Blood pressure and risk of cancer in the European Prospective Investigation into Cancer and Nutrition

Sofia Christakoudi [1,2]*, Artemisia Kakourou[3]*, Georgios Markozannes[3], Ioanna Tzoulaki[1,3], Elisabete Weiderpass[4], Paul Brennan[4], Marc Gunter[4], Christina C. Dahm[5], Kim Overvad[5,6], Anja Olsen[7], Anne Tjønneland[7,8], Marie-Christine Boutron-Ruault [9,10], Anne-Laure Madika[9,10,11], Gianluca Severi[9,10], Verena Katzke[12], Tilman Kühn[12], Manuela M. Bergmann[13], Heiner Boeing[13], Anna Karakatsani[14,15], Georgia Martimianaki[14], Paschalis Thriskos[14], Giovanna Masala[16], Sabina Sieri [17], Salvatore Panico[18], Rosario Tumino[19], Fulvio Ricceri [20,21], Antonio Agudo[22], Daniel Redondo-Sánchez[23,24], Sandra M. Colorado-Yohar[24,25,26], Olatz Mokoroa[27], Olle Melander[28], Tanja Stocks[29], Christel Häggström [30,31], Sophia Harlid[32], Bas Bueno-de-Mesquita[1,33,34,35], Carla H. van Gils[36], Roel C.H. Vermeulen[1,37,38], Kay-Tee Khaw[39], Nicholas J. Wareham[40], Tammy Y.N. Tong[41], Heinz Freisling[4], Mattias Johansson[4], Hannah Lennon[4], Dagfinn Aune[1,42,43], Elio Riboli[1], Dimitrios Trichopoulos[14,44,45]†, Antonia Trichopoulou[14] and Konstantinos K. Tsilidis[1,3]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom
[2]MRC Centre for Transplantation, King's College London, London, United Kingdom
[3]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece
[4]International Agency for Research on Cancer, World Health Organization, Lyon, France
[5]Department of Public Health, Aarhus University, Aarhus, Denmark
[6]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
[7]Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark
[8]Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[9]Centre de recherche en Epidemiologie et Sante des Populations (CESP), Fac. de médecine - Univ. Paris-Sud, Fac. de médecine - UVSQ, INSERM, Université Paris-Saclay, Villejuif, France

[10]Gustave Roussy, Villejuif, France

[11]Université Lille, CHU Lille, Lille, France

[12]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

[13]Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke (DIfE), Nuthetal, Germany

[14]Hellenic Health Foundation, Athens, Greece

[15]2nd Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" University Hospital, Haidari, Greece

[16]Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network – ISPRO, Florence, Italy

[17]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

[18]Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy

[19]Cancer Registry and Histopathology Department, "M.P. Arezzo" Hospital, ASP, Ragusa, Italy

[20]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

[21]Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco (TO), Italy

[22]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology-IDIBELL. L'Hospitalet de Llobregat, Barcelona, Spain

[23]Escuela Andaluza de Salud Pública. Instituto de Investigación Biosanitaria ibs.GRANADA, Universidad de Granada, Granada, Spain

[24]CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

[25]Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

[26]Research Group on Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia

[27]Public Health Division of Gipuzkoa, BioDonostia Research Institute, San Sebastian, Spain

[28]Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

[29]Department of Clinical Sciences Lund, Lund University, Lund, Sweden

[30]Department of Biobank Research, Umeå University, Umeå, Sweden

[31]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

[32]Department of Radiation Sciences, Umeå University, Umeå, Sweden

[33]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

[34]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands

[35]Dept. of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[36]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands

[37]Environmental Epidemiology Group, Institute of Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

[38]Public Health Department, University Medical Center, Utrecht, The Netherlands

[39]University of Cambridge, School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom

[40]MRC Epidemiology Unit, Institute of Metabolic Science, School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom

[41]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

[42]Department of Nutrition, Bjørknes University College, Oslo, Norway

[43]Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway

[44]Department of Epidemiology, Harvard School of Public Health, Boston, MA

[45]Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece

Cancer Epidemiology

Several studies have reported associations of hypertension with cancer, but not all results were conclusive. We examined the association of systolic (SBP) and diastolic (DBP) blood pressure with the development of incident cancer at all anatomical sites in the European Prospective Investigation into Cancer and Nutrition (EPIC). Hazard ratios (HRs) (95% confidence intervals) were estimated using multivariable Cox proportional hazards models, stratified by EPIC-participating center and age at recruitment, and adjusted for sex, education, smoking, body mass index, physical activity, diabetes and dietary (in women also reproductive) factors. The study included 307,318 men and women, with an average follow-up of 13.7 (standard deviation 4.4) years and 39,298 incident cancers. We confirmed the expected positive association with renal cell carcinoma: HR = 1.12 (1.08–1.17) per 10 mm Hg higher SBP and HR = 1.23 (1.14–1.32) for DBP. We additionally found positive associations for esophageal squamous cell carcinoma (SCC): HR = 1.16 (1.07–1.26) (SBP), HR = 1.31 (1.13–1.51) (DBP), weaker for head and neck cancers: HR = 1.08 (1.04–1.12) (SBP), HR = 1.09 (1.01–1.17) (DBP) and, similarly, for skin SCC, colon cancer, postmenopausal breast cancer and uterine adenocarcinoma (AC), but not for esophageal AC, lung SCC, lung AC or uterine endometroid cancer. We observed weak inverse associations of SBP with cervical SCC: HR = 0.91 (0.82–1.00) and lymphomas: HR = 0.97 (0.93–1.00). There were no consistent associations with cancers in other locations. Our results are largely compatible with published studies and support weak associations of blood pressure with cancers in specific locations and morphologies.

What's new?

Is there a link between high blood pressure and cancer? In this large, prospective study, the authors found that hypertension is indeed associated with a moderate increase in risk for several cancers, including renal, esophageal (only squamous cell carcinoma), head and neck, skin, colon, post-menopausal breast cancer, and uterine cancer (only adenocarcinoma). These results may potentially enhance screening and risk assessment. Further research may also identify shared mechanisms for both hypertension and cancer, such as inflammation, lipid peroxidation, etc.

Introduction

Hypertension and cancer are complex multifactorial conditions. Hypertension is a worldwide public health challenge, with systolic blood pressure (SBP) above 115 mm Hg ranked as the leading risk factor for the global burden of disease in 2017.[1] The global age-standardized prevalence of raised blood pressure (SBP ≥140 mm Hg or diastolic BP [DBP] ≥90 mm Hg) in adults was estimated as ≥20% in 2015.[2] However, although hypertension is a major risk factor for coronary heart disease and stroke, the evidence is much weaker for an association with cancer.[3]

A meta-analysis of ten longitudinal studies published in 2002 found that individuals with hypertension had higher risk of total cancer mortality: odds ratio (OR) = 1.23 (95% confidence interval [CI], 1.11–1.36), largely explained, based on 13 case–control studies, by a positive association for renal cell carcinoma (RCC) mortality: OR = 1.75 (1.61–1.90).[4] The results of subsequent studies have confirmed that hypertension is associated with a higher incidence of RCC.[5–8] While hypertension has not attracted much attention as a risk factor for other cancers, recent meta-analyses of observational studies, although summarizing only 5 to 12 prospective studies and with large between-study heterogeneity, have reported higher risks for endometrial, prostate, postmenopausal breast and colorectal cancer, comparing hypertensive with normotensive participants.[9–15] Furthermore, the largest to date prospective study examining the association of individual components of the metabolic syndrome (including BP measurements) and cancer in over half a million participants from Norway, Sweden and Austria: the Metabolic syndrome and Cancer project (Me-Can),[16] reported positive associations of high BP with the risk of cancers in locations other than the kidney in both men (oropharynx, colon, rectum and anus, lung with larynx and trachea, bladder, malignant melanoma and non-melanoma skin cancer) and women (liver, pancreas, corpus uteri, cervix and malignant melanoma).[3]

It is not clear whether the association of hypertension with cancer is causal or it could, at least partially, be explained by reverse causality or other biases. It is, however, possible that risk factors and mechanisms of pathogenesis are shared by the two conditions. For example, it has been hypothesized that predisposition to cancer is increased by chronic inflammation[17] and vascular inflammation could be involved in the pathogenesis of hypertension.[18] Lipid peroxidation, associated with hypertension and obesity, has also been proposed as a mechanism responsible for higher risk of RCC.[19] Furthermore, experimental studies have implicated a

potential role of the renin-angiotensin-aldosterone system (which regulates BP) in the biological processes of cellular proliferation, inflammation, angiogenesis and tissue remodeling.[20] Studies in mice have also provided preliminary evidence that blockade of the angiotensin II type 1 receptor attenuates the growth and metastatic potential of RCC.[21]

In the context of the above considerations, the aim of our study was to further explore the association between hypertension and cancer. We examined whether measured SBP and DBP were associated with the risk of incident cancer at all anatomical sites in the large and well-established European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, after taking into account obesity, smoking and other lifestyle and dietary factors (for both men and women) and indicators of sexual maturation and reproductive life (for women), which could be potential confounders or shared risk factors for cancer and hypertension.

