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Dietary Carbohydrates, Glycemic Index, Glycemic Load, and Endometrial Cancer Risk within the European Prospective Investigation into Cancer and Nutrition Cohort

Anne E. Cust[1,2,3], Nadia Slimani[1], Rudolf Kaaks[1,4], Marit van Bakel[1], Carine Biessy[1], Pietro Ferrari[1], Martine Laville[3,5], Anne Tjønneland[6], Anja Olsen[6], Kim Overvad[7], Martin Lajous[8,9], Francoise Clavel-Chapelon[8], Marie-Christine Boutron-Ruault[8], Jakob Linseisen[4], Sabine Rohrmann[4], Ute Nöthlings[10], Heiner Boeing[10], Domenico Palli[11], Sabina Sieri[12], Salvatore Panico[13], Rosario Tumino[14], Carlotta Sacerdote[15], Guri Skeie[16], Dagrun Engeset[16], Inger Torhild Gram[16], J. Ramón Quirós[17], Paula Jakszyn[18], María José Sánchez[19], Nerea Larrañaga[20], Carmen Navarro[21], Eva Ardanaz[22], Elisabet Wirfält[23], Göran Berglund[24], Eva Lundin[25], Göran Hallmans[26], H. Bas Bueno-de-Mesquita[27], Huaidong Du[27], Petra H. M. Peeters[28], Sheila Bingham[29,30], Kay-Tee Khaw[31], Naomi E. Allen[32], Timothy J. Key[32], Mazda Jenab[1], and Elio Riboli[33]

[1] Nutrition and Hormones Unit, International Agency for Research on Cancer, Lyon, France.
[2] School of Public Health, University of Sydney, Sydney, Australia.
[3] Center for Research in Human Nutrition Rhône-Alpes, Université Lyon 1, Lyon, France.
[4] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany.
[5] UMR Inserm U449/INRA 1235, Lyon, France.
[6] Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark.
[7] Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark.
[8] Inserm ERI 20, Paris-Sud University EA4045, and Institut Gustave Roussy, Villejuif, France.
[9] National Institute of Public Health, Center for Investigation on Population Health, Cuernavaca, Mexico.
[10] German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.
[11] Molecular and Nutritional Epidemiology Unit, CSPO-Scientific Institute of Tuscany, Florence, Italy.
[12] Nutritional Epidemiology Unit, National Cancer Institute, Milan, Italy.
[13] Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy.
[14] Cancer Registry, Azienda Ospedaliera "Civile M. P. Arezzo," Ragusa, Italy.
[15] CPO-Piemonte, Torino, Italy.
[16] Faculty of Medicine, Institute of Community Medicine, University of Tromsø, Tromsø, Norway.
[17] Public Health and Health Planning Directorate, Asturias, Spain.
[18] Department of Epidemiology and Cancer Registry, Catalan Institute of Oncology, Barcelona, Spain.
[19] Andalusian School of Public Health, Granada, Spain.
[20] Public Health Department of Gipuzkoa, Basque Government, San Sebastian, Spain.
[21] Epidemiology Department, Murcia Health Council, Murcia, Spain.
[22] Public Health Institute of Navarra, Pamplona, Spain.
[23] Nutrition Epidemiology, Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden.
[24] Department of Medicine, Lund University, Malmö University Hospital, Malmö, Sweden.
[25] Department of Medical Biosciences, Umeå University, Umeå, Sweden.
[26] Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.
[27] Centre for Nutrition and Health, National Institute of Public Health and the Environment, Bilthoven, The Netherlands.
[28] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, The Netherlands.
[29] MRC Dunn Human Nutrition Unit, Cambridge, United Kingdom.
[30] MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom.
[31] Clinical Gerontology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom.
[32] Cancer Research UK Epidemiology Unit, University of Oxford, Oxford, United Kingdom.
[33] Department of Epidemiology and Public Health, Imperial College London, London, United Kingdom.

Correspondence to Anne Cust, Level 2, K25 - Medical Foundation Building, School of Public Health, The University of Sydney, Sydney, NSW 2006, Australia (e-mail: annec@health.usyd.edu.au).

The associations of dietary total carbohydrates, overall glycemic index, total dietary glycemic load, total sugars, total starch, and total fiber with endometrial cancer risk were analyzed among 288,428 women in the European Prospective Investigation into Cancer and Nutrition cohort (1992–2004), including 710 incident cases diagnosed during a mean 6.4 years of follow-up. Cox proportional hazards models were used to estimate relative risks and 95% confidence intervals. There were no statistically significant associations with endometrial cancer risk for increasing quartile intakes of any of the exposure variables. However, in continuous models calibrated by using 24-hour recall values, the multivariable relative risks were 1.61 (95% confidence interval: 1.06, 2.45) per 100 g/day of total carbohydrates, 1.40 (95% confidence interval: 0.99, 1.99) per 50 units/day of total dietary glycemic load, and 1.36 (95% confidence interval: 1.05, 1.76) per 50 g/day of total sugars. These associations were stronger among women who had never used postmenopausal hormone therapy compared with ever users (total carbohydrates $p_{heterogeneity} = 0.04$). Data suggest no association of overall glycemic index, total starch, and total fiber with risk, and a possible modest positive association of total carbohydrates, total dietary glycemic load, and total sugars with risk, particularly among never users of hormone replacement therapy.

cohort studies; diet; dietary carbohydrates; dietary fiber; endometrial neoplasms; glycemic index; insulin; nutrition assessment

Abbreviations: EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy.

