Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies

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With the exception of renal cell carcinoma, studies assessing the association between hypertension and other cancers are inconsistent. We conducted a meta-analysis to assess this evidence. We included observational studies investigating the association between any definition of hypertension or systolic and diastolic blood pressure and risk of any cancer, after searching PubMed until November 2017. We calculated summary relative risks (RR) and 95% confidence intervals (CI) using inverse-variance weighted random effects methods. A total of 148 eligible publications were identified out of 39,891 initially screened citations. Considering only evidence from 85 prospective studies, positive associations were observed between hypertension and kidney, colorectal and breast cancer. Positive associations between hypertension and risk of oesophageal adenocarcinoma and squamous cell carcinoma, liver and endometrial cancer were also observed, but the majority of studies did not perform comprehensive multivariable adjustments. Systolic and diastolic blood pressure were positively associated with risk of kidney cancer but not with other cancers. In addition to the previously well-described association between hypertension and risk of kidney cancer, the current meta-analysis suggested that hypertensive individuals may also be at higher risk of colorectal and breast cancer. However, careful interpretation is required as most meta-analyses included relatively small number of studies, several relative risks had weak or moderate magnitude and maybe affected by residual confounding.

Hypertension and cancer are two multifactorial, severe and chronic conditions. Hypertension is a major health problem worldwide, as it affects approximately 3 in 10 adults over age 20, leading to high morbidity and mortality. It is responsible for almost 50% of heart disease, stroke, and heart failure and about 14% of total deaths in 2015 were related to hypertension. In addition, an estimated 10% of the healthcare spending is directly related to increased blood pressure and its complications.

Cancer is also a leading cause of morbidity and mortality. Worldwide, there were approximately 18 million new cases and 9.6 million cancer-related deaths in 2018, and these numbers are expected to rise within the next two decades. Therefore, if blood pressure and/or hypertension are associated with the risk of cancer, this may have important public health consequences.

Renal cell carcinoma is the only cancer type that has been consistently associated with hypertension, although it is not clear yet whether reverse causation explains part or all of this association. Claims of association also exist for colorectal, breast, endometrial and prostate cancer, but the evidence is inconsistent. But recently there has been an influx of new studies investigating the association of metabolic syndrome, which includes

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hypertension, and cancer risk, and therefore we conducted a systematic review and meta-analysis to summarize and evaluate this literature.

Methods

Literature search and data extraction. We searched for eligible published studies in PubMed from inception to November 2017 using the following search algorithm: (blood pressure OR hypertension OR "metabolic syndrome") AND (cancer OR neoplas* OR malignan* OR tumor OR carcinoma), and also hand-searched for potential missed studies in the references of eligible systematic or narrative reviews. We considered all cohort and case-control studies conducted in humans assessing the association between systolic blood pressure (SBP) or diastolic blood pressure (DBP) or hypertension and risk of any cancer development or cancer death. Hypertension was defined as any of the following: self-reported or measured SBP or DBP higher than predefined cut-off points (e.g. WHO or NCEP/ATP III criteria), self-reported medical history of hypertension or drug-treated hypertension. When the exposure was metabolic syndrome, we only used the hypertension component. We excluded narrative or systematic reviews, case-series or case-reports, cross-sectional studies, prognostic studies among cancer patients, studies in children, cohort studies with a sample size of less than 100 total individuals, case-control studies with less than 100 cancer cases, studies that did not provide enough information for calculating measures of association, studies in other than the English language and studies of pre-malignant outcomes (e.g., colorectal adenomas). Whenever published reports pertained to the same cohort evaluated at different follow-up periods, we retained the publication with the longer follow-up.

We recorded information from each eligible study on author name, year and journal of publication, study design, sample size, population characteristics, definition of hypertension, relative risk (RR), 95% confidence interval (CI) and adjustments for confounders. When results from multiple statistical models were reported, we always retained the most adjusted model. The literature search and data extraction were performed independently by two investigators (AS and XT), and data was re-checked for consistency by a third author (SC).

We used the “Newcastle-Ottawa Scale” to assess the quality of the included studies, and this task was performed independently by two investigators (AS and SC), and disagreements were resolved by a third author (KKT). Based on this tool, every study was judged on eight quality items, grouped into three categories: i) selection, ii) comparability of study groups and iii) exposure or outcome ascertainment for case-control and cohort studies, respectively. A star was awarded for every quality item for a maximum of 9 stars for the highest quality studies.