Materials and Methods

Study population

EPIC is an ongoing, multicenter, prospective cohort study designed to investigate the associations of diet, lifestyle and various medical and environmental risk factors with the incidence of cancer and other diseases. The source population (the majority aged between 25 and 70 years at the time of enrolment) and data collection methods have been described in detail previously.[22] Approval for our study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all the EPIC participating centers. Written informed consent was obtained from all participants before entry into the study.

Figure 1 shows a detailed flowchart of study participants with exclusions.

Assessment of BP and other variables

SBP and DBP were measured in millimeters of mercury (mm Hg) by trained personnel. Measurements were obtained during a visit to an EPIC center and within 6 months of recruitment in 91.5% of participants, except in France: all measurements obtained at the blood-collection visit, 3.8 years (standard deviation [SD], 1.3) after recruitment; Granada: 39.2% after 2.0 (0.9) years; San Sebastian: 78.4% after 1.6 (0.7) years; Oxford: 29.3% after 0.8 (0.2) years. Two readings (1–5 min apart) were performed with a standard mercury manometer or oscillometric device on the right arm in a sitting position (after at least 5 min initial resting time). The average value was used as the exposure variable, assuming differences are due to random measurement error. Exceptions were the Danish and

European Prospective Investigation into Cancer and Nutrition (EPIC) cohort
(*n* = 521,324, ca = 60,230)
Recruitment: 1991−1999 (*n* = 7 up to 2001); Follow-up: recruitment to 2013
Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, United Kingdom

Prevalent cancer at recruitment (*n* = 25,184, ca = 3,770)

Date of diagnosis missing (*n* = 20) **or follow-up time missing** (*n* = 4,128, ca = 2)

Lifestyle questionnaire not completed (*n* = 1,277, ca = 104)

Dietary questionnaire not completed (*n* = 4,982, ca = 811)

Energy intake to estimated energy requirement ratio (top/bottom 1% of cohort) (*n* = 9,573, ca = 1,084)

Blood pressure measured after malignant cancer diagnosis or administrative censoring (*n* = 631, ca = 400)

Blood pressure measurements missing (*n* = 168,211, ca = 14,761)
France (*n* = 47,600 (71%), ca = 3,456 (73%)); Germany (*n* = 15,509 (32%), ca = 1,708 (40%));
Norway (*n* = 33,975 (all participants), ca = 3,032); Spain (*n* = 33,709 (84%), ca = 3,556 (85%) including all participants
from Asturias (*n* = 8,279, ca = 791) and Navarra (*n* = 7,777, ca = 987));
United Kingdom (*n* = 35,223 (47%), ca = 2,777 (32%)); Other countries (*n* = 2,195 (1%), ca = 232 (0.8%))

Main analysis data set
(*n* = 307,318, ca = 39,298)

Sex		**Age at recruitment**		**Alcohol intake**	
Men	**Women**	**≤53 years**	**>53 years**	**≤12 g/day**	**>12 g/day**
n = 112,591	*n* = 194,727	*n* = 153,303	*n* = 154,015	*n* = 205,214	*n* = 102,104
ca = 17,452	ca = 21,846	ca = 12,018	ca = 27,280	ca = 24,429	ca = 14,869

First 2 years of follow-up excluded	**BMI**		**Smoking status**		**Antihypertensive treatment**	
	≤25 kg/m²	**>25 kg/m²**	**Never smokers**	**Ever smokers**	**No treatment**	**Treated**
n = 301,857	*n* = 146,326	*n* = 160,992	*n* = 141,931	*n* = 160,623	*n* = 227,336	*n* = 37,017
ca = 35,941	ca = 17,441	ca = 21,857	ca = 15,120	ca = 23,704	ca = 26,864	ca = 5,538

Figure 1. Flow diagram for EPIC participants included in the current study. Abbreviations: *n*, number of participants; ca, number of cancer cases.

Swedish centers, where one single measurement was taken in the supine position. Mean BP was defined as $(1/3)*SBP + (2/3)*DBP$[23] and not as the mean of SBP and DBP (mid-BP), used in the Me-Can study.[3] Self-reported information on treatment with antihypertensive medication (at baseline and/or in the past) was available for 264,353 participants (86.9%), of which 37,017 (14%) were receiving or had received treatment.

Information on sociodemographics, lifestyle characteristics, medical history and dietary intake was collected *via* questionnaires at the time of recruitment. Weight and height were measured at recruitment using a standardized protocol, except for part of the Oxford cohort and France, where height and weight

were self-reported. Body mass index (BMI) was calculated as weight/height² (kg/m²). Food and nutrient intakes were estimated from country-specific baseline dietary questionnaires.[22] A physical activity index was derived as previously described.[24]

Assessment of cancer
Incident cancer cases were identified through population cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden and the United Kingdom. In France, Germany and Greece, a combination of methods was used, including health insurance records, cancer pathology registries and active follow-up of study participants and their next of kin. Cancer incidence data were coded

according to the International Classification of Diseases for Oncology.[25] The presented analyses are focused on the first primary neoplasm. Participants subsequently diagnosed with a second (or third) cancer were censored at the date of diagnosis of the first cancer. We considered a joint group of any cancer and location (International Classification of Diseases for Oncology behavioral code 3 [malignant, primary site]) and separate groups for all major anatomical sites (excluding rare morphologies), with further subdivisions for specific locations or major morphologies (Table S1).

Statistical analyses

Hazard ratios (HRs) (95% CIs) were estimated using delayed-entry Cox proportional hazards models, with age at recruitment (5-year categories) and EPIC center ($n = 25$) as stratification variables. Origin of time was the date of birth, aligning individuals by birth cohort. Entry time was the date of BP measurement. Time of censorship was the date of first incidence of cancer (recruitment to 2013), or death, or last complete follow-up, whichever occurred first.

The main analyses examined the following exposures: SBP and DBP (considered in separate models and each as a continuous [per 10 mm Hg] variable); hypertension (defined as a dichotomous [yes/no] variable), according to BP measurements (SBP ≥140 mm Hg, or DBP ≥90 mm Hg) or self-reported information, and antihypertensive treatment in hypertensive individuals (a binary variable defined according to self-reported antihypertensive treatment [yes/no] for individuals fulfilling the hypertension criteria specified above). The latter analysis aimed to examine potential associations of antihypertensive drugs as exogenous chemicals and cancer. Although the results for hypertension (yes/no) would be useful for meta-analyses, the risk estimates per 10 mm Hg, based on the complete range of SBP and DBP, would be more informative than a dichotomous simplification. The secondary analyses examined SBP and DBP as categorical variables, with categories based on the definitions of the American[26] and the European Society of Hypertension[27] (Table S2), and mean BP, as a continuous variable and also categorized using cohort-wide quartiles (cut points at 88.8, 96.7 and 106.0 mm Hg). To test for trend, BP categories were analyzed as continuous variables, after assigning participants an ordinal score.

All statistical models were adjusted for the categorical variables listed in Table S2. Missing values were assigned to separate categories. For premenopausal breast cancers, analyses were restricted to participants with premenopausal status at recruitment (if known), or under the age of 46 (for unknown menopausal status) and were not adjusted for menopausal status or age at menopause. If breast cancer diagnosis was before 46 years of age, participants were considered "cases," otherwise they were censored at 46 years, if not censored by age 46 for death, loss to follow-up or other cancer. For postmenopausal breast cancer, analyses were restricted to participants with physiological or surgical menopause at recruitment, or with age ≥55 years (for unknown menopausal status).

Additionally, associations of BP with cancer were examined in strata according to age (cut point at 53 years, the cohort-wide median), sex, BMI (cut point at 25 kg/m^2), smoking status (ever smokers vs. never smokers), alcoholic beverages intake (cut point at 12 g ethanol/day, the largest ethanol unit used in Europe) and use of antihypertensive treatment in individuals with available information for the stratifying factor. Likelihood ratio tests, comparing nested models with and without the addition of interaction terms, were used to test for statistical interactions on a multiplicative scale. BP categories were included in the interaction models as ordinal variables. Examining potential biological interactions was beyond the scope of our study.

