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Anti-hypertensive drugs and skin cancer risk: a review of the literature and meta-analysis

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ABSTRACT

Introduction: Several anti-hypertensive drugs have photosensitizing properties, however it remains unclear whether long-term users of these drugs are also at increased risk of skin malignancies. We conducted a literature review and meta-analysis on the association between use of anti-hypertensive drugs and the risk of cutaneous melanoma and non-melanoma skin cancer (NMSC).

Methods: We searched PubMed, EMBASE, Google Scholar and the Cochrane Library, and included observational and experimental epidemiological studies published until February 28th, 2017. We calculated summary relative risk (SRR) and 95% confidence intervals (95% CI) through random effect models to estimate the risk of skin malignancies among users of the following classes of anti-hypertensive drugs: thiazide diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB) and β-blockers. We conducted sub-group and sensitivity analysis to explore causes of between-studies heterogeneity, and assessed publication bias using a funnel-plot based approach.

Results: Nineteen independent studies were included in the meta-analysis. CCB users were at increased skin cancer risk (SRR 1.14, 95% CI 1.07–1.21), and β-blockers users were at increased risk of developing cutaneous melanoma (SRR 1.21, 95% CI 1.05–1.40), with acceptable between-studies heterogeneity (I^2 < 50%). There was no association between thiazide diuretics, ACEi or ARB use and skin cancer risk. We found no evidence of publication bias affecting the results.

Conclusion: Family doctors and clinicians should inform their patients about the increased risk of skin cancer associated with the use of CCB and β-blockers and instruct them to perform periodic skin self-examination. Further studies are warranted to elucidate the observed associations.

1. Introduction

Cutaneous melanoma and non-melanoma skin cancer (NMSC) are the most frequent skin cancer types. Melanoma incidence has steadily increased over the past decades among fair-skinned populations of European ancestry (Erdmann et al., 2013). Melanoma has an excellent prognosis when diagnosed at an early stage, which is the most common occurrence; however, because of its high incidence and poor survival of advanced stages, its burden of disease is substantial in industrialized countries (Linos et al., 2009; Holterhues et al., 2013; Monshi et al., 2016). NMSC is the most common human malignancy and its incidence is increasing globally (Lomas et al., 2012). NMSC prognosis is usually excellent; however, it absorbs a significant amount of healthcare resources for its diagnosis and treatment (Guy and Ekwueme, 2011; Vallejo-Torres et al., 2014; Hollestein et al., 2014).

Despite originating from different cell types, melanoma and NMSC share some risk factors. Both skin cancer types are most common among fair-skinned individuals with blue/green eyes and blonde/red hair, who burn easily and have many naevi (Gandini et al., 2005a; Gandini et al., 2005b; Gandini et al., 2005c). The main environmental risk factor for

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BCC, basal cell cancer; CCB, calcium channel blockers; CI, confidence intervals; NMSC, non-melanoma skin cancer; RR, relative risk; SCC, squamous cell cancer; SRR, summary relative risks; UV, ultraviolet

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skin cancer development is exposure to ultraviolet (UV) radiation. Both solar radiation and UV-emitting tanning devices are classified as carcinogenic to humans (International Agency for Research on Cancer (IARC), 2017; Boniol et al., 2012).

Drug-induced photosensitivity is defined as the development of cutaneous disease due to the interaction between a chemical agent and UV radiation (Monteiro et al., 2016). Drug-induced skin disorders include a wide spectrum of acute phototoxic and photoallergic reactions triggered by exposure to sunlight or artificial UV radiation drugs. Photosensitizing agents include many medications that can be administered in a continuous way for the treatment of chronic conditions (e.g. oral hypoglycaemic agents, non-steroidal anti-inflammatory drugs, and antidepressants (Vitiligo Support International, 2017)), and there is concern that long-term users of these drugs may also be at increased skin cancer risk. In particular, several commonly used anti-hypertensive drugs are classified as photosensitizers, and this has been suggested as an explanation for the association between high blood pressure and skin cancer risk that emerged in a few studies (Rosengren et al., 1998; Nagel et al., 2012). In recent years, the hypothesis of a causal link between the treatment of hypertension and the risk to delevop skin cancer (melanoma and NMSC) has been investigated by several authors, with conflicting results (Ruiter et al., 2010; de Vries et al., 2012; Hole et al., 1998; Christian et al., 2008). To help clarify this issue, we conducted a literature review and meta-analysis of published papers on the association between use of anti-hypertensive drugs and risk to develop cutaneous melanoma and NMSC.

2. Materials and methods

The exposure of interest in this literature review and meta-analysis was the treatment with any of the following classes of anti-hypertensive drugs: thiazide diuretics, loop diuretics, potassium-sparing diuretics, aldosterone receptor antagonists, calcium channel blockers (CCB), β-blockers, angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARB). Outcomes of interest were cutaneous melanoma, NMSC and its two main subtypes, basal cell cancer (BCC) and squamous cell cancer (SCC).

