Hypertension and Risk of Endometrial Cancer: A Pooled Analysis in the Epidemiology of Endometrial Cancer Consortium (E2C2)

Talar S. Habeshian[1,2], Noah C. Peeri[3], Immaculata De Vivo[4,5], Leo J. Schouten[6], Xiao-ou Shu[7], Michele L. Cote[8], Kimberly A. Bertrand[9], Yu Chen[10], Megan A. Clarke[11], Tess V. Clendenen[10], Linda S. Cook[12], Laura Costas[13,14], Luigino Dal Maso[15], Jo L. Freudenheim[16], Christine M. Friedenreich[17], Grace Gallagher[3], Gretchen L. Gierach[18], Marc T. Goodman[19], Susan J. Jordan[20], Carlo La Vecchia[21], James V. Lacey[22], Fabio Levi[23], Linda M. Liao[18], Loren Lipworth[24], Lingeng Lu[25], Xavier Matias-Guiu[26], Kirsten B. Moysich[27], George L. Mutter[28], Renhua Na[29], Jeffin Naduparambil[3], Eva Negri[30], Kelli O'Connell[3], Tracy A. O'Mara[31], Irene Onieva Hernández[32], Julie R. Palmer[33], Fabio Parazzini[21], Alpa V. Patel[34], Kathryn L. Penney[35,36], Anna E. Prizment[37], Fulvio Ricceri[38], Harvey A. Risch[25], Carlotta Sacerdote[39], Sven Sandin[40,41], Rachael Z. Stolzenberg-Solomon[18], Piet A. van den Brandt[42], Penelope M. Webb[43], Nicolas Wentzensen[11], Akemi T. Wijayabahu[11], Lynne R. Wilkens[44], Wanghong Xu[45], Herbert Yu[46], Anne Zeleniuch-Jacquotte[47], Wei Zheng[7], Mengmeng Du[3], and Veronica Wendy Setiawan[1,48]

ABSTRACT

Background: The incidence rates of endometrial cancer are increasing, which may partly be explained by the rising prevalence of obesity, an established risk factor for endometrial cancer. Hypertension, another component of metabolic syndrome, is also increasing in prevalence, and emerging evidence suggests that it may be associated with the development of certain cancers. The role of hypertension independent of other components of metabolic syndrome in the etiology of endometrial cancer remains unclear. In this study, we evaluated hypertension as an independent risk factor for endometrial cancer and whether this association is modified by other established risk factors.

Methods: We included 15,631 endometrial cancer cases and 42,239 controls matched on age, race, and study-specific factors from 29 studies in the Epidemiology of Endometrial Cancer Consortium. We used multivariable unconditional logistic regression models to estimate ORs and 95% confidence intervals (CI) to evaluate the association between hypertension and endometrial cancer and whether this association differed by study design, race/ethnicity, body mass index, diabetes status, smoking status, or reproductive factors.

Results: Hypertension was associated with an increased risk of endometrial cancer (OR, 1.14; 95% CI, 1.09–1.19). There was significant heterogeneity by study design ($P_{het} < 0.01$), with a stronger magnitude of association observed among case–control versus cohort studies. Stronger associations were also noted for pre-/perimenopausal women and never users of postmenopausal hormone therapy.

Conclusions: Hypertension is associated with endometrial cancer risk independently from known risk factors. Future research should focus on biologic mechanisms underlying this association.

Impact: This study provides evidence that hypertension may be an independent risk factor for endometrial cancer.