Statistical analyses. Our primary analysis included only prospective studies (e.g., cohort or nested case-control designs), whereas analyses including case-control studies are provided in the online supplement. We conducted separate meta-analyses according to systolic or diastolic blood pressure and hypertension. Analyses for systolic and diastolic blood pressure used both a top to bottom category comparison approach and a dose-response approach per 10 mmHg. Studies that reported a dose-response estimate were either pooled directly or after re-scaling to the corresponding increment unit using the generalized weighted least-squares regression model approach. We summarized RRs and 95% CIs using fixed-effects and random-effects meta-analysis models, if three or more studies were available per exposure and outcome comparison. Between-study heterogeneity was assessed by the Cochran’s Q test and the I² statistic. 95% prediction intervals were also calculated to further assess heterogeneity, which represents the range in which the effect estimates of future studies will lie. Subgroup meta-analyses were conducted according to sex, study design (prospective vs. case-control) and adjustment factors (at least age vs. age plus further multivariable adjustment). Presence of small-study effects was assessed using the Egger's regression asymmetry test. Analyses were performed in STATA 12 (College Station, Texas). All p-values were two-tailed. The study is reported according to the MOOSE checklist.

Results

Study characteristics. Figure 1 presents the meta-analysis flowchart. A total of 148 individual studies met the eligibility criteria out of the 39,891 initially screened citations. Supplemental Table 1 provides a detailed description of the characteristics of all included studies. Specifically, we included 85 prospective studies, 72 of which were cohort studies, 11 were nested case-control studies, and 2 were record-linkage studies, and 63 case-control studies. Most studies (n = 133; 90%) investigated associations with cancer incidence. A total of 48 (32%) studies were conducted only in men, whereas 57 (39%) studies were conducted only in women. The majority of the studies (n = 51; 34%) were conducted in the USA followed by Scandinavian countries (n = 15; 10%), Italy (n = 13; 9%), UK and Korea (n = 7; 5%), and finally Japan with 6 studies (4%). Out of the 128 studies that used hypertension as the exposure of interest, this was defined in 20 studies (16%) using the NCEP-ATPIII criteria, in 17 studies (13%) used the WHO definition, in 4 studies (3%) used ≥160/95 mmHg, and in 38 studies (30%) pertained to self-reported hypertension, 16 studies (13%) used self-reported drug treatment for hypertension and 26 studies (20%) used a combination of self-reported disease and treatment, whereas 7 studies used other definitions.

Detailed information on the quality assessment for each study, using the Newcastle-Ottawa scale, can be found on Supplementary Table 2. For prospective studies, the median number of stars per study was 7, and the inter-quartile range (IQR) was 1. Case-control studies scored lower with a median of 6 and IQR of 2. However, the minority of prospective (31%) and case-control studies (19%) adjusted for age and three of the following five potential confounders, namely body mass index, smoking, alcohol, physical activity and family history of cancer.

Evidence Synthesis. For the primary analysis using only prospective studies, we conducted 30 meta-analyses of hypertension and 16 different cancers, and 29 meta-analyses between SBP or DBP and 11 cancers. Summary random effects relative risk estimates and 95% CIs per cancer site, heterogeneity statistics, 95%
prediction intervals and tests of small-study effects are summarized in Fig. 2 for hypertension, in Fig. 3 per 10 mmHg of systolic and diastolic blood pressure, and in Supplemental Fig. 1 for top vs. bottom category comparisons of systolic and diastolic blood pressure. Supplemental Table 3 describes in more detail the meta-analyses of prospective studies for the association between hypertension, systolic or diastolic blood pressure and risk of cancer, and Supplemental Table 4 includes meta-analyses of both prospective and case-control studies. Supplemental Figs 2–60 depict all forest plots by cancer site using only prospective studies, and Supplemental Figs 61–79 include both prospective and case-control studies.