Sensitivity analyses were also performed, excluding the first 2 years of follow-up (to explore possible reverse causation). Crude estimates of HR (omitting the adjustment variables, but retaining the stratification by age at recruitment and study center) were calculated to examine the influence of adjustment.

All analyses were performed with STATA software version 13. Plots and data summaries were generated in R version 3.4.3.

Results and Discussion

Characteristics of study participants

The study cohort consisted of 307,318 individuals (63.4% women), with a mean age 52.5 (SD = 9.9) years at recruitment. During an average follow-up of 13.7 (SD = 4.4) years, 39,298 incident cancers were diagnosed, with major anatomical sites: breast ($n = 8,154$ cases), prostate ($n = 5,848$), colorectum ($n = 4,625$) and lung ($n = 3,229$). Mean SBP was 131.5 mm Hg (SD = 19.7) and mean DBP was 81.1 mm Hg (SD = 10.9). BP measurements and numbers of cancer cases are summarized by country in Table S3. Participants with higher SBP or DBP were older, more likely to be men, to have low education or physical activity level, to have higher BMI, to have diabetes mellitus and to consume more alcohol and red meat, but less fruit and vegetables. Women with higher SBP or DBP were less likely to have ever used oral contraceptives. Cohort characteristics are summarized by hypertension and treatment status in Table 1 and by BP categories in Table S4.

Associations with the risk of malignant cancers

Results from all analyses are included in Table S5. The presentation below focuses on SBP and DBP examined as continuous variables in adjusted models. Forest plots with estimates of HR (95% CI) for SBP and DBP in the total dataset are shown in Figure 2; for hypertensive status and antihypertensive treatment in Figure 3 and for subgroups determined by sex, BMI, age at recruitment, smoking status, alcohol and antihypertensive treatment are shown in Figure S1. There were positive associations of BP with malignant cancers in several locations and with some specific morphologies. Analyses of BP categories were largely in agreement with the findings for BP examined on a continuous scale. The main findings are presented below, within the context of large published studies and meta-analyses. Anatomical cites and cancers, for which

Table 1. Baseline demographic, lifestyle and reproductive characteristics by hypertension and treatment status

	Total	No hypertension	Hypertension	Untreated hypertension	Treated hypertension
Characteristics (men and women)					
Cohort size	307,318	174,179	133,139	73,714	37,017
Female	194,727 (63.4)	117,264 (67.3)	77,463 (58.2)	41,779 (56.7)	23,736 (64.1)
Age at recruitment, years	52.5 (9.9)	49.8 (9.8)	56.1 (8.7)	54.9 (8.6)	57.8 (7.6)
Body mass index, kg/m^2	25.8 (4.2)	24.8 (3.7)	27.1 (4.5)	26.7 (4.3)	28.2 (4.7)
Alcohol intake, g/day	12.4 (17.1)	11.2 (15.2)	13.9 (19.2)	15.4 (20.2)	12.3 (18.0)
Fruit consumption, g/day	230.6 (176.7)	235.2 (182.3)	224.6 (169.0)	226.3 (172.6)	230.9 (164.4)
Vegetable consumption, g/day	200.9 (145.4)	205.0 (149.9)	195.6 (139.2)	190.9 (138.4)	195.9 (143.6)
Red meat consumption, g/day	48.2 (36.3)	46.5 (35.7)	50.5 (37.0)	53.1 (37.7)	47.4 (34.0)
Blood pressure, mm Hg					
Systolic blood pressure	131.5 (19.7)	119.4 (10.9)	147.3 (17.4)	146.7 (15.9)	147.9 (20.0)
Diastolic blood pressure	81.1 (10.9)	75.2 (7.5)	88.8 (9.8)	88.6 (9.1)	89.0 (10.6)
Diabetes					
Self-reported diabetes	8,588 (2.8)	2,516 (1.4)	6,072 (4.6)	2,410 (3.3)	3,067 (8.3)
Missing information	30,147 (9.8)	16,247 (9.3)	13,900 (10.4)	615 (0.8)	657 (1.8)
Smoking status					
Never smoker	141,931 (46.2)	80,450 (46.2)	61,481 (46.2)	33,057 (44.8)	18,603 (50.3)
Former smoker	86,314 (28.1)	45,575 (26.2)	40,739 (30.6)	21,901 (29.7)	11,154 (30.1)
Current smoker (≤20 pack-years)	32,226 (10.5)	21,711 (12.5)	10,515 (7.9)	6,539 (8.9)	2,716 (7.3)
Current smoker (›20 pack-years)	34,907 (11.4)	19,428 (11.2)	15,479 (11.6)	9,777 (13.3)	3,655 (9.9)
Missing information	11,940 (3.9)	7,015 (4.0)	4,925 (3.7)	2,440 (3.3)	889 (2.4)
Physical activity					
Inactive	67,194 (21.9)	32,680 (18.8)	34,514 (25.9)	16,013 (21.7)	11,191 (30.2)
Moderately inactive	100,295 (32.6)	57,476 (33.0)	42,819 (32.2)	23,828 (32.3)	12,268 (33.1)
Moderately active	70,977 (23.1)	42,530 (24.4)	28,447 (21.4)	16,954 (23.0)	7,300 (19.7)
Active	62,152 (20.2)	36,956 (21.2)	25,196 (18.9)	15,696 (21.3)	6,021 (16.3)
Missing information	6,700 (2.2)	4,537 (2.6)	2,163 (1.6)	1,223 (1.7)	237 (0.6)
Education					
None	9,377 (3.1)	3,478 (2.0)	5,899 (4.4)	2,863 (3.9)	2,973 (8.0)
Primary school completed	90,254 (29.4)	43,392 (24.9)	46,862 (35.2)	25,274 (34.3)	14,288 (38.6)
Technical/professional school	77,398 (25.2)	43,025 (24.7)	34,373 (25.8)	18,676 (25.3)	9,033 (24.4)
Secondary school	53,830 (17.5)	35,179 (20.2)	18,651 (14.0)	11,377 (15.4)	4,730 (12.8)
Longer education (Inc. University)	67,606 (22.0)	43,999 (25.3)	23,607 (17.7)	14,246 (19.3)	5,875 (15.9)
Missing information	8,853 (2.9)	5,106 (2.9)	3,747 (2.8)	1,278 (1.7)	118 (0.3)
Age at first menstrual period[1]					
‹12 years	27,085 (13.9)	16,544 (14.1)	10,541 (13.6)	5,521 (13.2)	3,116 (13.1)
≥12 and ‹15 years	125,828 (64.6)	76,353 (65.1)	49,475 (63.9)	27,400 (65.6)	15,450 (65.1)
≥15 years	32,391 (16.6)	17,996 (15.3)	14,395 (18.6)	7,842 (18.8)	4,618 (19.5)
Missing information	9,423 (4.8)	6,371 (5.4)	3,052 (3.9)	1,016 (2.4)	552 (2.3)
Age at first full-term pregnancy[1]					
≤21 years	36,839 (18.9)	20,636 (17.6)	16,203 (20.9)	8,514 (20.4)	5,607 (23.6)
›21 and ≤30 years	106,230 (54.6)	62,619 (53.4)	43,611 (56.3)	23,884 (57.2)	13,515 (56.9)
≥30 years	15,709 (8.1)	9,715 (8.3)	5,994 (7.7)	3,391 (8.1)	1,689 (7.1)
Missing information	35,949 (18.5)	24,294 (20.7)	11,655 (15.0)	5,990 (14.3)	2,925 (12.3)
Full-term pregnancies[1]					
None	25,571 (13.1)	16,963 (14.5)	8,608 (11.1)	4,966 (11.9)	2,397 (10.1)
One	28,796 (14.8)	17,156 (14.6)	11,640 (15.0)	6,350 (15.2)	3,656 (15.4)
Two	75,357 (38.7)	45,696 (39.0)	29,661 (38.3)	16,246 (38.9)	9,280 (39.1)
Three	33,031 (17.0)	18,740 (16.0)	14,291 (18.4)	7,483 (17.9)	4,664 (19.6)

(Continues)

Table 1. Baseline demographic, lifestyle and reproductive characteristics by hypertension and treatment status (Continued)

