Investigation of Dietary Factors and Endometrial Cancer Risk Using a Nutrient-wide Association Study Approach in the EPIC and Nurses' Health Study (NHS) and NHSII

Melissa A. Merritt[1], Ioanna Tzoulaki[1], Shelley S. Tworoger[2,3], Immaculata De Vivo[2,3,4], Susan E. Hankinson[2,3,5], Judy Fernandes[1], Konstantinos K. Tsilidis[6,7], Elisabete Weiderpass[8,9,10,11], Anne Tjønneland[12], Kristina E.N. Petersen[12], Christina C. Dahm[13], Kim Overvad[13], Laure Dossus[14,15,16], Marie-Christine Boutron-Ruault[14,15,16], Guy Fagherazzi[14,15,16], Renée T. Fortner[17], Rudolf Kaaks[17], Krasimira Aleksandrova[18], Heiner Boeing[18], Antonia Trichopoulou[19,20], Christina Bamia[21], Dimitrios Trichopoulos[3,19,20], Domenico Palli[22], Sara Grioni[23], Rosario Tumino[24], Carlotta Sacerdote[25,26], Amalia Mattiello[27], H.B(as). Bueno-de-Mesquita[1,28,29,30], N. Charlotte Onland-Moret[31], Petra H. Peeters[1,31], Inger T. Gram[8], Guri Skeie[8], J. Ramón Quirós[32], Eric J. Duell[33], María-José Sánchez[34,35], D. Salmerón[35,36,37], Aurelio Barricarte[35,38], Saioa Chamosa[39,40], Ulrica Ericson[41], Emily Sonestedt[41], Lena Maria Nilsson[42,43], Annika Idahl[44], Kay-Tee Khaw[45], Nicholas Wareham[46], Ruth C. Travis[47], Sabina Rinaldi[48], Isabelle Romieu[48], Chirag J. Patel[49], Elio Riboli[1], and Marc J. Gunter[1]

Abstract

Data on the role of dietary factors in endometrial cancer development are limited and inconsistent. We applied a "nutrient-wide association study" approach to systematically evaluate dietary risk associations for endometrial cancer while controlling for multiple hypothesis tests using the false discovery rate (FDR) and validating the results in an independent cohort. We evaluated endometrial cancer risk associations for dietary intake of 84 foods and nutrients based on dietary questionnaires in three prospective studies, the European Prospective Investigation into Cancer and Nutrition (EPIC; $N = 1,303$ cases) followed by validation of nine foods/nutrients (FDR ≤ 0.10) in the Nurses' Health Studies (NHS/NHSII; $N = 1,531$ cases). Cox regression models were used to estimate HRs and 95% confidence intervals (CI). In multivariate adjusted comparisons of the extreme categories of intake at baseline, coffee was inversely associated with endometrial cancer risk (EPIC, median intake 750 g/day vs. 8.6; HR, 0.81; 95% CI, 0.68–0.97, $P_{trend} = 0.09$; NHS/NHSII, median intake 1067 g/day vs. none; HR, 0.82; 95% CI, 0.70–0.96, $P_{trend} = 0.04$). Eight other dietary factors that were associated with endometrial cancer risk in the EPIC study (total fat, monounsaturated fat, carbohydrates, phosphorus, butter, yogurt, cheese, and potatoes) were not confirmed in the NHS/NHSII. Our findings suggest that coffee intake may be inversely associated with endometrial cancer risk. Further data are needed to confirm these findings and to examine the mechanisms linking coffee intake to endometrial cancer risk to develop improved prevention strategies. *Cancer Epidemiol Biomarkers Prev; 24(2); 466–71. ©2015 AACR.*

[1]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom. [2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. [3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts. [4]Program in Genetic Epidemiology and Statistical Genetics, Harvard School of Public Health, Boston, Massachusetts. [5]Division of Biostatistics and Epidemiology, University of Massachusetts, Amherst, Massachusetts. [6]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece. [7]Cancer Epidemiology Unit, University of Oxford, Oxford, United Kingdom. [8]Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway. [9]Department of Research, Cancer Registry of Norway, Oslo, Norway. [10]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden. [11]Department of Genetic Epidemiology, Samfundet Folkhälsan, Helsinki, Finland. [12]Danish Cancer Society Research Center, Copenhagen, Denmark. [13]Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark. [14]Inserm, Centre for Research in Epidemiology and Population Health (CESP), Villejuif, France. [15]University Paris Sud, Villejuif, France. [16]IGR, Villejuif, France. [17]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [18]Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany. [19]Hellenic Health Foundation, Athens, Greece. [20]Bureau of Epidemiologic Research, Academy of Athens, Athens, Greece. [21]Department of Hygiene, Epidemiology, and Medical Statistics, University of Athens Medical School, Athens, Greece. [22]Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute—ISPO, Florence, Italy. [23]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy. [24]Cancer Registry and Histopathology Unit, "Civic–M.P. Arezzo" Hospital, ASP, Ragusa, Italy. [25]Unit of Cancer Epidemiology, AO Citta' della Salute e della Scienza–University of Turin and Center for Cancer Prevention (CPO-Piemonte), Turin, Italy. [26]Human Genetics Foundation (HuGeF), Turin, Italy. [27]Dipartimento di Medicina Clinica e Chirurgia, Federico II University, Naples, Italy. [28]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands. [29]Department of Gastroenterology and Hepatology,