There is increasing evidence that insulin resistance, chronic hyperinsulinemia, and diabetes are implicated in the etiology of endometrial cancer (1–4). Obesity is a major determinant of hyperinsulinemia (5) and strongly increases endometrial cancer risk by aromatization of androgens to estrogens in adipose tissue (1). However, insulin could also influence risk through direct actions on endometrial tissue as a mitogenic and antiapoptotic growth factor or indirectly by increasing bioavailable estrogen and insulin-like growth factor 1 levels (1–3). Postprandial and average insulin concentrations are directly influenced by the type, amount, and rate of digestion of dietary carbohydrates (6–9). Thus, it has been speculated that the quantity and quality (i.e., type, source, component) of dietary carbohydrates could have a role in endometrial carcinogenesis (10).

Previous studies of the association between dietary carbohydrate intake and endometrial cancer risk (11–23), few of which used a cohort design (11–14), have observed inconsistent but generally non-statistically significant results. A common limitation is the large random error associated with using dietary questionnaires to estimate food and nutrient intakes that tends to attenuate relative risk estimates and make it difficult to detect true associations (24, 25).

Glycemic index and glycemic load reflect the metabolic effects of dietary carbohydrates (6, 26). The glycemic index ranks carbohydrate foods based on their postprandial blood glucose response and hence their effect on blood insulin levels (6, 8, 27). The glycemic load combines the glycemic index value and the quantity of carbohydrate to quantify the overall estimated glycemic effect of a portion of food (26, 27). Four previous studies (10, 11, 13, 28) examined the association between glycemic index, glycemic load, and endometrial cancer risk and observed generally null associations or modest increased risks. There were suggestions that the associations may differ according to menopausal status, obesity, physical activity, use of hormone replacement therapy (HRT), and diabetes status (10, 11, 13, 28).

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort is well suited to study the influence of diet on cancer risk because of the large variation in dietary patterns across the 10 collaborating western European countries (29, 30). Additionally, 24-hour recall values collected from a sample of EPIC participants are available that enable partial correction for dietary measurement errors. To our knowledge, this is the largest prospective analysis to examine the association of endometrial cancer risk with dietary total carbohydrates, glycemic index, and glycemic load.

MATERIALS AND METHODS

Study cohort

The EPIC study design, study population, and baseline data collection methods have been described in detail previously (31, 32), including baseline assessment of habitual diet (31, 33), lifestyle factors (31), physical activity (34), anthropometric measures (35), and menopausal status (34). Briefly, diet and lifestyle data were collected from approximately 370,000 women and 150,000 men aged 20–85 years enrolled between 1992 and 2000 in 23 centers throughout 10 western European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and United Kingdom) (31). Participants were mostly recruited from the general population residing in defined geographic areas (31). Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer (Lyon, France) and from all local

recruiting institutions. All participants provided written informed consent.

A total of 288,428 women were included in the present analysis after a priori exclusion of 19,246 with prevalent cancer (other than nonmelanoma skin cancer), 34,972 who reported a hysterectomy at enrollment, 4,158 for whom follow-up data were incomplete, 33 with in situ or nonepithelial incident endometrial cancers, and 6,104 who were in the top or bottom 1 percent of the distribution of the ratio of reported total energy intake to estimated energy requirement (36). All women from Greece ($n = 13,748$) were also excluded because of lack of access to data on the carbohydrate content of questionnaire food items, which prevented estimation of glycemic index and glycemic load.

Dietary measurement

Usual diet during the previous 12 months was assessed with country-specific, validated (33) dietary assessment instruments (31). Food frequency questionnaires were used in all centers, and some centers combined questionnaires with food records (United Kingdom) or a 7-day menu book (Malmö, Sweden) (31). Intakes (in grams per day) of total carbohydrate, sugars, starch, and fiber (including resistant starch) were estimated from the dietary instruments by using country-specific food composition tables, which were standardized to a certain extent across countries to allow calibration at the nutrient level. To improve comparability of dietary data across centers and to partially correct for dietary measurement error arising from center-specific bias and random and systematic within-person errors (24, 37), a second dietary measurement was taken from an 8 percent stratified random sample (a total of 36,900 participants) of the cohort by using a standardized, computer-assisted, 24-hour dietary recall method (38). A single 24-hour recall among a sufficiently large sample provides a good estimate of mean intakes of foods and nutrients at a population level (39).

A glycemic index database was compiled whereby published glycemic index values (26, 40, 41) were assigned to carbohydrate-providing food items to reflect their blood glucose response (detailed in the supplementary material posted on the *Journal*'s website (http://aje.oupjournals.org/)). Total dietary glycemic load was calculated by multiplying the digestible carbohydrate content of a given food item (g/100 g) by the quantity of that food item consumed per day and its glycemic index value and then summing the values for all food items reported (26). The overall glycemic index was calculated by dividing the total dietary glycemic load by the daily total dietary carbohydrate intake. The overall glycemic index reflects the average quality of carbohydrates consumed, whereas the total dietary glycemic load reflects both the average quantity and the quality of carbohydrates (26).