We found a statistically significant association between hypertension and risk of kidney cancer (Fig. 2; n = 18 prospective studies; summary random effects RR, 1.54; 95% CI, 1.39–1.70)⁴⁷,⁴⁸,⁵⁶,⁶⁶,⁶⁷,⁷⁶,⁸⁰,⁸³,⁹¹–⁹⁴,⁹⁹,¹⁰³,¹⁰⁵,¹⁰⁷,¹⁰⁹. We observed large heterogeneity (I², 63.1%), but no indication for small study effects (Supplemental Fig. 26). When we meta-analysed studies clearly mentioning that only renal cell carcinoma cases were used, similar results were obtained (n = 12 studies, RR, 1.55; 95% CI, 1.36–1.76; I², 64.7%)⁴⁶,⁵⁶,⁶⁶,⁷⁶,⁸³,⁹¹,⁹³,⁹⁴,¹⁰⁵,¹⁰⁸–¹⁰⁹,¹⁰⁹. The association between hypertension and kidney cancer was statistically significant in both women (n = 8 studies⁵⁶,⁶⁶,⁷⁶,⁸³,⁹¹,⁹³,⁹⁴,¹⁰⁵, RR, 1.63; 95% CI, 1.44–1.84; I², 0%) and men (n = 7 studies⁴⁶,⁵⁶,⁶⁶,⁷⁶,⁹³,⁹⁴,¹⁰⁵, RR, 1.29; 95% CI, 1.13–1.48; I², 0%) without between-study heterogeneity within each sex-specific analysis, but considerable larger estimates were observed in women (P-heterogeneity, 0.01). Similar results were obtained in subgroup meta-analyses of prospective studies that at least adjusted for age vs. studies that adjusted for age plus at least three of the following five risk factors: body mass index, smoking, alcohol, physical activity and family history of kidney cancer (Table 1). When 14 case-control studies were meta-analysed together with the prospective studies, a summary RR of 1.60 (95% CI, 1.48–1.73; I², 61.3%) was observed (Supplemental Table 4). We also observed statistically significant associations between SBP (Fig. 3; RR per 10 mmHg, 1.05; 95% CI 1.03–1.06; I², 57%) and DBP (RR, 1.07; 95% CI, 1.04–1.10; I², 55%) with kidney cancer, but these meta-analyses had evidence of small-study effects (Supplemental Figs 40–48; P 0.03).
Figure 2. Summary relative risks and 95% confidence intervals of prospective studies for the association between hypertension and cancer risk. Abbreviations: ACC, adenocarcinoma; SCC, squamous cell carcinoma; RL, record-linkage studies; HCC, hepatocellular carcinoma; ECC, extrahepatic cholangiocarcinoma; CNS, central nervous system, NA, Not applicable.

Figure 3. Summary relative risks and 95% confidence intervals of prospective studies for the association between cancer risk and 10 mmHg increase in systolic and diastolic blood pressure. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
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performed, because there were not enough studies using continuous BP data. Using data from 5 prospective studies, we also noted a statistically significant association between hypertension and liver cancer (Fig. 2; RR, 1.23; 95% CI, 1.16–1.30; I², 0%), but four out of the five studies did not perform comprehensive multi-variable adjustments.

The meta-analysis of 4 prospective studies between hypertension and esophageal adenocarcinoma yielded a statistically significant positive association (Fig. 2; RR 1.11; 95% CI, 1.01–1.21; I², 5.5%). We identified only 2 prospective studies on hypertension and esophageal squamous cell carcinoma, and the meta-analysis yielded a statistically significant estimate (RR, 1.74; 95% CI, 1.32–2.30; I², 0%), but was based only on 248 cases. Finally, the meta-analysis of all 6 prospective studies on total oesophageal cancer yielded a statistically not significant estimate (RR, 1.18; 95% CI, 1.00–1.38; I², 67.5%). Most of these studies however did not perform comprehensive multivariable adjustments.

We did not observe statistically significant associations between hypertension or SBP/DBP and cancer of stomach, gallbladder, pancreas, lung, cervix, prostate, bladder and brain. There were not enough studies using continuous BP data for these cancers. For colorectal cancer, we observed a 9% relative increase in colorectal cancer due to hypertension using both cohort and case-control studies. To our knowledge, no clear mechanism has been proposed to link hypertension to colorectal cancer, but hypertension is reported to increase cancer risk by blocking apoptosis. Current findings should be approached with caution given the scarcity of well-designed studies in the literature.

In a meta-analysis of 13 prospective studies, hypertension was associated with a 7% higher risk of total breast cancer. Only five of these studies performed comprehensive multivariable adjustments, where the risk was 10% for total breast cancer and 38% for post-menopausal disease comparing hypertensive to normotensive individuals. These findings are in agreement with a recent meta-analysis of 12 prospective studies by Han et al. that reported a 7% higher risk for total breast risk in hypertensive individuals regardless of performed adjustments. Suggestive mechanisms to explain this association include blocking of apoptosis, adipose tissue related hypoxia and chronic inflammation promoting reactive oxygen species formation.