Introduction

Higher endometrial cancer incidence rates in North America and Europe versus lower rates in Africa and South Asia (1) may be explained by endometrial cancer risk factors such as estrogen exposure and obesity, which are related to a westernized lifestyle (2); as diet is an important component of the westernized lifestyle, we hypothesized that dietary factors may also contribute to endometrial cancer etiology. The recent World Cancer Research Fund (WCRF) meta-analysis of 3,571 endometrial cancer cases reported an inverse association between coffee drinking and endometrial cancer risk (3); however, an important unanswered question is whether other dietary factors may play a role in endometrial cancer development.

We sought to investigate whether dietary factors were related to endometrial cancer risk by applying a "nutrient-wide association study" (NWAS) approach (4–6). The NWAS is an application of methods developed for GWAS to identify associations between dietary intake and risk of disease and includes adjustment for multiple comparisons by calculating the false discovery rate (FDR) (7) followed by external validation of results in an independent study. This method has been used to identify novel dietary risk associations for diabetes and blood pressure (4, 6). The current study is the first to use the NWAS method to prospectively evaluate dietary factors and risk of endometrial cancer in European and North American populations.

Materials and Methods

This NWAS investigated intakes of 84 foods/nutrients in relation to endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, calculated the associated FDR to select dietary factors and evaluated these factors and endometrial cancer risk in the validation cohorts, the Nurses' Health Study (NHS) and NHSII (Supplementary Fig. S1).

Study populations

The EPIC study includes 521,330 participants 25 to 70 years at enrollment (1992–2000; ref. 8). From 367,903 women in the EPIC study, individuals were excluded if they: reported a prevalent cancer except non-melanoma skin cancer ($n = 19,853$); were missing follow-up information ($n = 2,898$); had a hysterectomy ($n = 35,116$); did not complete a dietary questionnaire ($n = 2,855$);

were classified in the top or bottom 1% of energy intake to energy requirement ($n = 6,045$); were missing a lifestyle questionnaire ($n = 22$); or had outlying values for specific nutrient intakes ($n = 7$), leaving 301,107 participants in this study. Informed consent was provided by all participants and ethical approval for the study was obtained from the internal review board of the International Agency for Research on Cancer and from local ethics committees in each participating country.

The NHS was established in 1976 among 121,700 married, female registered nurses, ages 30 to 55 years, while the NHSII began in 1989 among 116,430 female registered nurses, ages 25 to 42 years (9, 10). Participants excluded at the study baseline (1980 for NHS and 1991 for NHSII) were women with a diagnosis of cancer except non-melanoma skin cancer or those who died (NHS = 3,630; NHSII = 1,321); those who reported a hysterectomy (NHS = 20,657; NHSII = 6,424); or were ineligible (e.g., duplicate ID; NHS = 36; NHSII = 199). Participants did not contribute person–time in cycles in which they were missing body mass index (BMI) or if they had a total caloric intake (<600 or >3,500 kcal/day) for the expanded food frequency questionnaire (FFQ; 1984 and thereafter), but they could re-enter the analysis for subsequent periods after these data became available. Informed consent was provided by all participants and the study design, data collection, and analyses were performed in accordance with the ethical standards of the institutional review board at the Brigham and Women's Hospital (Boston, MA).

Ascertainment of endometrial cancer cases

In the EPIC study, incident endometrial cancers were identified through population-based cancer registries or active follow-up, and mortality data were obtained from cancer or mortality registries (8). Tumors were classified as ICD-10 code C54. In total, 1,504 cases were identified and cases were censored if they were not the first incident tumor ($n = 54$), nonepithelial ($n = 68$), or missing tumor behavior ($n = 79$). Analyses of type I/II tumors were not conducted in the EPIC study because data on tumor histologic subtype and grade were incomplete.