	Total	No hypertension	Hypertension	Untreated hypertension	Treated hypertension
Four or more	14,897 (7.7)	7,360 (6.3)	7,537 (9.7)	3,601 (8.6)	2,832 (11.9)
Missing information	17,075 (8.8)	11,349 (9.7)	5,726 (7.4)	3,133 (7.5)	907 (3.8)
Menopausal status[1]					
Premenopausal	58,190 (29.9)	45,853 (39.1)	12,337 (15.9)	7,856 (18.8)	2,450 (10.3)
Postmenopausal	96,806 (49.7)	46,876 (40.0)	49,930 (64.5)	25,486 (61.0)	16,640 (70.1)
Peri-menopausal or unknown	33,371 (17.1)	21,490 (18.3)	11,881 (15.3)	6,918 (16.6)	3,292 (13.9)
Surgical postmenopausal	6,360 (3.3)	3,045 (2.6)	3,315 (4.3)	1,519 (3.6)	1,354 (5.7)
Age at menopause[1]					
‹40 years	4,301 (2.2)	2,106 (1.8)	2,195 (2.8)	1,067 (2.6)	769 (3.2)
≥40 and ≤46 years	18,912 (9.7)	9,058 (7.7)	9,854 (12.7)	4,754 (11.4)	3,650 (15.4)
›46 and ≤50 years	31,996 (16.4)	15,578 (13.3)	16,418 (21.2)	8,510 (20.4)	5,579 (23.5)
›50 and ≤56 years	29,427 (15.1)	13,238 (11.3)	16,189 (20.9)	8,327 (19.9)	5,619 (23.7)
›56 years	1,997 (1.0)	753 (0.6)	1,244 (1.6)	595 (1.4)	469 (2.0)
Missing or not applicable	108,094 (55.5)	76,531 (65.3)	31,563 (40.7)	18,526 (44.3)	7,650 (32.2)
Oral contraceptive use[1]					
Never	82,568 (42.4)	43,393 (37.0)	39,175 (50.6)	20,706 (49.6)	12,755 (53.7)
Former	91,622 (47.1)	58,870 (50.2)	32,752 (42.3)	18,294 (43.8)	9,916 (41.8)
Current	10,050 (5.2)	7,434 (6.3)	2,616 (3.4)	1,829 (4.4)	594 (2.5)
Missing information	10,487 (5.4)	7,567 (6.5)	2,920 (3.8)	950 (2.3)	471 (2.0)
Hormone replacement therapy[1]					
Never	129,049 (66.3)	79,952 (68.2)	49,097 (63.4)	26,920 (64.4)	14,842 (62.5)
Former	16,259 (8.3)	8,638 (7.4)	7,621 (9.8)	3,937 (9.4)	2,598 (10.9)
Current	30,133 (15.5)	17,724 (15.1)	12,409 (16.0)	6,596 (15.8)	3,891 (16.4)
Missing information	19,286 (9.9)	10,950 (9.3)	8,336 (10.8)	4,326 (10.4)	2,405 (10.1)

[1]Reproductive characteristics in women; Categorical variables: number of individuals (percentage from total number in category [for reproductive factors in women only]); Continuous variables: mean (standard deviation).

there was no overall association, are presented in Supplementary Results and Discussion.

Kidney cancer and cancers of the renal pelvis and ureter. The results of the current analyses confirmed our previous findings[6] of a positive association of BP with the risk of RCC: HR = 1.12 (1.08–1.17) for SBP and HR = 1.23 (1.14–1.32) for DBP (Fig. 2). We found no evidence for a difference between men (with $n = 431$ cases) and women ($n = 327$) (Figs. S1a and S1b). As cancers of the renal pelvis and ureter are mainly of transitional cell morphology, that is, different from the parenchymal cell morphology of RCC, they were considered as a negative control and, indeed, there was no association with BP in the total dataset ($n = 112$). There was, however, an indication for a positive association with SBP in the subgroup with BMI > 25 kg/m^2 ($n = 63$): HR = 1.16 (1.03–1.32). The risk was also higher in treated compared to untreated hypertensive individuals: HR = 2.21 (1.18–4.12) (Fig. 3), although for a small number of cases.

The association of hypertension with a higher risk of RCC is well established. In 1999, Grossman *et al.* reported a higher risk for users of diuretics relative to nonusers: OR = 1.55 (1.42–1.71), based on a meta-analysis of 9 case–control studies, and more than a two-fold increased risk, based on three cohort studies.[28] In 2007, a meta-analysis of 18 studies

reported a higher risk of RCC among hypertensive patients (estimated pooled OR = 1.62 [1.24–2.12]), also for treatment with diuretics and, in women, with non-diuretic drugs.[7] At the same time, Weikert *et al.* reported, based on 250 cases in the EPIC study, that high SBP and DBP are associated with a higher risk of RCC, both in men and women and found that individuals receiving antihypertensive treatment had higher risk only if hypertension was poorly controlled.[6] Earlier, Heath *et al.* had reported in a large cohort high age-adjusted risk ratio (RR) in women: RR = 3.1 (1.5–4.3), but not in men: RR = 0.8 (0.4–1.3) receiving antihypertensive medication, including diuretics[29] and Grossman *et al.* had reported from a meta-analysis of seven case–control studies a high risk in women: averaged OR = 2.01 (1.56–2.67), but slightly lower risk in men OR = 1.69 (1.34–2.13), but with heterogeneity between the studies.[28] However, Haggström *et al.* reported for the Me-Can project a higher risk only in men ($n = 592$): HR = 1.39 (1.24–1.56) per 10 mm Hg higher mid-BP, but not in women ($n = 263$): HR = 1.05 (0.89–1.24),[3] with similar findings for SBP and DBP examined separately.[30] Nevertheless, a more recent meta-analysis of 18 prospective studies, with a total of 8,097 cases, has confirmed an association of history of hypertension with kidney cancer: estimate RR = 1.67

Cancer type (cases) ^ subtype	Systolic blood pressure (10 mm Hg)	Diastolic blood pressure (10 mm Hg)
Any cancer (39,298)	1.01 (1.01–1.02) **	1.02 (1.01–1.03) **
Head and neck		
Head and neck (combined) (683)	1.08 (1.04–1.12) **	1.09 (1.01–1.17) *
^ Mouth and oropharynx (332)	1.07 (1.01–1.13) *	1.13 (1.02–1.25) *
^ Larynx (239)	1.12 (1.04–1.19) **	1.11 (0.98–1.25)
Digestive system		
Esophagus (387)	1.09 (1.03–1.15) **	1.15 (1.04–1.26) **
^ Esophageal AC (176)	1.04 (0.96–1.13)	1.08 (0.94–1.24)
^ Esophageal SCC (149)	1.16 (1.07–1.26) **	1.31 (1.13–1.51) **
Stomach (738)	1.00 (0.96–1.05)	1.06 (0.98–1.13)
^ Gastric AC (403)	1.01 (0.95–1.06)	1.05 (0.96–1.16)
Colorectal (4,625)	1.01 (0.99–1.03)	1.04 (1.01–1.07) **
^ Colon (3,003)	1.01 (0.99–1.03)	1.06 (1.02–1.10) **
^ Rectum and rectosigmoid junction (1,622)	1.01 (0.98–1.04)	1.01 (0.96–1.06)
Liver and bile ducts (653)	1.01 (0.97–1.05)	0.98 (0.90–1.05)
^ HCC (191)	1.05 (0.97–1.14)	0.92 (0.80–1.06)
^ Gallbladder and bile ducts (346)	0.99 (0.93–1.05)	1.01 (0.91–1.12)
Pancreas (990)	1.01 (0.98–1.05)	1.01 (0.95–1.08)
Respiratory system		
Lung (combined) (3,229)	1.03 (1.01–1.05) **	1.00 (0.97–1.04)
^ Lung AC (1,130)	1.02 (0.99–1.06)	0.98 (0.92–1.04)
^ Lung SCC (613)	0.99 (0.95–1.03)	0.97 (0.89–1.04)
^ Lung SmallCC (379)	1.04 (0.99–1.10)	0.99 (0.90–1.10)
^ Lung (other morphology) (1,107)	1.06 (1.02–1.09) **	1.05 (0.99–1.11)
Urinary system		
Kidney (758)	1.12 (1.08–1.16) **	1.22 (1.14–1.31) **
Renal pelvis and ureter (112)	1.05 (0.95–1.16)	0.97 (0.81–1.17)
Bladder (1,192)	1.01 (0.98–1.05)	1.00 (0.95–1.06)
Reproductive system		
Prostate (5,848)	0.99 (0.98–1.01)	1.01 (0.99–1.04)
Breast (female) (8,154)	1.03 (1.01–1.04) **	1.03 (1.01–1.06) **
^ Breast pre–menopausal (256)	1.07 (0.97–1.18)	1.06 (0.92–1.21)
^ Breast post–menopausal (4,786)	1.02 (1.01–1.04) **	1.04 (1.01–1.07) *
Ovary (1,007)	0.99 (0.96–1.03)	1.00 (0.94–1.06)
Corpus uteri (1,164)	1.04 (1.00–1.07) *	1.06 (1.00–1.12) *
^ Uterine AC (488)	1.06 (1.01–1.12) *	1.11 (1.02–1.22) *
^ Endometroid AC (546)	1.00 (0.96–1.05)	1.02 (0.93–1.10)
Cervix uteri (223)	0.99 (0.91–1.06)	0.98 (0.86–1.12)
^ Cervix SCC (145)	0.91 (0.82–1.00)	0.88 (0.74–1.05)
Anogenital (not cervix) (244)	0.98 (0.92–1.06)	0.97 (0.86–1.11)
^ Anogenital SCC (173)	1.02 (0.94–1.11)	1.00 (0.86–1.16)
Skin		
Skin SCC (1,399)	1.01 (0.98–1.04)	1.07 (1.02–1.13) *
Melanoma (skin) (1,617)	1.01 (0.98–1.04)	1.00 (0.95–1.05)
Nervous and endocrine system		
Brain and CNS (591)	1.00 (0.95–1.05)	0.97 (0.90–1.06)
^ Glioblastoma (297)	0.97 (0.91–1.04)	0.96 (0.85–1.07)
Thyroid (420)	1.02 (0.96–1.08)	1.03 (0.93–1.14)
Hematopoietic system		
Leukemia (1,308)	0.99 (0.96–1.02)	0.97 (0.92–1.03)
^ Multiple myeloma (475)	0.99 (0.94–1.05)	1.01 (0.92–1.11)
Lymphoma (all types) (1,058)	0.97 (0.93–1.00) *	0.96 (0.90–1.02)
^ Non–Hodgkin lymphomas (882)	0.96 (0.92–0.99) *	0.95 (0.89–1.02)
Other		
Other location AC (406)	1.08 (1.03–1.14) **	1.03 (0.93–1.13)
Other location or other morphology (2,492)	1.02 (0.99–1.04)	1.02 (0.98–1.06)