[1]Department of Population and Public Health Sciences, Keck School of Medicine of USC, University of Southern California, Los Angeles, California. [2]Department of Research and Evaluation, Division of Health Services Research and Implementation Science, Kaiser Permanente Southern California, Pasadena, California. [3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York. [4]Department of Epidemiology, Program in Genetic Epidemiology and Statistical Genetics, Harvard School of Public Health, Boston, Massachusetts. [5]Medicine, Harvard Medical School, Boston, Massachusetts. [6]Department of Epidemiology, GROW-Research Institute for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands. [7]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee. [8]Fairbanks School of Public Health, Department of Epidemiology, Indiana University Simon Comprehensive Cancer Center, Indianapolis, Indiana. [9]Slone Epidemiology Center, Boston University, Boston, Massachusetts. [10]Population Health, New York University School of Medicine, New York, New York. [11]Division of Cancer Epidemiology and Genetics, NCI, Rockville, Maryland. [12]Epidemiology, Colorado School of Public Health, Aurora, Colorado. [13]Cancer Epidemiology Research Programme, Institut Català d'Oncologia, Barcelona, Spain. [14]Consortium for Biomedical Research in Epidemiology and Public Health - CIBERESP, Carlos III Institute of Health, Madrid, Spain. [15]Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano, Italy. [16]Department of Epidemiology and Environmental Health, University at Buffalo, State University of New York, Buffalo, New York. [17]Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, Canada. [18]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland. [19]Cancer Prevention and Control Program, Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California. [20]School of Public Health, University of Queensland, Herston, Queensland, Australia. [21]Department of Clinical Medicine and Community Health, University of Milan, Milan, Italy. [22]Department of Computational and Quantitative Medicine, City of Hope, Duarte, California. [23]Epidemiology and Health Services Research, University of Lausanne, Lausanne, Switzerland. [24]Department of Medicine, Vanderbilt University, Nashville, Tennessee. [25]Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut. [26]Department of Pathology, University Hospital of Bellvitge, IDIBELL, Barcelona, Spain. [27]Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, New York. [28]Pathology, Brigham and Women's Hospital, Boston, Massachusetts. [29]Population Health, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia. [30]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. [31]Cancer Research

Introduction

Endometrial cancer is the most common gynecologic cancer and the fourth most common cancer among women in the United States (1). The incidence rates of endometrial cancer are increasing, particularly among younger women (aged <50 years) and women from racial/ethnic minority groups (2–4). The rising incidence rates may by explained, in part, by the rising prevalence of obesity, an established risk factor for endometrial cancer, globally (5–8).

Metabolic syndrome is a cluster of metabolic abnormalities that includes obesity, dyslipidemia, hyperglycemia, and hypertension (9). Several epidemiologic studies have established associations between some components of metabolic syndrome and increased risk of endometrial cancer, independent of obesity (10–16). However, the role of hypertension, independent of the other components of metabolic syndrome, in the etiology of endometrial cancer remains unclear.

Hypertension is a common cardiovascular disease that affects approximately 40% of women in the United States (17). The prevalence of hypertension increases with age: approximately 50% of women aged 40 to 59 years and 74% of women aged 60 years and over are affected (17). Emerging evidence suggests that hypertension may be associated with the development of certain cancers, particularly through inflammatory, hormonal, and metabolic pathways (18). The results from several epidemiologic studies assessing the association between hypertension and endometrial cancer risk have been inconsistent. Some have reported a positive association between hypertension and endometrial cancer risk, although these studies vary on whether they addressed the potential influence of body mass index (BMI) or diabetes on this association (13, 14, 19–22), while others have reported no association, particularly after adjusting for BMI and diabetes (23, 24). Therefore, further research is needed to clarify the role of hypertension in endometrial cancer etiology.

In this study, we examined the association between hypertension and endometrial cancer risk by combining individual-level data for 15,631 endometrial cancer cases and 42,239 controls from 29 studies in the Epidemiology of Endometrial Cancer Consortium (E2C2). Our large study population enabled us to evaluate whether the association between hypertension and endometrial cancer is modified by other risk factors for the disease. Understanding this association may enable us to better identify women at higher risk for endometrial cancer and operationalize clinical interventions related to high blood pressure management for cancer prevention.

Materials and Methods

Participants and data collection

The E2C2 is an international consortium established in 2006 to identify and evaluate genetic, lifestyle and environmental risk factors for endometrial cancer by pooling resources and data from many studies (25–28). For this study, we pooled data from 29 epidemiologic studies (13 cohort and 16 case–control) from the E2C2 (**Table 1**). Cohort studies were included as nested case–control studies. Up to four controls were selected per case from females with an intact uterus and without endometrial cancer before the index case diagnosis. For both case–control and cohort studies, within each study, controls were matched with cases by age and other study-specific factors (e.g., race/ethnicity). Informed consent was obtained from all study participants in accordance with each study's Institutional Review Board. We included only individuals who had complete information on hypertension status and the covariates of interest described below (n = 16,694 excluded). The analytic study population included 15,631 cases and 42,239 controls (Supplementary Fig. S1); all controls were matched to at least one case. Written informed consent was obtained from all study participants in accordance with each study's Institutional Review Board and the studies included were conducted in accordance with recognized ethical guidelines (The Declaration of Helsinki).