Follow-up for cancer incidence and mortality

Methods for follow-up for cancer incidence and vital status in each EPIC country have been described in detail

TABLE 1. Distribution of cases and intake of dietary carbohydrates, glycemic index, and glycemic load, by subcohort, European Prospective Investigation into Cancer and Nutrition, 1992–2004

Country	Cohort size (no.)	Mean (5th–95th centiles)		No. of person-years	No. of endometrial cancer cases	ASR*, †/100,000 person-years	95% CI*	Median (25th–75th centiles)		
		Age (years) at recruitment	No. of years of follow-up					Total carbohydrates (g/day)	Glycemic index (per day)	Glycemic load (per day)
France	60,912	52.4 (44.1–65.0)	8.4 (6.7–9.0)	511,801	224	49.8	42.4, 57.1	224 (179–275)	56.3 (53.6–58.8)	126 (98–157)
Italy	27,747	50.2 (37.1–63.4)	6.2 (3.4–8.1)	171,663	67	55.4	40.5, 70.3	238 (188–297)	55.4 (53.2–57.8)	132 (103–167)
Spain	22,750	47.9 (36.0–62.6)	6.6 (5.1–8.1)	150,053	50	53.0	36.4, 69.7	198 (161–242)	55.3 (52.5–57.9)	110 (87–136)
United Kingdom general population	13,939	56.5 (42.8–73.1)	5.5 (3.3–7.9)	76,998	48	69.3	46.3, 92.2	219 (178–267)	54.8 (52.7–56.9)	120 (96–147)
United Kingdom health conscious persons	32,333	41.9 (23.2–68.5)	5.4 (3.6–7.4)	173,620	22	35.3	16.7, 53.9	222 (181–269)	54.3 (52.3–56.4)	120 (98–146)
The Netherlands	22,679	49.7 (25.7–66.8)	6.5 (3.1–9.4)	147,061	48	40.1	27.9, 52.4	206 (171–245)	56.7 (54.4–58.9)	116 (96–140)
Germany	23,712	48.1 (36.0–63.0)	5.9 (3.6–7.7)	138,760	31	40.6	25.6, 55.5	195 (158–240)	53.0 (51.2–54.7)	103 (83–127)
Sweden	26,297	52.0 (30.2–69.8)	7.8 (5.6–10.2)	204,619	90	53.9	41.3, 66.5	205 (169–247)	56.5 (54.3–58.8)	116 (95–140)
Denmark	24,487	56.7 (50.8–64.2)	6.7 (5.7–8.2)	165,273	110	62.5	49.9, 75.0	204 (167–247)	58.9 (56.5–61.4)	120 (98–145)
Norway	33,572	48.0 (41.6–54.9)	3.1 (3.0–3.1)	103,146	20	37.9	18.2, 57.6	184 (151–220)	57.1 (55.3–58.9)	106 (86–126)
Total	288,428	50.1 (32.4–65.6)	6.4 (3.0–9.0)	1,842,995	710	51.7	47.5, 55.9	210 (170–257)	55.9 (53.4–58.4)	117 (94–144)

* ASR, age-standardized incidence rate; CI, confidence interval.

† Rates were calculated from a subset of 593 women (1,175,285 person-years) aged 50–69 years at baseline, using the European standard population as a comparison.

TABLE 2. Baseline demographic and lifestyle characteristics of 288,428 women* according to endometrial cancer status at the end of the follow-up period, European Prospective Investigation into Cancer and Nutrition, 1992–2004

Baseline demographic and lifestyle characteristics†	Incident endometrial cancer cases (n = 710)	Noncases (n = 287,718)
Age (years) at recruitment	54.1 (8.7)	49.9 (11.6)
Menopausal status‡		
Premenopausal	16.0	38.3
Perimenopausal	19.5	18.5
Postmenopausal	64.5	43.2
Reproductive factors		
Age (years) at menarche	12.8 (1.5)	13.0 (2.0)
Age (years) at menopause§	50.6 (4.3)	49.3 (6.1)
Nulliparous	16.2	16.0
Exogenous hormone use		
Ever used hormone replacement therapy§	48.2	44.8
Ever used oral contraceptives	41.8	62.4
Anthropometric factors		
Height (cm)	162.2 (6.0)	162.0 (8.0)
Body mass index¶	26.4 (4.0)	25.2 (5.3)
Obese (body mass index $\geq$30)	20.3	11.0
Smoking status		
Never smoker	63.2	55.6
Former smoker	20.6	24.0
Current smoker	16.2	20.4
Total physical activity		
Inactive	15.9	17.3
Moderately inactive	41.2	38.4
Moderately active	37.1	36.8
Active	5.9	7.5
Self-reported diabetes	3.5	2.0
Self-reported hypertension	26.2	17.3
Highest educational level		
None or primary school	29.6	24.4
Secondary or technical or professional school	50.7	50.7
University	19.6	25.0
Dietary intake#		
Total energy intake (kcal/day)	1,884.5 (220.9)	1,903.9 (204.1)
Total carbohydrate (g/day)	206.5 (29.7)	210.2 (30.3)
Overall glycemic index	55.6 (2.1)	55.5 (2.1)
Total dietary glycemic load	115.6 (18.5)	117.4 (18.7)
Total sugar (g/day)	98.6 (19.1)	100.4 (19.4)
Total starch (g/day)	104.4 (19.0)	106.6 (19.8)
Total fiber (g/day)	20.3 (3.9)	20.3 (3.9)
Saturated fats (g/day)	30.7 (7.3)	30.5 (6.8)
Monounsaturated fats (g/day)	26.9 (5.1)	27.6 (5.4)
Polyunsaturated fats (g/day)	11.2 (2.1)	12.2 (2.7)

* Unknown values were excluded from the calculations: age at menarche, 5.7%; parity, 6.8%; oral contraceptive therapy, 4.9%; smoking status, 2.3%; physical activity, 17.1%; diabetes, 4.3%; hypertension, 16.1%; educational level, 4.1%; and, in postmenopausal women, hormone replacement therapy, 7.5%; and age at menopause, 27.2%.