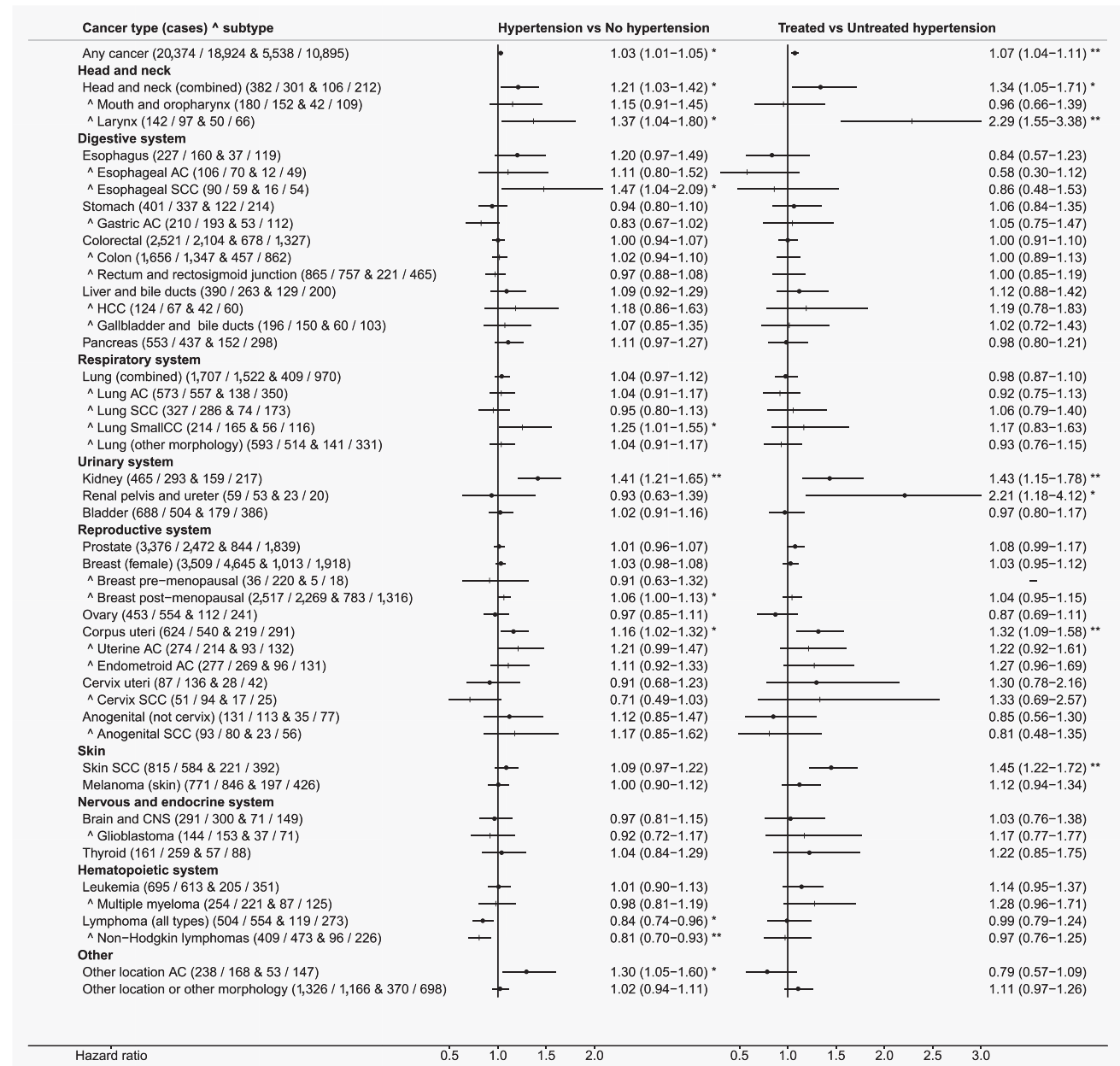Hazard ratio   0.8 0.9 1.0 1.1 1.2 1.3   0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5

Figure 2. Forest plot of hazard ratios for continuous systolic and diastolic blood pressure. Abbreviations: AC, adenocarcinoma; CNS, central nervous system; HCC, hepatocellular carcinoma; SCC, squamous cell carcinoma; SmallCC, small cell carcinoma; Vertical order, determined by body system (bold), followed by the main anatomical locations and the relevant specific locations or morphologies marked with ˆsymbols (other locations, not included in those specified, are shown last); Hazard ratios, estimates (95% confidence intervals) (per 10 mm Hg higher blood pressure) derived from Cox proportional hazards models, stratified by study center and age at recruitment (5-year categories) and adjusted for potential confounders and risk factors listed in Table S2). For cervical AC ($n = 37$): HR = 0.96 (0.79–1.17) for SBP and HR = 0.84 (0.59–1.19) for DBP and for other morphology in the cervix (non-SCC and non-AC) ($n = 41$): HR = 1.28 (1.10–1.48) for SBP and HR = 1.53 (1.17–2.01) for DBP (considered only in the main analyses and excluded to avoid the larger confidence intervals dominating the plot); *$p < 0.05$, **$p < 0.005$.