Data collection

Data were collected within each study via self-reported questionnaires or in-person interviews, including sociodemographic information, anthropometric measures, reproductive and menstrual information, comorbid conditions, and other known or potential risk factors for endometrial cancer. We used a published data harmonization pipeline to standardize variables across E2C2 study sites (28–32). Incident cases of endometrial cancer were identified by each study site using International Classification of Diseases for Oncology, third edition (ICD-O-3) primary site codes: C54.0-C54.3, C54.8-C54.9, and C55.9 (behavior code 3). Tumor information and characteristics (stage, grade, histology) were collected from medical records, pathology reports, and/or linkages to national cancer registries, where available.

Participating studies provided information on the main exposure of interest, hypertension, which was obtained from the baseline self-reported questionnaires or in-person interviews [reported as "ever diagnosed with hypertension" (yes/no)].

Program, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia. [32]Faculty of Medicine, Cancer Epidemiology Research Programme and University of Barcelona, Institut Català d'Oncologia, Barcelona, Spain. [33]Slone Epidemiology Center and Department of Medicine, Boston University, Boston, Massachusetts. [34]Population Science, American Cancer Society, Kennesaw, Georgia. [35]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [36]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts. [37]Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota. [38]Department of Clinical and Biological Sciences, University of Turin, Orbassano, Italy. [39]Unit of Cancer Epidemiology, Azienda Ospedaliera Citta' della Salute e della Scienza di Torino, Turin, Italy. [40]Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden. [41]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York. [42]Epidemiology, Maastricht University, Maastricht, the Netherlands. [43]Population Health Program, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia. [44]Department of Epidemiology, University of Hawaii Cancer Center, Honolulu, Hawaii. [45]Epidemiology, Fudan University School of Public Health, Shanghai, China. [46]Cancer Center, University of Hawaii, Honolulu, Hawaii. [47]Population health, New York University School of Medicine, New York, New York. [48]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California.

Corresponding Authors: Talar S. Habeshian, Department of Population and Public Health Sciences, Keck School of Medicine, University of Southern California, 1450 Biggy Street, NRT 1517N, Los Angeles, CA 90033. E-mail: habeshia@usc.edu; and Veronica Wendy Setiawan, vsetiawa@med.usc.edu

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Table 1. Descriptive characteristics of study population.

Risk factors	Cases ($N = 15,631$) *N* (%)	Controls ($N = 42,239$) *N* (%)
Age (years)		
Mean (SD)	63.3 (9.8)	64.2 (10.4)
Race		
White	12,485 (79.9)	34,687 (82.2)
Black	924 (5.9)	3,479 (8.2)
Asian	1,778 (11.4)	2,953 (7.0)
Other/Unknown	444 (2.8)	1,120 (2.7)
Body mass index, kg/m^2		
<25	5,368 (34.3)	21,098 (50.0)
25–29	4,595 (29.4)	13,183 (31.2)
30–34	2,833 (18.1)	5,145 (12.2)
≥35	2,835 (18.1)	2,813 (6.7)
Age at menarche, years		
<11	1,095 (7.0)	2,343 (5.6)
11–12	6,206 (39.7)	16,631 (39.4)
13–14	6,343 (40.6)	17,534 (41.5)
≥15	1,987 (12.7)	5,731 (13.6)
Parity		
0	2,741 (17.5)	5,579 (13.2)
1	2,574 (16.5)	5,827 (13.8)
2	4,494 (28.8)	12,483 (29.6)
3	3,186 (20.4)	9,315 (22.1)
≥4	2,636 (16.9)	9,035 (21.4)
Menopausal status		
Pre-/Perimenopausal	4,064 (26.0)	12,198 (28.9)
Postmenopausal	11,567 (74.0)	30,041 (71.1)
Oral contraceptive use		
Never	9,769 (62.5)	24,239 (57.4)
Ever	5,862 (37.5)	18,000 (42.6)
Postmenopausal hormone use		
Never	10,294 (65.9)	26,275 (62.2)
Ever	5,337 (34.1)	15,964 (37.8)
Smoking status		
Never	9,994 (63.9)	23,900 (56.6)
Former	4,180 (26.7)	12,249 (29.0)
Current	1,457 (9.3)	6,090 (14.4)
Diabetes status		
No	13,772 (88.1)	39,385 (93.2)
Yes	1,859 (12.0)	2,854 (6.8)