In the NHS/NHSII, information about new diagnoses was collected in each questionnaire. When a woman reported a cancer, permission was sought to obtain the relevant medical records and pathology reports, and study physicians reviewed these documents to confirm the diagnosis. Deaths in the cohort

University Medical Centre, Utrecht, the Netherlands. [30]Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. [31]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands. [32]Public Health Directorate, Asturias, Spain. [33]Unit of Nutrition, Environment, and Cancer, Cancer Epidemiology Research Program, Bellvitge Biomedical Research Institute (IDIBELL), Catalan Institute of Oncology (ICO), Barcelona, Spain. [34]Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria de Granada (Granada.ibs), Granada, Spain. [35]CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain. [36]Department of Epidemiology, Murcia Regional Health Council, Murcia, Spain. [37]Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain. [38]Navarre Public Health Institute, Pamplona, Spain. [39]Public Health Department of Gipuzkoa, Government of the Basque Country, San Sebastian, Spain. [40]BioDonostia Research Institute, San Sebastian, Spain. [41]Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden. [42]Public Health and Clinical Medicine, Nutritional Research, Umeå University, Umeå, Sweden. [43]Arcum, Arctic Research Centre at Umeå University, Umeå, Sweden. [44]Department

of Clinical Sciences, Obstetrics and Gynecology, Umeå University, Umeå, Sweden. [45]University of Cambridge, School of Clinical Medicine, Cambridge, United Kingdom. [46]MRC Epidemiology Unit, University of Cambridge, Cambridge, United Kingdom. [47]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. [48]International Agency for Research on Cancer, Lyon, France. [49]Center for Biomedical Informatics, Harvard Medical School, Boston, Massachusetts.

were identified by reports from family members, the U.S. Postal Service and the National Death Index. Cases were confirmed epithelial endometrial cancer (NHS = 1,254; NHSII = 277) and of these we further subclassified endometrial cancer as invasive (≥stage II) endometrial adenocarcinoma (NHS = 753; NHSII = 146).

Dietary assessment

The diet of the EPIC participants was assessed using validated dietary questionnaires or food records (8) and this analysis evaluated foods that were available in ≥8 countries (Supplementary Materials and Methods). The EPIC Nutrient Database was used to calculate standardized nutrient intake for the 10 countries and all standardized priority nutrients were analyzed.

In the NHS/NHSII, intakes of selected foods/nutrients were assessed from 1980 FFQ (NHS) or 1991 FFQ (NHSII) and every approximately 4 years thereafter until the end of follow-up using a validated and reproducible FFQ (11). Nutrient intakes were calculated by multiplying the frequency of intake by the nutrient content of specified portions based on the U.S. Department of Agriculture food composition data.

Measurement of other covariates

The following risk factors for endometrial cancer were adjusted for in all multivariate models; BMI, total energy, smoking status, age at menarche, oral contraceptive (OC) use, parity, and a combined variable for menopausal status and postmenopausal hormone (PMH) use (Supplementary Materials and Methods). In the EPIC study, we additionally adjusted the multivariate models for physical activity, height, education level, and alcohol intake and the risk estimates were very similar; therefore, these covariates were not included in the final models. Family history of endometrial cancer was not available.

Statistical analysis

Cox proportional hazards (PH) regression was used to estimate the HRs and 95% confidence intervals (CI). In the EPIC study, age was the underlying time metric for Cox regression with the subjects' age at recruitment as the entry time and their age at cancer diagnosis, death, emigration, or last follow-up as the exit time. Nutrient intakes were energy-adjusted using the regression residual method and levels of food/nutrient intake were categorized into quartiles unless stated otherwise. To account for multiple comparisons, we estimated the FDR for each

food/nutrient, which is the ratio of the number of false positives to the total number of positive associations, or the percentage of findings drawn from the null distribution at a given significance level (7). To compute the FDR, we used an analytic method that estimates the number of false positive results by creating a "null distribution" of regression test statistics; this was accomplished by randomly assigning the endometrial cancer case status, running the Cox proportional hazards model and collecting the associated P value over 1,000 permutations (4, 6).

In the NHS/NHSII, we evaluated dietary intake at the study baseline as well as the cumulative average intake for foods/nutrients that were identified in the analysis in the EPIC study with FDR≤0.10 (Supplementary Material and Methods). The cumulative average intake analyses included a 2- to 6-year time lag between the diet assessment and the start of follow-up; thus each participant accrued person-time beginning with the 1984 (NHS) or 1995 (NHSII) FFQ until their date of endometrial cancer or other cancer diagnosis, hysterectomy, death or the end of follow-up (NHS: June 1, 2010; NHSII: June 1, 2011). Cox PH regression was carried out using age (months) and the biannual questionnaire cycle as the time scale.