(1.46–1.90) and an association also of SBP and DBP in both men and women,[8] in agreement with our findings. A potential relationship between hypertension and the risk of renal pelvis and ureter cancer is less well studied, but an early case–control study reported a positive association for hypertension history longer than 5 years: OR = 1.3 (1.0–1.8) and, in agreement with

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Cancer type (cases) ^ subtype	Hypertension vs No hypertension	Treated vs Untreated hypertension
Any cancer (20,374 / 18,924 & 5,538 / 10,895)	1.03 (1.01–1.05) *	1.07 (1.04–1.11) **
Head and neck		
Head and neck (combined) (382 / 301 / 106 / 212)	1.21 (1.03–1.42) *	1.34 (1.05–1.71) *
^ Mouth and oropharynx (180 / 152 & 42 / 109)	1.15 (0.91–1.45)	0.96 (0.66–1.39)
^ Larynx (142 / 97 / 50 / 66)	1.37 (1.04–1.80) *	2.29 (1.55–3.38) **
Digestive system		
Esophagus (227 / 160 / 37 / 119)	1.20 (0.97–1.49)	0.84 (0.57–1.23)
^ Esophageal AC (106 / 70 & 12 / 49)	1.11 (0.80–1.52)	0.58 (0.30–1.12)
^ Esophageal SCC (90 / 59 & 16 / 54)	1.47 (1.04–2.09) *	0.86 (0.48–1.53)
Stomach (401 / 337 & 122 / 214)	0.94 (0.80–1.10)	1.06 (0.84–1.35)
^ Gastric AC (210 / 193 & 53 / 112)	0.83 (0.67–1.02)	1.05 (0.75–1.47)
Colorectal (2,521 / 2,104 & 678 / 1,327)	1.00 (0.94–1.07)	1.00 (0.91–1.10)
^ Colon (1,656 / 1,347 & 457 / 862)	1.02 (0.94–1.10)	1.00 (0.89–1.13)
^ Rectum and rectosigmoid junction (865 / 757 & 221 / 465)	0.97 (0.88–1.08)	1.00 (0.85–1.19)
Liver and bile ducts (390 / 263 & 129 / 200)	1.09 (0.92–1.29)	1.12 (0.88–1.42)
^ HCC (124 / 67 & 42 / 60)	1.18 (0.86–1.63)	1.19 (0.78–1.83)
^ Gallbladder and bile ducts (196 / 150 & 60 / 103)	1.07 (0.85–1.35)	1.02 (0.72–1.43)
Pancreas (553 / 437 & 152 / 298)	1.11 (0.97–1.27)	0.98 (0.80–1.21)
Respiratory system		
Lung (combined) (1,707 / 1,522 & 409 / 970)	1.04 (0.97–1.12)	0.98 (0.87–1.10)
^ Lung AC (573 / 557 & 138 / 350)	1.04 (0.91–1.17)	0.92 (0.75–1.13)
^ Lung SCC (327 / 286 & 74 / 173)	0.95 (0.80–1.13)	1.06 (0.79–1.40)
^ Lung SmallCC (214 / 165 & 56 / 116)	1.25 (1.01–1.55) *	1.17 (0.83–1.63)
^ Lung (other morphology) (593 / 514 & 141 / 331)	1.04 (0.91–1.17)	0.93 (0.76–1.15)
Urinary system		
Kidney (465 / 293 & 159 / 217)	1.41 (1.21–1.65) **	1.43 (1.15–1.78) **
Renal pelvis and ureter (59 / 53 & 23 / 20)	0.93 (0.63–1.39)	2.21 (1.18–4.12) *
Bladder (688 / 504 & 179 / 386)	1.02 (0.91–1.16)	0.97 (0.80–1.17)
Reproductive system		
Prostate (3,376 / 2,472 & 844 / 1,839)	1.01 (0.96–1.07)	1.08 (0.99–1.17)
Breast (female) (3,509 / 4,645 & 1,013 / 1,918)	1.03 (0.98–1.08)	1.03 (0.95–1.12)
^ Breast pre–menopausal (36 / 220 & 5 / 18)	0.91 (0.63–1.32)	–
^ Breast post–menopausal (2,517 / 2,269 & 783 / 1,316)	1.06 (1.00–1.13) *	1.04 (0.95–1.15)
Ovary (453 / 554 & 112 / 241)	0.97 (0.85–1.11)	0.87 (0.69–1.11)
Corpus uteri (624 / 540 & 219 / 291)	1.16 (1.02–1.32) *	1.32 (1.09–1.58) **
^ Uterine AC (274 / 214 & 93 / 132)	1.21 (0.99–1.47)	1.22 (0.92–1.61)
^ Endometroid AC (277 / 269 & 96 / 131)	1.11 (0.92–1.33)	1.27 (0.96–1.69)
Cervix uteri (87 / 136 & 28 / 42)	0.91 (0.68–1.23)	1.30 (0.78–2.16)
^ Cervix SCC (51 / 94 & 17 / 25)	0.71 (0.49–1.03)	1.33 (0.69–2.57)
Anogenital (not cervix) (131 / 113 & 35 / 77)	1.12 (0.85–1.47)	0.85 (0.56–1.30)
^ Anogenital SCC (93 / 80 & 23 / 56)	1.17 (0.85–1.62)	0.81 (0.48–1.35)
Skin		
Skin SCC (815 / 584 & 221 / 392)	1.09 (0.97–1.22)	1.45 (1.22–1.72) **
Melanoma (skin) (771 / 846 & 197 / 426)	1.00 (0.90–1.12)	1.12 (0.94–1.34)
Nervous and endocrine system		
Brain and CNS (291 / 300 & 71 / 149)	0.97 (0.81–1.15)	1.03 (0.76–1.38)
^ Glioblastoma (144 / 153 & 37 / 71)	0.92 (0.72–1.17)	1.17 (0.77–1.77)
Thyroid (161 / 259 & 57 / 88)	1.04 (0.84–1.29)	1.22 (0.85–1.75)
Hematopoietic system		
Leukemia (695 / 613 & 205 / 351)	1.01 (0.90–1.13)	1.14 (0.95–1.37)
^ Multiple myeloma (254 / 221 & 87 / 125)	0.98 (0.81–1.19)	1.28 (0.96–1.71)
Lymphoma (all types) (504 / 554 & 119 / 273)	0.84 (0.74–0.96) *	0.99 (0.79–1.24)
^ Non–Hodgkin lymphomas (409 / 473 & 96 / 226)	0.81 (0.70–0.93) **	0.97 (0.76–1.25)
Other		
Other location AC (238 / 168 & 53 / 147)	1.30 (1.05–1.60) *	0.79 (0.57–1.09)
Other location or other morphology (1,326 / 1,166 & 370 / 698)	1.02 (0.94–1.11)	1.11 (0.97–1.26)

Hazard ratio

Figure 3. Forest plot of hazard ratios for dichotomous hypertension and antihypertensive treatment. Abbreviations: AC, adenocarcinoma; CNS, central nervous system; HCC, hepatocellular carcinoma; SCC, squamous cell carcinoma; SmallCC, small cell carcinoma; Hypertension, defined as systolic blood pressure (SBP) ≥140 mm Hg, or diastolic BP (DBP) ≥90 mm Hg at the BP measurement visit, or self-reported history of hypertension; Antihypertensive treatment status, either self-reported or no treatment assumed, if there was self-reported absence of diagnosis of hypertension; Cases, numbers per group (hypertension/no hypertension and treated/untreated hypertension); Vertical order, determined by body system (bold), followed by the main anatomical locations and the relevant specific locations or morphologies marked with ˆsymbols, as per Fig. 2 (other locations, not included in those specified, are shown last); Hazard ratios, estimates (95% confidence intervals) (per 10 mm Hg higher BP) were derived from Cox proportional hazards models, stratified by study center and age at recruitment (5-year categories) and adjusted for potential confounders and risk factors listed in Table S2. For cervical AC ($n = 37$): HR = 1.23 (0.58–2.06) and for other morphology in the cervix (non-SCC and non-AC) ($n = 41$): HR = 1.82 (0.92–3.63) (considered only in the main analyses and omitted from the plot to avoid the larger confidence intervals dominating the plot); *$p < 0.05$, **$p < 0.005$.

our findings, among users of antihypertensive drugs: OR = 2.4 (1.1–4.9).[31] However, as antihypertensive treatment may be related to the type and severity of hypertension, it is difficult to separate their effects in an observational study.

Cancers of the upper aerodigestive tract and lung. We found a positive association of BP with the risk of esophageal carcinoma, but more specifically with squamous cell carcinoma (SCC) ($n = 149$): HR = 1.16 (1.07–1.26) for SBP and HR = 1.31

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(1.13–1.51) for DBP and not with esophageal adenocarcinoma (AC) (*n* = 176) (Fig. 2). We also found a weak positive association for head and neck cancers (89% of which were SCC morphology): HR = 1.08 (1.04–1.12) for SBP and HR = 1.09 (1.01–1.17) for DBP (similarly for mouth and oropharynx and for larynx). For mouth and oropharynx, the positive associations were statistically significant only in women, in individuals older than 53 years at recruitment and for alcohol intake >12 g/day and for head and neck cancers and esophageal SCC only for alcohol intake >12 g/day and not below. There were, however, fewer cases among never smokers and the 95% CIs were too wide to make meaningful conclusions for smoking (Figs. S1*g* and S1*h*).

For lung cancer, there was no overall evidence for association of BP with SCC, AC or small cell carcinoma morphologies (Fig. 2). In subgroup analyses, we observed an inverse association of DBP with lung AC among individuals with BMI > 25 kg/m^2 (*n* = 528): HR = 0.90 (0.83–0.98) and a positive association of SBP with lung SCC in individuals receiving antihypertensive treatment (*n* = 74): HR = 1.14 (1.01–1.28). A weak positive association of SBP with the risk of total lung cancer was mainly accountable for by other morphologies (predominantly unclassified or large cell): HR = 1.06 (1.02–1.09).