Information on established risk factors for endometrial cancer were also obtained and evaluated as covariates of interest, including age (continuous), race (Asian, Black, White, Other/Unknown), BMI (continuous and categorical: normal <25, overweight 25–29, obese 30–34, severely obese ≥35 kg/m^2), age at menarche (<11, 11–12, 13–14, ≥15 years), parity (0, 1, 2, 3, or ≥4 live births), menopausal status (pre-/perimenopausal, postmenopausal), oral contraceptive use (never, ever), postmenopausal hormone use (never, ever), smoking status (never, former, current), and diabetes status (no, yes; refs. 26, 27, 33–37). For the included cohort studies, participating study sites provided information on covariates closest to the date of diagnosis. If no follow-up was available for a particular study site, covariates reflected cohort baseline. Two studies, the Netherlands Cohort Study on Diet and Cancer and NYU Women's Health Study, did not include information on livebirths only, hence information on livebirths and stillbirths combined was used as a proxy for parity.

Statistical analysis

To estimate the association between hypertension and endometrial cancer risk, we used individual-level data and performed a pooled complete-case analysis using multivariable unconditional logistic regression to estimate ORs and 95% confidence intervals (CI). All models were adjusted for factors including age (at diagnosis for cases or at index date for controls), race/ethnicity, study site, BMI, age at menarche, parity, menopausal status, oral contraceptive use, postmenopausal hormone therapy use, smoking status, and diabetes status. To examine whether the association between hypertension and endometrial cancer risk is more pronounced among obese or women with diabetes, we stratified by BMI and diabetes status, separately. We also assessed whether the association differed by study design, race/ethnicity, smoking status, or reproductive risk factors including age at menarche, parity, menopausal status, oral contraceptive use, and postmenopausal hormone therapy use. We included interaction terms in models and examined heterogeneity of ORs across subgroups using the Wald test.

To address possible residual confounding by BMI, we reran our models by adjusting for BMI as a continuous variable, however, the effect estimates of these models were not materially different, so we kept our original models adjusting for BMI as a categorical variable. We also conducted a sensitivity analysis excluding BMI as a covariate to test whether BMI is an intermediate factor of the association between hypertension and endometrial cancer.

All reported *P* values are two-sided and an alpha level of 0.05 was used to define statistical significance. All analyses were conducted using SAS version 9.4.

Data availability

Deidentified epidemiologic data are available to researchers through a formal protocol submission process. Researchers can request access via the E2C2 website hosted by the NCI (https://epi.grants.cancer.gov/eecc/). Interested parties can follow the information on our E2C2 website to request access to the deidentified data.

Results

Study characteristics of all E2C2 studies included in this analysis are presented in Supplementary Table S1. This study included 15,631 endometrial cancer cases and 42,239 controls (**Table 1**). The mean age at diagnosis for cases was 63.3 years and the mean index age for controls was 64.2 years. Women with endometrial cancer were more likely to be obese (18.1% vs. 12.2% in controls) or severely obese (18.1% vs. 6.7%), have an early age of menarche (< 11 years; 7.0% vs. 5.6%), be nulliparous (17.5% vs. 13.2%), post-menopausal (74.0% vs. 71.1%), and have diabetes (12.0% vs. 6.8%) compared with controls. Cases were less likely to ever use oral contraceptives (37.5% vs. 42.6%), ever use postmenopausal hormone therapy (34.1% vs. 37.8%), and be former (26.7% vs. 29.0%) or current smokers (9.3% vs. 14.4%) compared with controls.

Nearly 40% of cases had a history of hypertension compared with 31% of controls. After multivariable adjustment, hypertension was associated with an increased risk of endometrial cancer (OR, 1.14; 95% CI, 1.09–1.19; **Table 2**). While the associations in the cohort (OR, 1.08; 95% CI, 1.02–1.14) and case–control (OR, 1.15; 95% CI, 1.07–1.23) studies were both statistically significant, there was significant heterogeneity by study design ($P_{het} < 0.01$). Study-specific effect estimates are shown in Supplementary Fig. S2.