The P value for the test of linear trend was calculated by assigning participants the median value for each dietary intake category and this variable was modeled as a continuous term. Random effects meta-analysis was used to combine HRs across studies. Analyses were performed using "survival" and "rmeta" packages in R v3.0.2.

Results

In a total of 2,834 incident endometrial cancers that were evaluated, 1,303 were from the EPIC study (mean follow-up = 11 years) and 1,531 were from the NHS/NHSII (mean follow-up = 25 years). The characteristics of the study populations are summarized in Table 1. Of the 84 foods/nutrients that were evaluated in the EPIC study, 10 were associated with endometrial cancer risk (FDR≤0.10) including butter, yogurt, cheese, potatoes, coffee, cream desserts, total fat, monounsaturated fat, carbohydrates, and phosphorus (Supplementary Table S1) while the remainder did not meet the FDR cutoff (Fig. 1; Supplementary Table S2).

Intake of most of the nine foods/nutrients at baseline was similar in the EPIC and NHS/NHSII cohorts with the following exceptions; the EPIC versus NHS/NHSII populations,

**Table 1.** Age-standardized characteristics at baseline of the EPIC study and the NHS and NHSII

	EPIC[a]	NHS[a]	NHSII[a]
Participants, n	301,107	68,063	87,343
Means (SD)			
Age, y[b]	49.8 (9.9)	45.3 (7.2)	35.9 (4.6)
Age at menarche, y	13.1 (1.5)	12.4 (1.8)	12.4 (1.4)
Body mass index, kg/m²	24.9 (4.4)	24.3 (4.5)	24.5 (5.3)
Total energy (kcal/day)	1934 (541)	1570 (501)	1794 (548)
Percentages			
Parous	84	94	73
Ever use oral contraceptives	60	50	83
Postmenopausal	44	27	1
Ever smoked	43	57	34
Ever use postmenopausal hormones	18	8	1

[a]Exposures at the study baseline (1980 in the NHS; 1991 in the NHSII).
[b]Values are not age-standardized.

Figure 1.
"Manhattan plot" showing results from the nutrient-wide association study method to evaluate the association between dietary intake of various foods and nutrients and endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The y-axis indicates the $-\log_{10}$ of the FDR P value of the multivariate adjusted Cox proportional hazards regression coefficient for the comparison of extreme quartiles or categories of dietary intake. Colors represent the dietary intake categories that were evaluated. Within each category, factors are arranged from left to right in order from the lowest to highest HR. The red horizontal line is $-\log_{10} = 1$ (FDR $P = 0.10$). Dietary factors that were selected for confirmation in the NHS/NHSII are labeled with the HR from the EPIC study for the comparison of the highest versus lowest category of dietary intake in relation to risk of endometrial cancer.
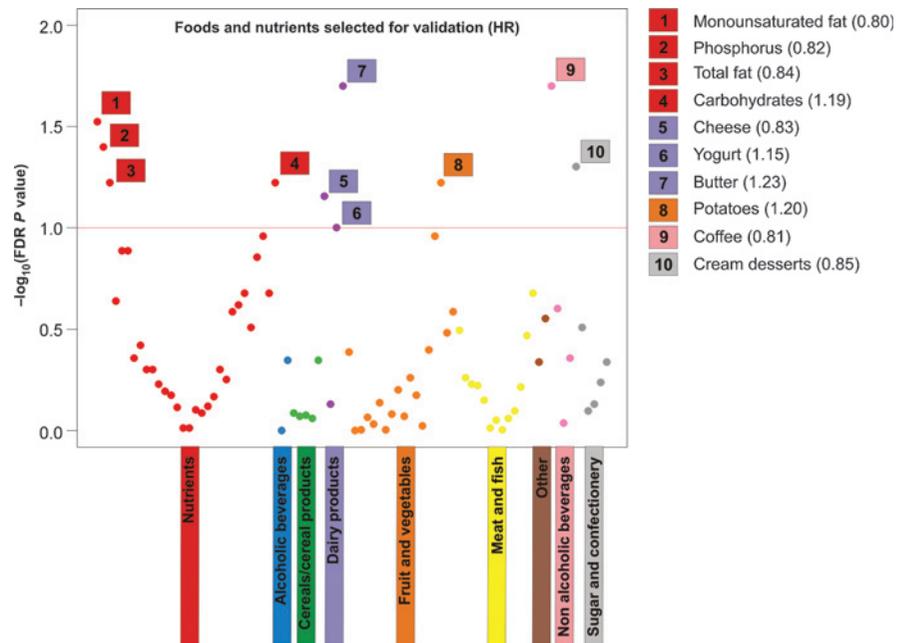
respectively, had higher total energy intake (mean = 1,934 kcal/day vs. ≤1,794) and consumed more yogurt (mean = 65.1 g/day vs. ≤32.6), cheese (mean = 39.2 g/day vs. ≤13.6), and butter (mean = 4.0 g/day vs. ≤2.6) (Table 1 and Supplementary Table S3). Cream dessert was not available in the NHS/NHSII cohorts. Of the nine foods/nutrients that were investigated in the NHS/NHSII, only the association with coffee was replicated (highest vs. lowest categories of intake; overall HR, 0.82; 95% CI, 0.73–0.92; Fig. 2; Supplementary Table S4). A positive association with butter intake was observed in the meta-analysis of all three cohorts (highest versus lowest categories of intake; overall HR, 1.14; 95% CI, 1.02–1.27).