† Continuous variables are presented as mean (standard deviation), adjusted by age and center (except age, which was adjusted by center only). Categorical variables are presented as percentages.

‡ Excludes three cases and 836 noncases with bilateral ovariectomy.

§ Among postmenopausal women only.

¶ Weight (kg)/height (m)^2.

Calibrated mean daily dietary intakes were obtained by regression of the 24-hour diet recall values on the main dietary questionnaires.

elsewhere (31). Vital status was known for 98.4 percent of EPIC participants at the end of April 2004. Endometrial cancers were classified by using the *International Classification of Diseases for Oncology*, second edition (code C54). There were 710 eligible incident endometrial cancer cases identified by the end of censoring periods ending between December 1999 and March 2004 in the EPIC centers. Cancer diagnosis was microscopically verified for 89.3 percent of cases and by clinical examination for 8.5 percent; the remaining 2.2 percent were verified by self-report, tomography scan, surgery, autopsy, or death certificate. Morphology was specified for 239 (34 percent) cases, of which 229 cases (96 percent) were classified as type I and 10 cases (4 percent) as type II (42).

Statistical methods

Age- and center-adjusted Pearson's partial correlation coefficients were estimated to assess the correlations between nutrient intakes. Dietary exposure intakes were analyzed as both continuous and categorical variables. We used Cox proportional hazards models to calculate hazard ratios as estimates of relative risks and 95 percent confidence intervals. Age was used as the underlying time variable, with entry and exit time defined as the subject's age at recruitment and age at endometrial cancer diagnosis or censoring date, respectively. Quartile cutpoints were based on study-wide energy-adjusted nutrient intake distributions, computed as the residuals from a linear regression of nutrient

TABLE 3. Relative risk estimates and 95% confidence intervals for endometrial cancer, by quartiles* of energy-adjusted total carbohydrates, glycemic index, glycemic load, and other carbohydrate components, European Prospective Investigation into Cancer and Nutrition, 1992–2004

Dietary variable and quartile	No. of cases	No. of person-years	Adjusted for age, center, and total energy intake		Multivariable† adjusted	
			RR‡	95% CI‡	RR	95% CI
Total carbohydrates (g/day)						
Quartile 1	162	472,011	1.00		1.00	
Quartile 2	176	447,659	1.16	0.94, 1.44	1.17	0.94, 1.45
Quartile 3	182	449,894	1.17	0.95, 1.46	1.18	0.95, 1.47
Quartile 4	190	473,431	1.13	0.91, 1.39	1.16	0.93, 1.43
p_{trend}			0.29		0.20	
Uncalibrated (per 100 g/day)			1.16	0.94, 1.44	1.20	0.97, 1.50
Calibrated (per 100 g/day)			1.48	0.99, 2.22	1.61	1.06, 2.45
Glycemic index						
Quartile 1	182	471,723	1.00		1.00	
Quartile 2	185	447,953	1.16	0.95, 1.43	1.17	0.95, 1.44
Quartile 3	168	450,978	1.07	0.87, 1.33	1.08	0.88, 1.34
Quartile 4	175	472,341	1.03	0.83, 1.27	1.04	0.84, 1.28
p_{trend}			0.97		0.90	
Uncalibrated (per 5 units/day)			1.01	0.91, 1.11	1.01	0.92, 1.12
Calibrated (per 5 units/day)			1.01	0.81, 1.27	1.03	0.82, 1.30
Glycemic load						
Quartile 1	180	477,786	1.00		1.00	
Quartile 2	163	445,897	1.01	0.81, 1.25	1.01	0.82, 1.26
Quartile 3	167	444,498	1.04	0.84, 1.29	1.05	0.85, 1.31
Quartile 4	200	474,813	1.12	0.92, 1.38	1.15	0.94, 1.41
p_{trend}			0.24		0.16	
Uncalibrated (per 50 units/day)			1.11	0.94, 1.30	1.14	0.96, 1.34
Calibrated (per 50 units/day)			1.32	0.94, 1.85	1.40	0.99, 1.99

Table continues

intake on total energy intake (24, 43) with additional adjustment for country. Trend tests were estimated on integer scores (1–4) applied to the quartiles and were entered as a continuous term in the regression models.

All Cox models were stratified by study center to control for differences in questionnaire design and follow-up procedures, and by age at recruitment in 1-year categories. All models were also adjusted for total energy intake by using the residual method (24, 43) to control partly for the error in nutrient intake (44–46) and because we were primarily interested in dietary composition rather than absolute intake (43, 44). The multivariable models were additionally adjusted for body mass index (kg/m^2, continuous), height (cm, continuous; representing lean body mass (43)), and total physical activity level (inactive, moderately inactive, moderately active, active, unknown), to control for other determinants of energy balance (43, 45, 47), and for cigarette smoking status (never, former, current, unknown) because it was associated with nutrient intake and its inclusion in the models influenced the risk estimates. Using body mass index squared, log(body mass index), or sqrt(body mass index) as potentially nonlinear confounders did not further influence the associations. Other potential confounders examined, but not included in the final models because their inclusion had little influence on the risk estimates, were age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of HRT, ever use of oral contraceptives, self-reported presence of hypertension or diabetes, and education.