We present subgroup-specific results from the pooled analysis of the association between hypertension and endometrial cancer risk in **Table 3**. When stratified by race, we observed a statistically significant association between hypertension and endometrial cancer risk in White women (OR_{White}, 1.14; 95% CI, 1.09–1.20). In Black, Asian, and Other race women, the magnitude of the effect estimates was comparable w those in White women, but not statistically significant, likely due to smaller cell sizes ($OR_{Black} = 1.09$, 95% CI, 0.92–1.29; $OR_{Asian} = 1.12$, 95% CI, 0.97–1.30; $OR_{Other} = 1.20$, 95% CI, 0.91–1.59; $P_{het} = 0.43$).

Hypertension was consistently associated with increased risk of endometrial cancer across most BMI strata, with the strongest association observed among women with BMI > 30 kg/m^2 ($OR_{BMI\ 30–34\ kg/m2} = 1.24$, 95% CI, 1.12–1.37; $OR_{BMI \geq 35\ kg/m2} = 1.17$, 95% CI, 1.04–1.32). Among overweight women, we observed a borderline statistically significant association between hypertension and endometrial cancer risk, when compared with women without hypertension ($OR_{BMI\ 25–29\ kg/m2} = 1.07$, 95% CI, 0.99–1.15; $P_{het} = 0.08$). Hypertension was also associated with increased risk of endometrial cancer among the leanest women ($OR_{BMI\ <25\ kg/m2} = 1.16$; 95% CI, 1.07–1.26). In the sensitivity analysis excluding BMI as a covariate, the association between hypertension and endometrial cancer was stronger (OR, 1.39; 95% CI, 1.34–1.45) compared with the main model (OR, 1.14; 95% CI, 1.09–1.19).

We additionally performed stratified analyses by age at menarche, parity, oral contraceptive use, menopausal status, postmenopausal hormone therapy use, smoking status, and diabetes status. We observed statistically significant differences across groups for menopausal status ($P_{het} = 0.03$) and postmenopausal hormone therapy use ($P_{het} < 0.01$). Associations of hypertension and endometrial cancer risk were similar by age at menarche, parity, oral contraceptive use, smoking status, and diabetes status (P_{het} for all > 0.05). We present results for the association between hypertension and endometrial cancer by histologic subtype removing cases with unknown histology (Supplementary Table S2). Hypertension was associated with an increased risk for both endometrioid (OR, 1.56; 95% CI, 1.39–1.76) and nonendometrioid cancers (OR, 1.51; 95% CI, 1.33–1.71).

Discussion

In this pooled analysis of individual-level data from almost 58,000 women, including nearly 16,000 cases, we found that hypertension is associated with a 14% increased risk of endometrial cancer, independent of diabetes, BMI, and reproductive factors.

Our results are consistent with several published studies that found that hypertension is a risk factor for endometrial cancer, independent of other known metabolic syndrome risk factors (13, 14, 19–21). A systematic review and meta-analysis of six cohort studies and 19 case–control studies reported that hypertension was associated with a 61%

Table 2. Association of hypertension status with endometrial cancer by study design.

	Study design								
	Cohort			Case–Control			Total		
	No. of cases (%)	No. of controls (%)	OR (95% CI)	No. of cases (%)	No. of controls (%)	OR (95% CI)	No. of cases (%)	No. of controls (%)	OR (95% CI)
Hypertension status									
No	5,170 (62.5)	20,922 (68.4)	1.00 (-)	4,291 (58.3)	8,306 (71.4)	1.00 (-)	9,461 (60.5)	29,228 (69.2)	1.00 (-)
Yes	3,103 (37.5)	9,687 (31.7)	1.08 (1.02–1.14)	3,067 (41.7)	3,324 (28.6)	1.15 (1.07–1.23)	6,170 (39.5)	13,011 (30.8)	1.14 (1.09–1.19)
P_{het}								*<0.01*	

Note: ORs were adjusted for age, race, study site, BMI, age at menarche, parity, menopausal status, oral contraceptive use, postmenopausal hormone use, smoking status, and diabetes status.

Table 3. Association of hypertension with endometrial cancer by risk factors.

