

Citation:

Cust AE, Slimani N, Kaaks R, van Bakel M, Biessy C, Ferrari P, Laville M, Tjønneland A, Olsen A, Overvad K, Lajous M, Clavel-Chapelon F, Boutron-Ruault MC, Linseisen J, Rohrmann S, Nothlings U, Boeing H, Palli D, Sieri S, Panico S, Tumino R, Sacerdote C, Skeie G, Engeset D, Gram IT, Quiros JR, Jakszyn P, Sanchez MJ, Larranaga N, Navarro C, Ardanaz E, Wirfalt E, Berglund G, Lundin E, Hallmans G, Bueno-de-Mesquita HB, Du H, Peeters PHM, Bingham S, Khaw KT, Allen NE, Key TJ, Jenab M, Riboli E. Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort *Am J Epidemiol*. 2007 Oct 15;166(8):912-23.

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Study Design:

Prospective cohort study

Class:

B - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the association of endometrial cancer risk with dietary total carbohydrates, glycemic index, and glycemic load.

Inclusion Criteria:

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort collected diet and lifestyle data 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).

Exclusion Criteria:

- 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 were excluded.
- 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.

Description of Study Protocol:

Recruitment

Participants of EPIC were mostly recruited from the general population residing in defined geographic areas.

Design: Prospective cohort study

Blinding used (if applicable): not applicable

Intervention (if applicable): not applicable

Statistical Analysis

- Age- and center-adjusted Pearson's partial correlation coefficients were estimated to assess the correlations between nutrient intakes
- Cox proportional hazards models were used to estimate relative risks and 95% confidence intervals
- 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.

Data Collection Summary:

Timing of Measurements

Baseline data collection were done between 1992 and 2003. Follow-up vital status was known for 98.4% of EPIC participants at the end of April 2004. Cancer cases were identified by the end of censoring periods ending between December 1999 and March 2004 in the EPIC centers

Dependent Variables

- Endometrial cancer: International Classification of Diseases for Oncology, second edition (code C54). Cancer diagnosis was microscopically verified for 89.3% of cases and by clinical examination for 8.5 percent; the remaining 2.2% were verified by self-report, tomography scan, surgery, autopsy, or death certificate. Morphology was specified for 239 (34%) cases, of which 229 cases (96%) were classified as type I and 10 cases (4%) as type II

Independent Variables

- Overall glycemic index or glycemic load: Usual diet during the previous 12 months was assessed with country-specific, validated dietary assessment instruments.
- 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, a second dietary measurement was taken from an 8% stratified random sample (a total of 36,900 participants) of the cohort by using a standardized, computer-assisted, 24-hour dietary recall method.
- A glycemic index database was compiled whereby published glycemic index values were assigned to carbohydrate-providing food items to reflect their blood glucose response.
- 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.

Control Variables

- All models were also adjusted for total energy intake by using the residual method to control partly for the error in nutrient intake.
- The multivariable models were additionally adjusted for body mass index (kg/m², continuous), height (cm, continuous; representing lean body mass), and total physical activity level (inactive, moderately inactive, moderately active, active, unknown), to control for other determinants of energy balance, 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.
- 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.

Description of Actual Data Sample:

Initial N: 288,428 (100% women) after exclusions

Attrition (final N): 710 eligible incident endometrial cancer cases among 288,428 women

Age: endometrial cancer cases = 54.1 ± 8.7 years; noncases = 49.9 ± 11.6 years

Ethnicity: no data

Other relevant demographics: Postmenopausal: endometrial cancer cases = 64.5%; noncases = 43.2%

Anthropometrics: BMI: endometrial cancer cases = 26.4 (4.0 SD); noncases = 25.2 (5.3 SD)

Location: 10 western European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and United Kingdom)

Summary of Results:

Relative risk estimates and 95% confidence intervals for endometrial cancer, by quartiles* of energy-adjusted glycemic index and glycemic load, European Prospective Investigation into Cancer and Nutrition, 1992–2004

Dietary variable and quartile	No. of cases	No. of person-years	Multivariable adjusted RR*	95% CI	
Glycemic index					
Quartile 1	182	471,723	1.00		
Quartile 2	185	447,953	1.17	0.95,	1.44
Quartile 3	168	450,978	1.08	0.88,	1.34
Quartile 4	175	472,341	1.04	0.84,	1.28

p for trend			0.90		
Calibrated (per 5 units/day)			1.03	0.82,	1.30
Glycemic load					
Quartile 1	180	477,786			
Quartile 2	163	445,897	1.01	0.82,	1.26
Quartile 3	167	444,498	1.05	0.85,	1.31
Quartile 4	200	474,813	1.15	0.94,	1.41
p for trend			0.16		
Calibrated (per 50 units/day)			1.40	0.99,	1.99

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

Other Findings

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.

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 combined with ever users (total carbohydrates P for heterogeneity = 0.04).

Author Conclusion:

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.

Reviewer Comments:

Authors note the following limitations:

- *Estimating food and nutrient intakes by questionnaires is associated with large random error that tends to attenuate relative risk estimates*
- *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*
- *Some caution is needed when interpreting these calibrated estimates, particularly because of several statistically marginal associations and some associations that were seen only with the calibrated estimates*
- *Diet and other covariates were measured at baseline only, thus the researchers were unable to adjust for possible changes in exposures, including diet and exogenous hormones, which may have occurred during follow-up*
- *Reference glycemic index values have been determined primarily with United States and*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	N/A

Validity Questions

1.	Was the research question clearly stated?	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	Was the selection of study subjects/patients free from bias?	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	Were study groups comparable?	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	N/A

3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	Was method of handling withdrawals described?	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	Was blinding used to prevent introduction of bias?	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A

6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	N/A
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	N/A
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	N/A
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes

8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes

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