Our findings for esophageal cancer are in agreement with the similarly sized Me-Can project, for which Stocks *et al.* reported a positive association of mid-BP with total esophageal cancer (*n* = 285): HR = 1.33 (1.13–1.57) per 10 mm Hg higher BP.[3] Lindkvist *et al.* further showed that this was accountable for by a higher risk of SCC (*n* = 184): HR = 1.30 (1.17–1.44) and not AC (*n* = 114): HR = 1.03 (0.89–1.19), with no major differences between subgroups of never, former and current smokers.[32] For head and neck cancers, Stocks *et al.* did report for the Me-Can project an association of mid-BP with the risk of cancers of the lip, oral cavity and pharynx, but only in men (*n* = 561): HR = 1.31 (1.15–1.48) per 10 mm Hg increase, but not in women (*n* = 177): HR = 1.05 (0.85–1.28). They also found a positive association for the combined group of cancer of the larynx, trachea and lung in men (*n* = 2,810): HR = 1.09 (1.03–1.16), but not in women (*n* = 905): HR = 1.00 (0.92–1.10).[3] Our study includes a similar number of lung cancer cases (*n* = 3,229), but we have examined separately cancer of the larynx and individual lung morphologies. While smoking is a major risk factor for both esophageal and lung SCC cancers and can also lead to hypertension, as shown in an animal model[33] and some epidemiological studies,[34,35] we could find a positive association with hypertension only for esophageal and not for lung SCC, after adjustment for smoking. If there was any residual confounding by smoking, it is likely that we would have observed a positive association for lung, as well as for esophageal SCC. In fact, we could find no positive association of hypertension with lung SCC even without adjustment for confounders (crude HRs in Fig. S2). Furthermore, a positive association for esophageal AC was observed only in unadjusted analyses but was lost after adjustment for confounders, indicating that the adjustment, has removed, to a great extent, the confounding by smoking. This leads

us to conclude that smoking is not likely to explain the association of high BP with the risk of SCC in the upper aerodigestive tract. Alcohol, however, may have an influence (Figs. S1*i* and S1*j*), but further investigations are needed to clarify our observations.

Gastric and colorectal cancers. We could not find association of BP with the risk of gastric cancer (*n* = 738), including gastric AC (*n* = 403), in the total cohort (Fig. 2). We only found a positive association for gastric AC among individuals receiving antihypertensive treatment (*n* = 53): HR = 1.22 (1.06–1.40) for SBP and HR = 1.65 (1.27–2.15) for DBP. We also found a weak positive association of DBP with the risk of cancer of the colon (*n* = 3,003) (75% of which had AC [code 8140/3] morphology): HR = 1.06 (1.02–1.10) for DBP, similarly for men and women (Fig. S1*b*), but not the rectum and rectosigmoid junction (*n* = 1,622) (81% AC) (Fig. 2). There was also a weak positive association of SBP with the risk of colorectal cancer (similarly for colon and rectum, including rectosigmoid junction) in men, but not in women (in men colon [*n* = 1,304]: HR = 1.03 [1.00–1.06] and rectum [*n* = 876]: HR = 1.03 [0.99–1.07]). We also found a positive association in the subgroup analyses for participants with BMI > 25 kg/m^2 (colon: *n* = 1,813, rectum: *n* = 966) and for the participants who reported alcohol intake >12 g/d (colon: *n* = 1,091, rectum: *n* = 685) (Figs. S1*c*, S1*d*, S1*i* and S1*j*).

Our data are broadly compatible with results from previous large studies, which suggest that high BP is associated with the risk of colorectal cancer in men but not in women. In 2001, Tenenbaum *et al.* reported, in a cohort of patients with stable angina or previous myocardial infarction, higher risk of colon cancer (*n* = 96) in individuals receiving diuretics compared to nonusers: HR = 2.0 (1.2–3.2).[36] More recently, in a large case–control study in Italy, Pelucchi *et al.* found that history of treated hypertension was associated with colorectal cancer risk in men (*n* = 1,310) OR = 1.24 (1.03–1.48) but not in women (*n* = 946) OR = 0.87 (0.71–1.06).[37] Stocks *et al.*, considering SBP, DBP and mid-BP in the prospective Me-Can study, also reported a positive association for cancer of the colon in men (*n* = 1,747): HR = 1.10 (1.03–1.19) per 10 mm Hg higher mid-BP, but not in women (*n* = 1,265): HR = 0.95 (0.88–1.02),[3,38] with similar findings for cancer of the rectum and anus.[3] Esposito *et al.* have subsequently reported in a meta-analysis based on 9 studies a RR = 1.09 (1.01–1.18) for high BP, although considering jointly men and women.[13] For gastric AC, Lindkvist *et al.*, similar to our total cohort results, could not find in the Me-Can project evidence supporting an association with mid-BP (*n* = 1,210), but they did not consider antihypertensive treatment.[39]

Breast cancer. In our study, representing a cohort with the largest to date number of breast cancer cases, we found a weak but statistically significant positive association with both, SBP and DBP (*n* = 8,154): HR = 1.03 (1.01–1.04) for SBP and HR = 1.03 (1.01–1.06) for DBP. The association was similar for postmenopausal cancers (*n* = 4,786), but the number of premenopausal cancers was considerably smaller and the 95% CIs were too wide

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to permit conclusions. In subgroup analyses, the positive association of SBP with the risk of postmenopausal breast cancer was retained only in ever smokers ($n = 2,180$) and there was some suggestion for a positive association of SBP with premenopausal breast cancer in women with alcohol intake ≤12 g/day ($n = 201$) (Figs. S1g and S1i).

Literature reports on breast cancer are conflicting. In an early case–control study in Italy, Soler et al. described a higher risk of breast cancer in women with treated hypertension ($n = 3,406$): OR = 1.2 (1.1–1.4) and more specifically in postmenopausal ($n = 2,184$), at age 55 years or older ($n = 1,580$), in drinking women ($n = 2,400$) and at BMI > 25 kg/m^2 ($n = 1,266$) and not in premenopausal and perimenopausal women.[40] However, Bjorge et al. in the Me-Can project did not find associations of SBP or DBP with the risk of incident breast cancer ($n = 4,862$), but they reported a higher risk of breast cancer mortality for age ≥60 years.[41] Similarly, Largent et al., defining high BP as treated hypertension in the California Teachers Study cohort ($n = 4,151$), found a higher risk associated with antihypertensive treatment longer than 5 years: HR = 1.18 (1.02–1.36),[42] but no association with hypertension overall. Nevertheless, in the largest to date meta-analysis ($n = 11,643$), Han et al. (in agreement with an earlier meta-analysis[12] and with our findings) have reported a higher risk of breast cancer in hypertensive women, based on 18 retrospective case–control studies: RR 1.29 (1.14–1.47) and on 12 prospective studies: RR = 1.07 (1.01–1.14), but only for postmenopausal women (13 studies): RR = 1.20 (1.09–1.31) and not for premenopausal (9 studies): RR = 0.97 (0.84–1.12).[15]

Endometrial cancer. For cancers located in corpus uteri, we found a weak positive association, which could be traced only to AC morphology (code 8140/3): HR = 1.06 (1.01–1.12) for SBP and HR = 1.11 (1.02–1.22) for DBP, but not to the endometroid morphology (code 8380/3): HR = 1.00 (0.96–1.05) for SBP and HR = 1.02 (0.93–1.10) for DBP (Fig. 2). In subgroup analyses, the association for AC morphology was retained only at BMI > 25 kg/m^2 and in never smokers (Figs. S1c, S1d, S1g and S1h). The differences between morphologies, however, would need further clarification, as the relative proportions of the two morphologies differed considerably between the individual countries in the EPIC cohort (Table S3).