In sensitivity analyses in the NHS/NHSII, there were similar associations for the cumulative average diet (Supplementary Table S5) and when restricting the case group to invasive endometrial adenocarcinomas (Supplementary Table S6). There were no consistent differences in the risk associations when stratifying by BMI or PMH use in the EPIC study or the NHS/NHSII (data not shown).

Discussion

We used the NWAS method to examine consumption of 84 foods/nutrients in the EPIC study and identified 10 dietary factors for which the highest versus lowest consumption levels were associated with increased risk (butter, yogurt, potatoes, carbohydrates) or decreased risk (cheese, coffee, cream desserts, total fat, monounsaturated fat, phosphorus) of endometrial cancer (FDR≤0.10). The inverse association between coffee intake and endometrial cancer risk was confirmed in the NHS/NHSII, suggesting that the other associations in our discovery effort may be false positives. Butter intake was positively associated with endometrial cancer risk in the meta-analysis of all three studies; to our knowledge, butter has not been investigated in previous prospective studies.

The inverse association between coffee intake and endometrial cancer risk is consistent with two recent meta-analyses (3, 12) and an earlier NHS report (13). Obesity is a strong risk factor for endometrial cancer (2) and may act by increasing exposure to estrogen (14) and/or hyperinsulinemia (15). Coffee may relate to these exposures; for example, in a cross-sectional study of >2,000 healthy NHS women, a high coffee intake was associated with lower levels of C-peptide which suggests a possible reduction in insulin secretion by coffee drinkers (16). Increasing consumption of caffeine and caffeine-containing coffee was associated with higher levels of adiponectin in the NHS which may benefit insulin sensitivity (17), and also with elevated levels of sex hormone-binding globulin (SHBG) that may decrease bioavailable estrogen based on a report focusing on postmenopausal women in the Rancho Bernardo community-based study (18). However, epidemiologic evidence suggests that noncaffeine components of coffee may be important for the risk reduction based on observations in the WCRF meta-analysis (3) that the decreased risk for endometrial cancer is similar in magnitude for decaffeinated coffee, and because drinking tea which also contains caffeine does not appear to be related to endometrial cancer risk in the current study and in the earlier NHS report (13) and WCRF meta-analysis (3).