Nutrient intakes including total energy intake were calibrated by using a multivariable fixed-effects linear model in which 24-hour recall values were regressed on the main dietary questionnaire values for the calibration study participants (refer to the supplementary online material for further details). The calibration model was used to compute individual predicted values for each of the dietary exposures of interest. Cox regression models were run by using the predicted (calibrated) values on a continuous scale, for all main models. The standard error of the deattenuated coefficient was estimated with bootstrap sampling to take into account the uncertainty related to measurement error correction (48).

TABLE 3. Continued

Dietary variable and quartile	No. of cases	No. of person-years	Adjusted for age, center, and total energy intake		Multivariable† adjusted	
			RR	95% CI	RR	95% CI
Total sugars (g/day)						
Quartile 1	156	465,307	1.00		1.00	
Quartile 2	168	455,771	1.01	0.80, 1.25	1.01	0.81, 1.27
Quartile 3	173	456,231	0.98	0.78, 1.22	1.00	0.80, 1.24
Quartile 4	213	465,686	1.16	0.94, 1.43	1.20	0.97, 1.48
p_{trend}			0.19		0.10	
Uncalibrated (per 50 g/day)			1.11	0.98, 1.27	1.14	1.00, 1.30
Calibrated (per 50 g/day)			1.30	1.01, 1.68	1.36	1.05, 1.76
Total starch (g/day)						
Quartile 1	207	479,758	1.00		1.00	
Quartile 2	162	447,479	0.87	0.70, 1.07	0.87	0.70, 1.07
Quartile 3	172	442,780	0.96	0.78, 1.18	0.95	0.77, 1.18
Quartile 4	169	472,978	0.90	0.73, 1.11	0.90	0.73, 1.11
p_{trend}			0.49		0.48	
Uncalibrated (per 50 g/day)			0.98	0.86, 1.11	0.98	0.87, 1.11
Calibrated (per 50 g/day)			1.04	0.74, 1.45	1.04	0.74, 1.47
Total fiber (g/day)						
Quartile 1	156	464,761	1.00		1.00	
Quartile 2	180	452,886	1.12	0.91, 1.40	1.11	0.90, 1.39
Quartile 3	173	452,904	1.05	0.84, 1.31	1.04	0.83, 1.29
Quartile 4	201	472,443	1.05	0.84, 1.31	1.13	0.91, 1.40
p_{trend}			0.32		0.41	
Uncalibrated (per 10 g/day)			1.09	0.96, 1.23	1.08	0.95, 1.22
Calibrated (per 10 g/day)			1.24	0.97, 1.58	1.27	0.99, 1.63

* Quartile cutpoints were based on study-wide energy-adjusted nutrient intake distributions, computed as the residuals from a linear regression of nutrient intake on total energy intake with additional adjustment for country.

† Stratified by age and center and adjusted for total energy intake (residual method), body mass index, height, physical activity level, and smoking status.

‡ RR, relative risk; CI, confidence interval.

We used multivariate nutrient density models (24, 49) to evaluate the possible confounding effects of other macronutrients. We estimated the effect of a 5 percent increase in the percentage of energy from carbohydrates relative to an identical decrease in the percentage of energy from another macronutrient, enabling us to compare isocaloric diets. Additionally, we examined macronutrient composition by using the energy decomposition (partition) method (24) (refer to the supplementary online material).

On the basis of previous reports of possible effect modification, we examined heterogeneity of risk estimates according to body mass index (<25, $25–<30$, ≥ 30 kg/m^2), waist-hip ratio (<0.78, ≥ 0.78 cm), menopausal status (premenopausal, perimenopausal, postmenopausal), total physical activity level (inactive + moderately inactive, moderately active + active), use of HRT by postmenopausal women (never/ever used), use of oral contraceptives (never/ever used), self-reported diabetes (yes/no), and country. Chi-square tests were used to calculate the deviations of beta coefficients obtained from continuous uncalibrated models in each of the subgroups relative to the overall beta coefficients. All analyses were performed by using SAS software (version 9.1; SAS Institute, Inc., Cary, North Carolina), and statistical significance was inferred at two-sided $p < 0.05$.

RESULTS

During a mean 6.4 years and 1,842,995 person-years of follow-up, 710 incident endometrial cancer cases were diagnosed among 288,428 women (table 1). Women who developed endometrial cancer during follow-up were, at baseline, more likely to be older, be obese, be never smokers, have diabetes, and have different patterns of exogenous hormone use compared with women who did not develop cancer, but they had similar dietary intake and physical activity levels (table 2). When the dietary questionnaire variables were categorized into quartiles, the mean values in the fourth quartiles were two- to threefold higher than those in the first quartiles, except for glycemic index, where the

TABLE 4. Multivariable* relative risk estimates and 95% confidence intervals for endometrial cancer, by quartiles† of energy-adjusted total carbohydrates and total sugars, according to body mass index, menopausal status, and use of exogenous hormones, European Prospective Investigation into Cancer and Nutrition, 1992–2004