Large European case–control and cohort studies ($n > 700$ in each), although not accounting for specific morphologies, have consistently reported, in agreement with our findings, a higher risk of endometrial cancer with high BP,[40,43,44] especially in obese women,[43,44] while a relatively smaller case–control study in the United States ($n = 469$) found a higher risk only in women receiving thiazide diuretics.[45] Nevertheless, recent meta-analyses, have corroborated a positive association: RR = 1.32 (1.12–1.56) (6 prospective studies, 11,469 cases),[9] RR = 1.81 (1.08–3.03) (5 studies, 3,112 cases).[10]

Cervical cancer. For cervical SCC ($n = 145$), but not for total cervical cancers ($n = 223$), we found an inverse association (Fig. 2),

which was especially pronounced in women with BMI > 25 kg/m^2 ($n = 68$): HR = 0.81 (0.71–0.93) for SBP and HR = 0.74 (0.57–0.95) for DBP (Figs. S1c and S1d), while we found no evidence for association of BP with cervical AC ($n = 37$) and a positive association for the remaining morphologies ($n = 41$): HR = 1.28 (1.10–1.48) for SBP and HR = 1.53 (1.17–2.01) for DBP, which would have contributed to the absence of an overall association for total cervical cancers, but with a small number of cases, this could be a chance finding.

In contrast to our findings, Stocks et al. reported a higher risk of total cervical cancer in the Me-Can study ($n = 424$): HR = 1.17 (1.01–1.34) per 10 mm Hg higher mid-BP.[3] Furthermore, Ulmer et al. examined individual morphological subtypes and reported, similar to esophageal cancer, a positive association for cervical SCC ($n = 337$): HR = 1.28 (1.05–1.57) per SD higher mid-BP, but not for cervical AC ($n = 59$): HR = 1.09 (0.65–1.83).[46]

Prostate cancer. Our study, based on a reasonably large number of incident cases ($n = 5,848$), provided no evidence for association of SBP or DBP with the risk of prostate cancer: HR = 0.99 (0.98–1.01) for SBP and HR = 1.01 (0.99–1.04) for DBP, except for some weak inverse association, mainly with SBP, which was found only in never smokers ($n = 1,937$): HR = 0.97 (0.95–1.00).

Contrary to our findings, the Cohort of Norway study ($n = 1,974$)[47] has reported a weak positive association between SBP and DBP and the risk of prostate cancer and recent meta-analyses have confirmed this.[11,14] Based on ten studies ($n = 4,343$), Esposito et al. reported RR = 1.15 (1.01–1.30)[11] and Gacci et al. (seven studies) reported RR = 1.10 (1.01–1.19).[14] However, the Me-Can study ($n = 6,673$)[48] found only a positive association of SBP and DBP with prostate cancer death, while Stocks et al. reported in the Swedish Construction Workers cohort an inverse association with the risk of total prostate cancer ($n = 10,002$) and nonaggressive tumors ($n = 2,817$), but a positive association of DBP with the risk of aggressive tumors ($n = 2,402$).[49] In the light of these discrepancies, it would be important to examine further the impact of cancer aggressiveness or grading in EPIC, but this was beyond the scope of the current study.

Blood and lymphoid cancers. Our data revealed an inverse association of BP with the risk of all-type lymphomas ($n = 1,058$), and specifically with non-Hodgkin lymphomas ($n = 882$): HR 0.96 (0.92–0.99) for SBP and borderline for DBP: HR = 0.95 (0.89–1.02), while we found no evidence for association with leukemia ($n = 1,308$), or specifically with multiple myeloma ($n = 475$) (Fig. 2).

In the Me-Can study, Nagel et al. considered a total of 2,751 cases of myeloid and lymphoid neoplasms and their results did not support associations with mid-BP, except for a suggestion, based on a small number of cases ($n = 46$), for an inverse association with the risk of T-cell non-Hodgkin lymphomas in men: HR = 0.54 (0.29–1.01).[50] Lymphoid cells are closely involved in inflammatory processes and recent studies have specifically linked T-cell subtypes with vascular remodeling and the

development of hypertension,[51] so there may be some mechanistic explanation, but this would need a more detailed investigation.

Skin cancer. We found evidence for a positive association with the risk of skin SCC for DBP (*n* = 1,399): HR = 1.07 (1.02–1.13) and for antihypertensive treatment among hypertensive individuals: HR = 1.45 (1.22–1.72).

The Me-Can project also reported higher risk of skin SCC, but only in men (*n* = 566): HR = 1.11 (0.95–1.31) for one SD higher mid-BP and not in women (*n* = 286): HR = 0.95 (0.76–1.19).[52] Several studies have also reported higher risk in association with antihypertensive drugs, especially diuretics,[53] but there were no sufficient treatment details in EPIC to explore further.

Sensitivity analyses

Excluding the first two years of follow-up did not have material influence on the findings (Fig. S2), except for abolishing the inverse association for cervical SCC (without changing it to positive), which may be the result of selection bias introduced by the exclusion. However, crude HRs (unadjusted) (Fig. S3) had indicated some associations, which were lost or mitigated after adjustment for confounders. Thus, crude HRs indicated positive associations of SBP and DBP not only with esophageal SCC or the endometroid cancer morphology in corpus uteri, but also of the AC morphology in both locations, and further positive associations of DBP with gastric cancer (total and AC morphology) and of SBP, not only DBP, with cancers of the rectum and rectosigmoid junction, as well as with colon cancer. Additionally, crude HRs indicated positive associations of SBP and DBP with bladder cancer, of SBP with liver cancer (accountable for only by hepatocellular carcinoma) and of DBP with multiple myeloma. In addition, in the absence of adjustment for confounders, a weak inverse association was observed for SBP with prostate cancer (SBP only) and DBP with lung AC. Associations observed only in crude and not in adjusted HR estimates suggest that the differences in the selection of adjustment variables in our and other studies may be responsible for some of the discrepancies in the findings. Of note, we have included adjustment for dietary factors, information on which was either not available or not included in the analyses in other published studies. This may be of particular relevance to cancers of the gastrointestinal tract. Similarly, we have used detailed information on reproductive factors in women, although adjustment did not affect our findings for breast and cervical cancers (Fig. S3).

Strengths and limitations

Our study has several strengths and limitations. Major advantages are the prospective design and the large sample size, including several European countries. Furthermore, BP was measured by trained personnel and was not self-reported. Detailed information on lifestyle, diet and, in women, reproductive history and

hormonal treatments was also available, enabling adjustment for potential confounders and shared risk factors.

The main limitation of our study is that BP was measured only at one time point. Moreover, specific information on the type of antihypertensive medications in treated individuals was unavailable. Theoretically, antihypertensive treatment could lead to a lower "observed" BP, that is, measured during the investigation, compared to the "underlying" BP, that is, the BP that could be reached without treatment. If high BP is causally associated with cancer, controlling BP would mitigate the association, but if high BP and cancer share common mechanisms, the association would remain when BP is controlled, unless treatment targets the mechanism of BP development. In practice, however, a single time point measurement may not be representative of the commonly "observed" BP, and this applies to untreated and treated individuals alike. Individuals receiving treatment are also likely to have a more sustained high BP, confirmed by a doctor. Treated individuals in our study showed, indeed, considerably higher SBP (mean difference 19.8 mm Hg [95% CI 19.6–20.1]) and DBP (9.5 mm Hg [9.4–9.6]) compared to cohort participants without antihypertensive treatment and even showed marginally higher SBP (1.2 mm Hg [1.0–1.4]) and DBP (0.4 mm Hg [0.3–0.5]) compared to untreated hypertensive individuals (self-reported or with "observed" high BP; Table 1). Therefore, when there was a positive association for both hypertension and antihypertensive treatment, as for kidney cancer, we could not discriminate associations related to the severity and duration of high BP from association related to the administration of antihypertensive medication (Fig. 3). Nevertheless, a positive association only for treated compared to untreated hypertension, as for cancers of the renal pelvis and ureter, might be more suggestive of the involvement of treatment (Fig. 3). There is a growing body of literature evaluating associations between antihypertensive medication and cancer development, but with overall inconclusive findings. An involvement of drugs in cancer pathogenesis is possible, because they are exogenous chemical compounds administered often for very long time,[54] but we have not reviewed this literature, because our study could not contribute reliably to the debate.

Finally, information about potential confounders and shared risk factors was self-reported, which may have contributed to misclassification bias and there are always potentially unmeasured risk factors, which may result in residual confounding.

Conclusions

The results of our study, involving over 300,000 participants, are largely compatible with published studies. We confirmed a positive association between BP and RCC and additionally found a positive association of BP with malignant cancers in several anatomical cites, including postmenopausal breast and colon cancers, and with specific morphologies, that is, SCC in the upper aerodigestive tract and the skin or AC in corpus uteri and other unspecified locations. We also found an inverse association of BP with the risk of non-Hodgkin lymphomas and cervical SCC. These associations, however, are mainly weak and future research

is required to clarify potential shared mechanisms. Admittedly, observations based on smaller number of cases could be chance findings, but they could also give some directions for further studies.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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