Of those dietary factors that were investigated but not confirmed, consumption of carbohydrates (19–21) and total fat (22) were previously evaluated and, consistent with our final conclusions, there was no association with endometrial cancer risk. It is possible that other participant characteristics that differed between the EPIC, NHS, and NHSII cohorts, including differences in dietary intake levels for certain foods/nutrients, could explain why some of the dietary associations were not confirmed. A meta-analysis of a large number of cohort studies would therefore be useful to further evaluate a range of nutrients/foods in relation to endometrial cancer risk.
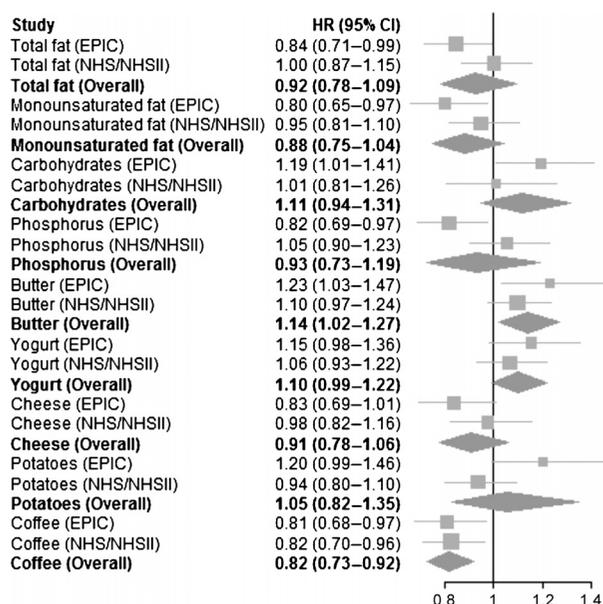
Study	HR (95% CI)
Total fat (EPIC)	0.84 (0.71–0.99)
Total fat (NHS/NHSII)	1.00 (0.87–1.15)
Total fat (Overall)	**0.92 (0.78–1.09)**
Monounsaturated fat (EPIC)	0.80 (0.65–0.97)
Monounsaturated fat (NHS/NHSII)	0.95 (0.81–1.10)
Monounsaturated fat (Overall)	**0.88 (0.75–1.04)**
Carbohydrates (EPIC)	1.19 (1.01–1.41)
Carbohydrates (NHS/NHSII)	1.01 (0.81–1.26)
Carbohydrates (Overall)	**1.11 (0.94–1.31)**
Phosphorus (EPIC)	0.82 (0.69–0.97)
Phosphorus (NHS/NHSII)	1.05 (0.90–1.23)
Phosphorus (Overall)	**0.93 (0.73–1.19)**
Butter (EPIC)	1.23 (1.03–1.47)
Butter (NHS/NHSII)	1.10 (0.97–1.24)
Butter (Overall)	**1.14 (1.02–1.27)**
Yogurt (EPIC)	1.15 (0.98–1.36)
Yogurt (NHS/NHSII)	1.06 (0.93–1.22)
Yogurt (Overall)	**1.10 (0.99–1.22)**
Cheese (EPIC)	0.83 (0.69–1.01)
Cheese (NHS/NHSII)	0.98 (0.82–1.16)
Cheese (Overall)	**0.91 (0.78–1.06)**
Potatoes (EPIC)	1.20 (0.99–1.46)
Potatoes (NHS/NHSII)	0.94 (0.80–1.10)
Potatoes (Overall)	**1.05 (0.82–1.35)**
Coffee (EPIC)	0.81 (0.68–0.97)
Coffee (NHS/NHSII)	0.82 (0.70–0.96)
Coffee (Overall)	**0.82 (0.73–0.92)**

Figure 2.
Forest plots showing multivariate HRs and 95% CIs for comparisons of the highest versus lowest categories of intake of nine selected foods and nutrients reported in the baseline dietary assessment in relation to endometrial cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Nurses' Health Study (NHS/NHSII). Foods and nutrients were evaluated if they had a FDR $\leq$ 0.10 for the comparison of extreme quartiles or categories of dietary intake in the EPIC study. The overall multivariate adjusted HR (95% CI) was estimated using random effects meta-analysis. P values for heterogeneity (P_{het}) comparing the EPIC study and the NHS/NHSII were $\geq$0.12 with the following exceptions: phosphorus ($P_{het} = 0.03$) and potatoes ($P_{het} = 0.05$). Multivariate models were adjusted for BMI, total energy intake, smoking status, age at menarche, oral contraceptive use, parity, and a combined variable for menopausal status and postmenopausal hormone use and were stratified by age and study center (EPIC) or stratified by age, cohort, and the 2-year questionnaire cycle (NHS/NHSII). Contrasts and median intake values were total fat [EPIC, quartile 4 (Q4, 73.7 g/day) vs. quartile 1 (Q1, 49.7 g/day); NHS/NHSII, Q4, 81.0 g/day vs. Q1, 52.0 g/day], monounsaturated fat (EPIC, Q4, 29.0 g/day vs. Q1, 16.2 g/day; NHS/NHSII, Q4, 34.0 g/day vs. Q1, 19.1 g/day), carbohydrates (EPIC, Q4, 212.0 g/day vs. Q1, 148.1 g/day; NHS/NHSII, Q4, 247.0 g/day vs. Q1, 131.0 g/day), phosphorus (EPIC, Q4, 1490 mg/day vs. Q1, 984 mg/day; NHS/NHSII, Q4, 1597 mg/day vs. Q1, 951 mg/day), butter (EPIC, highest, 10.3 g/day vs. lowest, 0 g/day; NHS/NHSII, highest, 5.0 g/day vs. lowest, 0 g/day), yogurt (EPIC, Q4, 145.3 g/day vs. Q1, 0 g/day; NHS/NHSII, highest, 105.4 g/day vs. lowest, 0 g/day), cheese (EPIC, Q4, 74.7 g/day vs. Q1, 7.5 g/day; NHS/NHSII, highest, 28.0 g/day vs. lowest, 2.0 g/day), potatoes (EPIC, Q4, 142.2 g/day vs. Q1, 20.8 g/day; NHS/NHSII, highest, 146.2 g/day vs. lowest, 25.9 g/day), and coffee (EPIC, Q4, 750.0 g/day vs. Q1, 8.6 g/day; NHS/NHSII, highest, 1066.5 g/day vs. lowest, 0 g/day).