Subgroup	No. of cases per quartile (1, 2, 3, 4)	RR‡ and 95% CI‡ for quartiles							p_{trend}§	Continuous units¶			
		Quartile 1	Quartile 2		Quartile 3		Quartile 4			Uncalibrated		Calibrated	
		RR	RR	95% CI	RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Total carbohydrates													
Body mass index#													
<25	86, 87, 89, 103	1.00	1.12	0.83, 1.52	1.12	0.83, 1.52	1.07	0.80, 1.43	0.69	1.19	0.89, 1.60	1.70	1.00, 2.90
25–<30	40, 52, 59, 50	1.00	1.36	0.89, 2.07	1.46	0.97, 2.21	1.29	0.84, 1.98	0.23	1.32	0.86, 2.02	1.77	0.78, 4.00
≥30	36, 37, 34, 37	1.00	1.05	0.66, 1.68	1.01	0.62, 1.63	1.21	0.76, 1.93	0.49	1.01	0.60, 1.71	1.01	0.42, 2.43
Menopausal status at baseline**													
Premenopausal	31, 33, 27, 22	1.00	1.41	0.86, 2.32	1.17	0.69, 1.99	0.85	0.49, 1.47	0.51	0.94	0.57, 1.57	1.01	0.32, 3.19
Perimenopausal	35, 31, 37, 35	1.00	0.98	0.60, 1.61	1.16	0.72, 1.88	1.06	0.66, 1.72	0.67	1.16	0.70, 1.90	1.66	0.69, 3.99
Postmenopausal	96, 111, 116, 133	1.00	1.16	0.88, 1.53	1.16	0.88, 1.53	1.26	0.96, 1.65	0.12	1.31	0.99, 1.73	1.73	1.03, 2.89
Ever use of HRT‡ among postmenopausal women††													
Ever used	50, 46, 53, 51	1.00	1.01	0.67, 1.51	1.15	0.77, 1.70	1.00	0.67, 1.49	0.84	1.02	0.68, 1.54	1.18	0.55, 2.52
Never used	38, 52, 50, 75	1.00	1.34	0.88, 2.05	1.18	0.77, 1.82	1.70	1.14, 2.53	0.02	1.87	1.25, 2.80	3.09	1.48, 6.43
Ever use of oral contraceptives among all women‡‡													
Ever used	72, 76, 67, 65	1.00	1.26	0.91, 1.74	1.19	0.84, 1.66	1.07	0.76, 1.50	0.77	1.15	0.82, 1.62	1.48	0.80, 2.75
Never used	88, 86, 104, 112	1.00	1.01	0.75, 1.36	1.18	0.88, 1.58	1.18	0.89, 1.57	0.15	1.25	0.93, 1.68	1.66	0.94, 2.92
Total sugars													
Body mass index#													
<25	75, 88, 84, 118	1.00	1.08	0.79, 1.48	0.98	0.72, 1.35	1.25	0.93, 1.68	0.19	1.24	1.04, 1.48	1.72	1.25, 2.37
25–<30	46, 49, 59, 47	1.00	0.97	0.64, 1.46	1.09	0.73, 1.62	0.91	0.60, 1.37	0.80	0.99	0.76, 1.27	0.98	0.58, 1.66
≥30	35, 31, 30, 48	1.00	0.84	0.51, 1.38	0.86	0.52, 1.42	1.48	0.95, 2.32	0.07	1.11	0.82, 1.49	1.26	0.77, 2.05
Menopausal status at baseline**													
Premenopausal	33, 26, 26, 28	1.00	1.00	0.59, 1.69	1.06	0.62, 1.79	1.14	0.68, 1.91	0.60	1.06	0.78, 1.44	1.08	0.54, 2.16
Perimenopausal	40, 33, 24, 41	1.00	0.74	0.46, 1.18	0.56	0.33, 0.93	1.06	0.68, 1.66	0.98	1.15	0.85, 1.57	1.52	0.87, 2.64
Postmenopausal	82, 108, 122, 144	1.00	1.14	0.85, 1.53	1.19	0.89, 1.58	1.31	1.00, 1.73	0.05	1.17	1.00, 1.38	1.41	1.02, 1.94
Ever use of HRT among postmenopausal women††													
Ever used	42, 40, 57, 61	1.00	0.84	0.54, 1.31	1.14	0.76, 1.72	1.13	0.76, 1.68	0.28	1.07	0.83, 1.37	1.22	0.76, 1.95
Never used	35, 52, 54, 74	1.00	1.38	0.89, 2.13	1.32	0.86, 2.04	1.60	1.07, 2.41	0.04	1.37	1.10, 1.72	1.87	1.18, 2.96

Ever use of oral contraceptives among all women‡‡													
Ever used	65, 51, 79, 85	1.00	0.80	0.55, 1.16	1.20	0.86, 1.68	1.27	0.91, 1.76	0.04	1.17	0.96, 1.44	1.42	0.96, 2.10
Never used	85, 99, 83, 123	1.00	1.10	0.82, 1.47	0.83	0.61, 1.13	1.13	0.85, 1.49	0.74	1.12	0.94, 1.33	1.29	0.92, 1.81

* Stratified by age and center and adjusted for total energy intake (residual method), body mass index, height, physical activity level, and smoking status.

† Quartile cutpoints were based on study-wide energy-adjusted nutrient intake distributions, computed as the residuals from a linear regression of nutrient intake on total energy intake with additional adjustment for country.

‡ RR, relative risk; CI, confidence interval; HRT, hormone replacement therapy.

§ p_{trend} estimated on integer scores (1–4) applied to the quartiles and entered as a continuous term in the models.

