patients' skin regularly as well. In case of a positive history of skin cancer or extreme worry of the patient, a switch to chlorthalidone or indapamide could be proposed. If people are really concerned by the risk of lung cancer while taking antihypertensive medications, they should first stop smoking and promote clean air legislation.

Disclosure statement

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