The objective of the current study was to use the NWAS method as it may identify novel dietary risk associations with disease as demonstrated by studies of blood pressure and diabetes (4, 6). Advantages of this study design were the ability to systematically evaluate a range of dietary factors in relation to endometrial cancer risk while accounting for multiple testing and validating results in the NHS/NHSII; this provided an additional level of confidence in the findings. We verified the generally null associations between most dietary factors and endometrial cancer risk (3) which addresses the issue of selective reporting biases that favor statistically significant results (5, 23). Limitations included the single assessment of diet in the EPIC study; however,

in the NHS/NHSII, there were similar results for the cumulative average dietary intake, which suggests that our findings were not an artifact of a single dietary assessment. Both studies utilized a self-reported dietary assessment, which could lead to possible measurement error in dietary intake. We did not account for the correlated nature of the foods and nutrients in this analysis; doing so would lower the effective number of statistical tests and the corresponding threshold for statistical significance. Finally, it is possible that other dietary associations may exist for specific subgroups of endometrial cancer, for specific foods/nutrients that were not assessed in this analysis or that combinations of foods or dietary patterns may influence risk.

In summary, we used the NWAS method to evaluate dietary intake of 84 foods and nutrients in the EPIC study and nine dietary factors were investigated in the NHS/NHSII. Consistent with previous findings, coffee intake appears inversely associated with endometrial cancer risk. Further research is needed to identify the mechanisms linking coffee intake to endometrial carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

Authors' Contributions

Conception and design: M.A. Merritt, I. Tzoulaki, E. Weiderpass, A. Tjønneland, K. Overvad, H. Boeing, C. Bamia, R. Tumino, H.B(as). Bueno-de-Mesquita, P.H. Peeters, A. Barricarte, K.-T. Khaw, M.J. Gunter
Development of methodology: M.A. Merritt, I. Tzoulaki, E. Weiderpass, H. Boeing, D. Palli, R. Tumino, H.B(as). Bueno-de-Mesquita, C.J. Patel, M.J. Gunter
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.S. Tworoger, S.E. Hankinson, E. Weiderpass, A. Tjønneland, K.E.N. Petersen, K. Overvad, M.-C. Boutron-Ruault, R.T. Fortner, R. Kaaks, H. Boeing, A. Trichopoulou, C. Bamia, D. Trichopoulos, D. Palli, R. Tumino, C. Sacerdote, A. Mattiello, H.B(as). Bueno-de-Mesquita, P.H. Peeters, G. Skeie, J.R. Quiros, J.R. Quiros, M.-J. Sanchez, A. Barricarte, A. Idahl, K.-T. Khaw, N. Wareham
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.A. Merritt, I. Tzoulaki, S.S. Tworoger, I. De Vivo, S.E. Hankinson, J. Fernandes, K.K. Tsilidis, E. Weiderpass, C.C. Dahm, R.T. Fortner, N.C. Onland-Moret, I.T. Gram, M.-J. Sanchez, D. Salmerón, R.C. Travis, C.J. Patel, M.J. Gunter
Writing, review, and/or revision of the manuscript: M.A. Merritt, I. Tzoulaki, S.S. Tworoger, I. De Vivo, S.E. Hankinson, K.K. Tsilidis, E. Weiderpass, A. Tjønneland, K.E.N. Petersen, C.C. Dahm, K. Overvad, L. Dossus, M.-C. Boutron-Ruault, G. Fagherazzi, R.T. Fortner, R. Kaaks, K. Aleksandrova, H. Boeing, A. Trichopoulou, C. Bamia, D. Trichopoulos, D. Palli, S. Grioni, R. Tumino, C. Sacerdote, A. Mattiello, H.B(as). Bueno-de-Mesquita, N.C. Onland-Moret, P.H. Peeters, I.T. Gram, G. Skeie, J.R. Quiros, E.J. Duell, M.-J. Sanchez, D. Salmerón, A. Barricarte, S. Chamosa, U.C. Ericson, E. Sonestedt, L.M. Nilsson, A. Idahl, K.-T. Khaw, N. Wareham, R.C. Travis, S. Rinaldi, I. Romieu, E. Riboli, M.J. Gunter
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.A. Merritt, E. Weiderpass, H. Boeing, D. Trichopoulos, R. Tumino, C. Sacerdote, H.B(as). Bueno-de-Mesquita, G. Skeie, M.-J. Sanchez, A. Idahl, K.-T. Khaw
Study supervision: I. Tzoulaki, E. Weiderpass, R. Tumino, H.B(as). Bueno-de-Mesquita, P.H. Peeters