	Hypertension						
	No			Yes			
Risk factors	**No. of cases (%)**	**No. of controls (%)**	**OR**	**No. of cases (%)**	**No. of controls (%)**	**OR (95% CI)**	P_{het}
Race/Ethnicity							*0.43*
White	7,744 (81.9)	24,891 (85.2)	1.00	4,741 (76.8)	9,796 (75.3)	1.14 (1.09–1.20)	
Black	360 (3.8)	1,609 (5.5)	1.00	564 (9.1)	1,870 (14.4)	1.09 (0.92–1.29)	
Asian	1,108 (11.7)	2,006 (6.9)	1.00	670 (10.9)	947 (7.3)	1.12 (0.97–1.30)	
Other[a]	249 (2.6)	722 (2.5)	1.00	195 (3.2)	398 (3.1)	1.20 (0.91–1.59)	
BMI							*0.08*
<25 kg/m^2	4,104 (43.4)	16,739 (57.3)	1.00	1,264 (20.5)	4,359 (33.5)	1.16 (1.07–1.26)	
25–29 kg/m^2	2,870 (30.3)	8,621 (29.5)	1.00	1,725 (28.0)	4,562 (35.1)	1.07 (0.99–1.15)	
30–34 kg/m^2	1,333 (14.1)	2,689 (9.2)	1.00	1,500 (24.3)	2,456 (18.9)	1.24 (1.12–1.37)	
≥35 kg/m^2	1,154 (12.2)	1,179 (4.0)	1.00	1,681 (27.2)	1,634 (12.6)	1.17 (1.04–1.32)	
Age at menarche, years							*0.98*
<11	604 (6.4)	1,549 (5.3)	1.00	491 (8.0)	794 (6.1)	1.22 (1.02–1.45)	
11–12	3,678 (38.9)	11,322 (38.7)	1.00	2,528 (41.0)	5,309 (40.8)	1.13 (1.06–1.22)	
13–14	3,939 (41.6)	12,369 (42.3)	1.00	2,404 (39.0)	5,165 (39.7)	1.13 (1.05–1.21)	
≥15	1,240 (13.1)	3,988 (13.6)	1.00	747 (12.1)	1,743 (13.4)	1.15 (1.02–1.31)	
Parity							*0.55*
0	1,779 (18.8)	4,080 (14.0)	1.00	962 (15.6)	1,499 (11.5)	1.14 (1.01–1.28)	
1	1,614 (17.1)	4,096 (14.0)	1.00	960 (15.6)	1,731 (13.3)	1.05 (0.94–1.18)	
2	2,791 (29.5)	8,913 (30.5)	1.00	1,703 (27.6)	3,570 (27.4)	1.16 (1.07–1.26)	
3	1,877 (19.8)	6,363 (21.8)	1.00	1,309 (21.2)	2,952 (22.7)	1.13 (1.02–1.24)	
≥4	1,400 (14.8)	5,776 (19.8)	1.00	1,236 (20.0)	3,259 (25.0)	1.19 (1.08–1.32)	
Oral contraceptive use							*0.11*
Never	5,659 (59.8)	16,275 (32.4)	1.00	4,100 (66.6)	7,964 (61.2)	1.15 (1.09–1.21)	
Ever	3,802 (40.2)	12,953 (44.3)	1.00	2,060 (33.4)	5,047 (38.8)	1.12 (1.04–1.21)	
Menopausal status							*0.03*
Pre-/Perimenopausal	2,872 (30.4)	9,459 (32.4)	1.00	1,192 (19.3)	2,739 (21.1)	1.25 (1.13–1.37)	
Postmenopausal	6,589 (69.6)	19,769 (67.6)	1.00	4,978 (80.7)	10,272 (78.9)	1.12 (1.06–1.17)	
Postmenopausal hormone use[b]							*<0.01*
Never	3,745 (56.8)	10,862 (54.9)	1.00	3,331 (66.9)	6,065 (59.0)	1.17 (1.10–1.26)	
Ever	2,844 (43.2)	8,907 (45.1)	1.00	1,647 (33.1)	4,207 (41.0)	1.05 (0.97–1.13)	
Smoking status							*0.07*
Never	5,999 (63.4)	16,569 (56.7)	1.00	3,995 (64.7)	7,331 (56.3)	1.16 (1.09–1.23)	
Former	2,505 (26.5)	8,271 (28.3)	1.00	1,675 (27.1)	3,978 (30.6)	1.13 (1.04–1.23)	
Current	957 (10.1)	4,388 (15.0)	1.00	500 (8.1)	1,702 (13.1)	1.10 (0.95–1.26)	
Diabetes status							*0.86*
No	8,885 (93.9)	28,195 (96.5)	1.00	4,887 (79.2)	11,190 (86.0)	1.13 (1.08–1.18)	
Yes	576 (6.1)	1,033 (3.5)	1.00	1,283 (20.8)	1,821 (14.0)	1.26 (1.09–1.47)	