¶ 100 g/day for total carbohydrates and 50 g/day for total sugars. *p* values for heterogeneity were estimated from the uncalibrated continuous estimates. For total carbohydrates and total sugars, the *p* values for heterogeneity were, respectively: 0.75 and 0.34 for body mass index, 0.54 and 0.84 for menopausal status, 0.04 and 0.14 for ever use of HRT among postmenopausal women, and 0.73 and 0.74 for ever use of oral contraceptives among all women.

Weight (kg)/height $(m)^2$.

** Excludes three cases and 836 noncases with bilateral ovariectomy.

†† Excludes 41 cases and 9,294 noncases with missing HRT data.

‡‡ Excludes 40 cases and 14,213 noncases with missing oral contraceptive therapy data.

difference in means was only 10 glycemic index units (data not shown).

Total energy intake was strongly correlated with carbohydrate intake ($r = 0.86$) and total dietary glycemic load ($r = 0.84$) but weakly correlated with overall glycemic index ($r = 0.11$) (data not shown). After adjustment for total energy intake in addition to age and center, the following correlations were observed: total carbohydrate intake with total dietary glycemic load ($r = 0.93$), overall glycemic index ($r = 0.17$), and total fats ($r = -0.71$); and overall glycemic index with total dietary glycemic load ($r = 0.51$), total starch ($r = 0.66$), total sugars ($r = -0.44$), and total fiber ($r = 0.00$).

We found no statistically significant associations or dose-response trends with endometrial cancer risk for increasing quartile intakes of any of the nutrient exposure variables (table 3). However, when total carbohydrates, total dietary glycemic load, total sugars, and total fiber were analyzed with continuous scales, the associations for these dietary factors were marginally statistically significant, and the point estimates more than doubled when calibrated data were used to partially control for measurement error (table 3). Additional adjustment for total dietary fiber did not appreciably alter the relative risk estimates, but the fiber-risk association was partly attenuated after adjustment for total carbohydrates (data not shown), suggesting no independent association of total fiber with risk. There was no association between overall glycemic index or total starch intake and risk, and neither adjustment for potential confounders nor calibration appreciably affected these relative risk estimates (table 3).

In isocaloric multivariable nutrient density models (data not shown in tables), increasing the energy intake from total carbohydrates by 5 percent was associated with a marginally statistically significant increased risk when offset by a 5 percent decrease in the percentage of energy from total fats (relative risk = 1.07, 95 percent confidence interval: 1.00, 1.15), polyunsaturated fats (relative risk = 1.18, 95 percent confidence interval: 0.97, 1.44), and, to a lesser extent, monounsaturated fats (relative risk = 1.08, 95 percent confidence interval: 0.90, 1.29). However, there was no association when increased energy from carbohydrates was offset by an identical decrease in energy intake from saturated fats, protein, or alcohol.

In subgroup analyses (table 4), the associations between total carbohydrates, total sugars, and risk were stronger among postmenopausal women who had never used HRT compared with ever users ($p_{\text{heterogeneity}} = 0.04$ for total carbohydrates, $p_{\text{heterogeneity}} = 0.14$ for total sugars). Among women who had never used HRT, there were statistically significant dose-response trends with increasing quartiles and use of continuous measures. The risk estimates appeared slightly stronger among postmenopausal women than among premenopausal women, but the tests for heterogeneity were not statistically significant. When stratified by body mass index subgroups, the calibrated continuous models suggested a possibly stronger association among normal-weight women, but this finding was not reflected in the quartile risk estimates. Similarly, risk estimates for total carbohydrates and total sugars appeared higher for women with a waist-hip ratio below the median versus above the median, but there was no

significant heterogeneity ($p_{\text{heterogeneity}} = 0.10$ and $p_{\text{heterogeneity}} = 0.31$, respectively; data not shown in tables). There was no evidence that use of oral contraceptives, physical activity, or diabetes modified the associations, nor was there any evidence of heterogeneity of risk estimates across countries. The subgroup results for total dietary glycemic load were very similar to those for total carbohydrates. The association between overall glycemic index and risk did not differ by any of the subgroup factors examined ($p_{\text{heterogeneity}} > 0.10$ for all comparisons). The relative risk estimates did not meaningfully change in sensitivity analyses that excluded women with less than 1 year of follow-up, women with self-reported diabetes, or in analyses restricted to cases with known type I tumors.

We also examined the associations between main carbohydrate-providing food groups (29) and endometrial cancer risk (supplementary online table 1). None of the associations was statistically significant, although there was a marginally significant positive trend for potatoes ($p_{\text{trend}} = 0.06$).

DISCUSSION

Overall, no significant association with endometrial cancer risk was observed for quartile intakes of any of the exposure variables. However, when continuous estimates were used, there was a suggestion of a modest increased risk associated with dietary carbohydrates, particularly total sugars, which was further supported by the calibrated estimates. Our results also indicate that HRT may modify the carbohydrate-risk association.

Most previous studies (11, 13, 14, 17–19) observed a null association between dietary carbohydrate intake and endometrial cancer, whereas other studies have suggested positive (12, 15, 16) or inverse (20–23) associations. We found that total sugars, but not total starch, might increase risk. Studies in animals and humans have found that diets high in sugars, particularly fructose and sucrose, increase insulin concentrations to a larger extent than starch-rich diets and are associated with insulin resistance (50, 51). Other epidemiologic studies have found no convincing association of total sugars (13, 52) or total starch (22) with endometrial cancer. Studies that examined dietary fiber intake have generally reported possible inverse (16, 18, 21, 22) or null (12, 19, 53) associations. It is possible that the association may differ according to different fiber fractions such as soluble and insoluble fiber; however, these data were not available in our study.