Acknowledgments

The authors thank all of the study participants for their valuable contribution to this research. Razvan Sultana provided assistance with programming. The authors also thank the participants and staff of the Nurses' Health Study (NHS) and NHSII for their valuable contributions as well as the following state cancer

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France; 2013.
2. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:1531–43.
3. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Endometrial Cancer; 2013. Available from: http://www.dietandcancerreport.org
4. Patel CJ, Bhattacharya J, Butte AJ. An environment-wide association study (EWAS) on type 2 diabetes mellitus. PLoS ONE 2010;5:e10746.
5. Patel CJ, Cullen MR, Ioannidis JP, Butte AJ. Systematic evaluation of environmental factors: persistent pollutants and nutrients correlated with serum lipid levels. Int J Epidemiol 2012;41:828–43.
6. Tzoulaki I, Patel CJ, Okamura T, Chan Q, Brown IJ, Miura K, et al. A nutrient-wide association study on blood pressure. Circulation 2012;126: 2456–64.
7. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B 1995;57: 289–300.
8. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–24.
9. Colditz GA, Hankinson SE. The nurses' health study: lifestyle and health among women. Nat Rev Cancer 2005;5:388–96.
10. Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Spiegelman D, et al. Physical activity and breast cancer risk in a cohort of young women. J Natl Cancer Inst 1998;90:1155–60.
11. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
12. Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: findings from a large up-to-date meta-analysis. Int J Cancer 2012;131: 1700–10.
13. Je Y, Hankinson SE, Tworoger SS, De V, I,Giovannucci E. A prospective cohort study of coffee consumption and risk of endometrial cancer over a 26-year follow-up. Cancer Epidemiol Biomarkers Prev 2011;20:2487–95.
14. Key TJ, Pike MC. The dose-effect relationship between `unopposed' oestrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer 1988;57:205–12.
15. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Manson JE, Li J, et al. A prospective evaluation of insulin and insulin-like growth factor-I as risk factors for endometrial cancer. Cancer Epidemiol Biomarkers Prev 2008;17:921–9.
16. Wu T, Willett WC, Hankinson SE, Giovannucci E. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. Diabetes Care 2005;28: 1390–6.
17. Williams CJ, Fargnoli JL, Hwang JJ, van Dam RM, Blackburn GL, Hu FB, et al. Coffee consumption is associated with higher plasma adiponectin concentrations in women with or without type 2 diabetes: a prospective cohort study. Diabetes Care 2008;31:504–7.
18. Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. Am J Epidemiol 1996;144:642–4.
19. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: A prospective study of Swedish women. Int J Cancer 2007;120:1103–7.
20. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycaemic index, glycaemic load and risk of endometrial cancer: a prospective cohort study. Public Health Nutr 2005;8:912–9.
21. Zheng W, Kushi LH, Potter JD, Sellers TA, Doyle TJ, Bostick RM, et al. Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa women's health study. Am J Epidemiol 1995;142:388–94.
22. Jain MG, Rohan TE, Howe GR, Miller AB. A cohort study of nutritional factors and endometrial cancer. Eur J Epidemiol 2000;16:899–905.
23. Tsilidis KK, Papatheodorou SI, Evangelou E, Ioannidis JP. Evaluation of excess statistical significance in meta-analyses of 98 biomarker associations with cancer risk. J Natl Cancer Inst 2012;104:1867–78.

Investigation of Dietary Factors and Endometrial Cancer Risk Using a Nutrient-wide Association Study Approach in the EPIC and Nurses' Health Study (NHS) and NHSII

Melissa A. Merritt, Ioanna Tzoulaki, Shelley S. Tworoger, et al.

Updated version	Access the most recent version of this article at: http://cebp.aacrjournals.org/content/24/2/466
Supplementary Material	Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2015/02/17/24.2.466.DC1

Cited articles	This article cites 21 articles, 6 of which you can access for free at: http://cebp.aacrjournals.org/content/24/2/466.full#ref-list-1
Citing articles	This article has been cited by 2 HighWire-hosted articles. Access the articles at: http://cebp.aacrjournals.org/content/24/2/466.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/24/2/466. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.