Note: ORs were adjusted for age, race/ethnicity, study site, body mass index, age at menarche, parity, menopausal status, oral contraceptive use, postmenopausal hormone use, smoking status, and diabetes status.
[a]Other = Mixed, Other, Hawaiian or Pacific Islander.
[b]Analyses restricted to postmenopausal women only.

increase in endometrial cancer risk, with a weaker association observed among cohort studies when compared with case–control studies (19), consistent with our study findings. However, our results were not as pronounced as that systematic review, likely because the meta-analysis included effect estimates from studies that did not adjust for all known risk factors for endometrial cancer, particularly BMI. Another possible explanation is publication bias in the meta-analysis. In a case–control study evaluating the association between metabolic syndrome and endometrial cancer risk using SEER-Medicare linked data, hypertension was associated with a 13% increase in endometrial cancer risk, independent of body weight (13). Another case–control study found a 57% increase in endometrial cancer risk in women with hypertension, adjusted for known risk factors and other components of metabolic syndrome (21). A population-based cohort study evaluating hypertension and gynecological cancer risk found an 88% increased risk of endometrial cancer, adjusting for known risk factors and relevant comorbidities, although they did not adjust for BMI (20). Taken together, these data suggest that hypertension may be a modifiable risk factor for endometrial cancer development. However, of note, several previous studies did not observe an increased risk of endometrial cancer by hypertension after adjusting for BMI (23, 24), although one did find that hypertension was associated with an increased risk of endometrial cancer among obese women (24). It is important to note that these studies had small sample sizes.

The relationship between hypertension and endometrial cancer may be related to the influence of hypertension on hormonal, metabolic, and inflammatory pathways. However, the link between hypertension and cancer in general remains unclear (38). There is some evidence that suggests hypertension may play a role in

inhibiting apoptosis, leading to the development of cancer (39–41). Hypertension has also been linked to increased levels of cytosolic calcium, which is related to cell proliferation activated by oncogenes and certain hormones that have mitogenic effects, such as angiotensin II, catecholamines, vasopressin, insulin, and growth hormone (41, 42). Further research evaluating these biologic mechanisms are needed to help inform the role of hypertension in endometrial cancer risk.

Strengths of our study include the large sample size and heterogeneous study population; this pooled analysis is one of the largest studies to examine the association between hypertension and endometrial cancer risk, to date. Our study design allowed us to combine individual-level data from 29 studies while consistently defining hypertension and other covariates across study sites. In addition, few studies have comprehensively examined the association between hypertension and endometrial cancer risk. Most published literature on this topic has evaluated hypertension as part of the constellation of components of metabolic syndrome (10). Our study's large sample size also allowed us to evaluate the association between hypertension and endometrial cancer risk within strata of established endometrial cancer risk factors. Our study also has several limitations to be noted. We did not have any information on antihypertensive drug use and the timing of hypertension diagnosis in relation to endometrial cancer diagnosis. Because we are unsure if the women in our study were receiving treatment for hypertension, we may not be observing the full effect of hypertension on endometrial cancer. It is important to note, however, that even with treatment information, not knowing whether individuals are compliant with their prescribed antihypertensive mediation and, therefore, whether individuals' hypertension diagnoses are managed well or unmanaged is a major issue across studies evaluating hypertension as a risk factor. Obtaining this information would be crucial in further evaluating hypertension as a modifiable risk factor for endometrial cancer risk. In addition, self-reported data was utilized, which may have resulted in residual confounding and misclassification of these variables towards the null, although self-report is an established method in epidemiologic studies. In addition, through the data harmonization process, there may be residual confounding introduced through collapsing of more detailed covariate data. There is potential for recall and selection bias for exposure and covariate data, particularly among the case–control studies, although estimates for risk factors published from the E2C2 have been similar across cohort and case–control study design (26). Cohort study sites provided information on menopausal status closest to the time of diagnosis if available, however some study sites were only able to provide menopausal status at baseline. This may have resulted in misclassification of some of the women. However, endometrial cancer is traditionally a disease affecting older women (74% of cases included were diagnosed postmenopause), thus misclassification is likely to be minimal. Some of the case–control studies included in this pooled analysis are hospital-based. Thus, there is the potential for findings to be influenced by selection bias (i.e., Berkson's bias). However, after stratifying by study design the effect estimates were generally comparable. Finally, 82% of our study population was White and thus, our race/ethnicity stratified analysis is limited by small sample sizes.