We abided by the MOOSE guidelines in planning, conducting and reporting the present literature review and meta-analysis (Stroup et al., 2000). We searched studies published until February 28th, 2017, in PubMed, EMBASE, Google Scholar, the Cochrane Library, the Grey Literature Report website (www.greylit.org) and the OpenGrey repository (www.opengrey.eu/). We conducted the literature search using several strings all having the general structure “exposure AND outcome”, in which one of the following terms was used as the exposure of interest: “hypertension”, “anti-hypertensive”, “diuretic(s)”, “β(beta)-blocker(s)”, “calcium channel blocker(s)”, “calcium antagonist(s)”, “angiotensin converting enzyme inhibitor(s)”, and “angiotensin receptor blocker(s)”; and one of the following terms was used as the outcome of interest: “melanoma”, “basal cell cancer”, “squamous cell cancer”, and “skin cancer”. No time or language restrictions were applied, as long an abstract was available in English. Papers were initially screened by perusing their title and abstract: those that were considered as potentially eligible were obtained and read in full copy (after being translated into English when necessary). The reference list of all retrieved papers was searched to find additional publications. No attempt was made to contact authors for obtaining missing data.

To be considered eligible for inclusion, a paper should report (or provide sufficient information to estimate) a measure of relative risk (RR) (i.e. incidence rate ratio, hazard ratio, risk ratio, odds ratio, or standardized incidence ratio) and a corresponding measure of statistical uncertainty (i.e. 95% confidence intervals [CI], standard errors, variance, or exact *p*-value) for the association between the treatment with a class of anti-hypertensive drugs (or a single drug) and the risk of developing skin cancer (melanoma, NMSC, BCC or SCC) during the treatment. We included papers that compared the risk of skin cancer between drug users vs. non-drug users (cohort studies with internal comparison, case-control studies and randomized clinical trials), or between drug users vs. the general population (cohort studies with external comparison). Instead, we excluded papers which:

- compared the risk of skin cancer among users of different classes of anti-hypertensive drugs (Pasternak et al., 2011);.
- Made no distinction between different classes of anti-hypertensive drugs with diuretic activity (McDonald et al., 2014), or between ACEi and ARB (Xiong et al., 2013; Dyer et al., 2012; Moscarelli et al., 2010);.
- Focused on premalignant skin lesions or skin malignancies other than melanoma and NMSC (Placzek et al., 1999; Traianou et al., 2012; Jahan-Tigh et al., 2013);.
- Evaluated the effect of anti-hypertensive drugs on melanoma survival (De Giorgi et al., 2013; Moser et al., 2014);.
- Reported on the association between blood pressure/hypertension and skin cancer risk (Rosengren et al., 1998; Nagel et al., 2012; Lindgren et al., 2005; Stocks et al., 2012).

Ecological studies, case reports, editorials, reviews and meta-analysis were not included. Two authors (SG and SC) independently decided on the eligibility of each paper; all conflicts were solved via consensus.

Only one RR estimate (adjusted for the maximum number of confounding variables) for the association between the treatment with a given class of anti-hypertensive drugs and the risk of a given skin cancer type was extracted from each study. The RR estimates for specific drugs (e.g. enalapril) were only extracted when there was no measure of relative risk for the corresponding class of anti-hypertensive drugs taken as a whole (e.g. ACEi); in case an RR estimate was available for two or more drugs belonging to the same class of anti-hypertensive drugs (e.g. enalapril and captopril), but not for the class taken as a whole e.g. ACEi, as in the paper by Kaae et al. (Kaae et al., 2010), we used the RR estimate relating to the drug that was used by the highest number of study participants (e.g. enalapril in the example above). When an RR estimate was available from two or more studies that were not independent from one another, we used the estimate from the study with the largest number of skin cancer cases or, in case of equal sample size, from the most recent study. An exception to the latter criterion was made for the study by Kaae et al. (Kaae et al., 2010): when the lower and/or upper 95%CI were overlapping with the point estimate of relative risk (which did not allow to calculate a standard error), we inputted data from Schmidt et al. (Schmidt et al., 2015), which was based on a smaller study population (Northern Denmark instead of the entire country) and included a lower number of skin cancer cases.

All RR estimates and corresponding 95%CI were transformed into log relative risk and corresponding variance using the Greenland’s formula (Greenland, 1987), ignoring the distinction between the different measures of relative risk. We extracted the following information from each study: study design; country and years in which the study was conducted; source, number, and gender and age distribution of cases and controls/non-cases; average follow-up time (for prospective studies); type of matching (if any) and variables used to match; exact definition of exposure; statistical methods and variables used for adjustment.

We used random effect models with maximum likelihood estimation (van Houwelingen et al., 2002) to calculate summary relative risks (SRR) and corresponding 95%CI (assuming an underlying t distribution) for the association between the treatment with a class of anti-hypertensive drugs and skin cancer risk (and separately for its subtypes: melanoma, NMSC, BCC and SCC) whenever there were RR estimates from three or more independent studies. Dose-response analysis was conducted using a two-step procedure: in the first step, a linear model was fitted to estimate the relative risk of skin cancer corresponding to a linear increase in exposure in each study (Greenland and Longnecker,