Although glycemic load, by definition, is a product of carbohydrate quantity and quality, it was correlated much more strongly with total carbohydrates than with overall glycemic index in this study. As such, the risk estimates for total dietary glycemic load were very similar to those for total carbohydrates. Similar correlations were reported in a recent study (54), in which the authors suggested that the narrow range of observed glycemic index values could partly explain the low correlation between glycemic load and glycemic index, and the lack of association between glycemic index and risk. Four previous studies (10, 11, 13, 28) examined the association between glycemic load, glycemic index, and endometrial cancer. Consistent with our results, these studies generally observed a weak positive association between total dietary glycemic load and risk. For glycemic index, two studies (11, 28) observed no association between overall glycemic index and risk, and two studies (10, 13) reported positive associations.

The associations between total carbohydrates, total sugars, total dietary glycemic load, and endometrial cancer risk were modified by HRT use, such that risk was increased for never users but not ever users. The underlying mechanisms are unclear, although it is possible that exogenous estrogens in HRT preparations modify circulating hormone levels to such an extent that dietary factors have little additional effect. Two previous studies (13, 28) did not observe statistically significant heterogeneity between glycemic load and risk according to HRT use. Kasum et al. (55) observed an inverse association between intake of whole grains and risk among never users but not ever users.

Contrary to our results, Silvera et al. (13) reported a possibly stronger association between glycemic load, glycemic index, and risk for women who were premenopausal at baseline; however, there was no significant heterogeneity, and many of those women would have experienced menopause during the mean 16-year study follow-up. Our study also measured only baseline menopausal status, but mean follow-up was shorter (6.4 years) and so would be less affected by changes in menopausal status. Although previous studies have reported possibly stronger associations between overall glycemic index or total dietary glycemic load and endometrial cancer risk for women who are overweight or obese (10, 11, 13), inactive (11, 13), or nondiabetic (28), we did not find clear evidence for effect modification by these factors.

Under isocaloric conditions, increasing the proportion of carbohydrates in the diet increased risk only when carbohydrates replaced energy from total fats, monounsaturated fats, and polyunsaturated fats, but not energy from saturated fats, protein, or alcohol. There is evidence from other studies (7, 8, 40, 56, 57) that the amount and type of dietary fat can modify the glycemic and insulinemic response to a carbohydrate food, and that insulin sensitivity may be improved by monounsaturated fats but worsened by saturated fats (58, 59). Future studies should consider exploring further the associations of dietary patterns with risk.

The main mechanisms by which carbohydrate-rich foods and their glycemic index could influence endometrial cancer risk relate to the development or exacerbation of insulin resistance, chronic hyperinsulinemia, hyperglycemia, obesity, or diabetes (1, 6, 8, 27, 60). The type and amount of carbohydrates directly influence the glycemic and insulinemic response (6–8, 50), and some evidence suggests that slowly absorbed, low glycemic index foods improve insulin sensitivity through their maintenance of relatively low plasma fatty acid levels (6, 8, 27). Furthermore, dietary interventions that modify carbohydrate and fat intake and overall glycemic index have been shown to significantly alter peptide and sex steroid hormone levels (61, 62).

A major strength of this study is its large, prospective cohort design; the wide variation in consumption of carbohydrate-rich foods between EPIC countries (29); and information on many potential confounders. Our study also has several limitations common to observational dietary studies.

Estimating food and nutrient intakes by questionnaires is associated with large random error that tends to attenuate relative risk estimates (24, 25). It is also probable that differential systematic error was present because of underreporting of intake within specific population subgroups of women, such as obese women (36). Because total energy and many nutrients have correlated errors, adjustment for total energy is thought to partly remove some errors in estimated nutrient intakes (44, 45).

The calibration method used to correct for dietary measurement errors may not completely account for measurement error because of likely correlated errors between the 24-hour recalls and the dietary questionnaires (25, 46). Thus, the relative risk estimates observed in this study may be underestimates of the true association. On the other hand, some caution is needed when interpreting these calibrated estimates, particularly because of several statistically marginal associations and some associations that were seen with only the calibrated estimates. Measurement error correction will generally always strengthen associations away from the null because of imperfect associations between the dietary questionnaires and the 24-hour recall data. Calibrated estimates are thought to give a more precise point estimate but not a more precise estimate of statistical significance.

Diet and other covariates were measured at baseline only; thus, we were unable to adjust for possible changes in exposures, including diet and exogenous hormones, which may have occurred during follow-up. Some limitations also affect the estimation and interpretation of glycemic index and glycemic load. Reference glycemic index values have been determined primarily by using US and Australian foods; however, botanical variation, processing, and cooking methods, which have a significant impact on glycemic index (9, 26, 40), may differ in European countries. Glycemic index values have been determined for only a limited number of foods, and the methods used to assign glycemic index values to food items can differ between studies. It has also been suggested that glycemic index and glycemic load may not always adequately reflect the glycemic or insulinemic response to food when used in the context of a usual diet (56, 57, 63).

In conclusion, our data suggest no association of overall glycemic index, total starch, and total fiber with risk, and a possible modest positive association of total carbohydrates, total dietary glycemic load, and total sugars with risk, particularly among never users of HRT.

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