In summary, we found that hypertension was associated with endometrial cancer risk, independent of known risk factors. Future risk stratification efforts to identify women at high risk of endometrial cancer should include hypertension as one of many predictive factors. In addition, research to evaluate whether existing intervention strategies to lower blood pressure (i.e., use of antihypertensive mediations, diet, and exercise) may help mitigate the rising burden of endometrial cancer. Further research is warranted evaluating the biological mechanisms underlying the observed association.

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Authors' Contributions

T.S. Habeshian: Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing–original draft, project administration. **N.C. Peeri:** Formal analysis, writing–review and editing. **I. De Vivo:** Funding acquisition, methodology, writing–review and editing. **L.J. Schouten:** Writing–review and editing. **X.-o. Shu:** Writing–review and editing. **M.L. Cote:** Writing–review and editing. **K.A. Bertrand:** Writing–review and editing. **Y. Chen:** Writing–review and editing. **M.A. Clarke:** Writing–review and editing. **T.V. Clendenen:** Writing–review and editing. **L.S. Cook:** Writing–review and editing. **L. Costas:** Writing–review and editing. **L. Dal Maso:** Writing–review and editing. **J.L. Freudenheim:** Writing–review and editing. **C.M. Friedenreich:** Writing–review and editing. **G. Gallagher:** Writing–review and editing. **G.L. Gierach:** Writing–review and editing. **M.T. Goodman:** Writing–review and editing. **S.J. Jordan:** Writing–review and editing. **C. La Vecchia:** Writing–review and editing. **J.V. Lacey:** Writing–review and editing. **F. Levi:** Writing–review and editing. **L.M. Liao:** Writing–review and editing. **L. Lipworth:** Writing–review and editing. **L. Lu:** Writing–review and editing. **X. Matías-Guiu:** Writing–review and editing. **K.B. Moysich:** Writing–review and editing. **G.L. Mutter:** Writing–review and editing. **R. Na:** Writing–review and editing. **J. Naduparambil:** Writing–review and editing. **E. Negri:** Writing–review and editing. **K. O'Connell:** Writing–review and editing. **T.A. O'Mara:** Writing–review and editing. **I. Onieva Hernández:** Writing–review and editing. **J.R. Palmer:** Writing–review and editing. **F. Parazzini:** Writing–review and editing. **A.V. Patel:** Writing–review and editing. **K.L. Penney:** Writing–review and editing. **A.E. Prizment:** Writing–review and editing. **F. Ricceri:** Writing–review and editing. **H.A. Risch:** Writing–review and editing. **C. Sacerdote:** Writing–review and editing. **S. Sandin:** Writing–review and editing. **R.Z. Stolzenberg-Solomon:** Writing–review and editing. **P.A. van den Brandt:** Writing–review and editing. **P.M. Webb:** Writing–review and editing. **N. Wentzensen:** Writing–review and editing. **A.T. Wijayabahu:** Writing–review and editing. **L.R. Wilkens:** Writing–review and editing. **W. Xu:** Writing–review and editing. **H. Yu:** Writing–review and editing. **A. Zeleniuch-Jacquotte:** Writing–review and editing. **W. Zheng:** Writing–review and editing. **M. Du:** Resources, funding acquisition, methodology, writing–review and editing. **V.W. Setiawan:** Conceptualization, resources, funding acquisition, methodology, project administration, writing–review and editing.

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