We did not observe associations between hypertension or blood pressure and risk of stomach, gallbladder, pancreas, lung, cervix, prostate, bladder and brain cancer. A recent meta-analysis examining the association between hypertension and risk of prostate cancer used 21 cohort and case-control studies and found a statistically significant 8% higher risk, but again this report shaped its conclusions without taking into consideration individual study design and quality.

Discussion
In this meta-analysis of observational studies, we summarized the associations between hypertension or blood pressure and risk of 18 cancers. We confirmed the positive association between hypertension and risk of kidney cancer, but also found possible positive associations between hypertension and risk of colorectal, breast, endometrial, liver and oesophageal cancer. We did not observe statistically significant associations for cancers of the stomach, gallbladder, pancreas, lung, breast, cervix, prostate, bladder and brain.

Over the past few decades, many prospective observational studies have investigated the association between hypertension and risk of kidney cancer. Most of these studies have showed a positive association, which summarized in our meta-analysis to a 54% higher risk that was stronger in women compared to men (63% vs. 29%). Furthermore, a dose-response approach revealed a 5% and 7% higher risk for kidney cancer per every 10 mmHg higher SBP and DBP, respectively. Similar associations have been reported in previous meta-analyses. However, this association is complex and it is still unclear whether it is causal, as both hypertension and cancer are affected by similar risk factors such as smoking, obesity, alcohol consumption and physical inactivity. Several studies have not adjusted for many of these potential confounders, but four prospective studies that did follow a comprehensive adjustment approach still observed positive associations as outlined in the current and other meta-analyses. Future large prospective studies or consortia thereof and Mendelian randomization studies are needed to clarify if the observed association is likely causal. A recent Mendelian randomization study of renal cell cancer showed a positive association with diastolic but not with systolic blood pressure. The biological mechanisms underlying the association between hypertension and kidney cancer remain unclear, but are hypothesized to involve chronic renal hypoxia, lipid peroxidation and deregulation of renin-angiotensin system and specifically the overexpression of angiotensin receptors and the down-regulation of the angiotensin-converting enzyme.

We also estimated a positive summary association between hypertension and risk of colorectal cancer with a higher risk of 11% for hypertensive individuals. This meta-analysis included data from 13 prospective studies, only four of which performed comprehensive multivariable adjustments and the potential higher risk was 30% for hypertensive individuals in these studies. Esposito et al. published another meta-analysis in 2013, which found a 9% relative increase in colorectal cancer due to hypertension using both cohort and case-control studies. To our knowledge, no clear mechanism has been proposed to link hypertension to colorectal cancer, but hypertension has been shown to increase cancer risk by blocking apoptosis. Current findings should be approached with caution given the scarcity of well-designed studies in the literature.
Strengths of the present meta-analysis include the comprehensive search strategy with the inclusion of “metabolic syndrome” in the search algorithm, the wide scope of investigating associations with many individual cancers and the detailed sensitivity and subgroup analyses. There are also limitations in this work. First, the association between hypertension and malignancy may be due to shared risk factors such as age, smoking, alcohol consumption, diet and adiposity. Unfortunately, the majority of the literature in this field contains studies that did not perform comprehensive multivariable adjustments, which raises concerns over the robustness of individual study findings even for the well-described association between hypertension and kidney cancer. Second, most studies did not perform subgroup analyses by potential effect modifiers (e.g. anti-hypertensive medication use), which would have allowed a more accurate assessment of associations in different patient subgroups. Third, detection bias may also account for some of the reported associations, as individuals treated for hypertension are under closer medical surveillance that may lead to easier detection of cancer compared to untreated persons. Future well-designed prospective studies and Mendelian randomization studies should assist in estimating valid measures of association.

In conclusion, the currently available published observational evidence across 18 cancer sites showed that hypertensive individuals were at higher risk of kidney, colorectal and breast cancer. However, careful interpretation is required as most meta-analyses included relatively small number of studies, several relative risks had weak or moderate magnitude and maybe affected by residual confounding.

**Data Availability**

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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The study was conceived by K.K.T. and E.E.N. The literature search and data extraction was conducted by A.S., X.T. and S.C. The quality assessment was performed by A.S. and S.C. The statistical analysis was performed by K.K.T. The write-up and approved submission. A.S., G.M., D.S.L. and K.K.T., A.S. and K.K.T. wrote the paper and all authors provided critical contributions to the write-up and approved submission.

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