Citation:

Sieri S, Pala V, Brighenti F, Pellegrini N, Muti P, Micheli A, Evangelista A, Grioni S, Contiero P, Berrino F, Krogh V. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study.*Am J Clin Nutr.* 2007 Oct; 86(4): 1,160-1,166.

PubMed ID: 17921397

Study Design:

Prospective Cohort Study

Class:

B - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To determine whether glycemic index (GI) and glycemic load (GL) were associated with the risk of breast cancer in a cohort of Italian women volunteers from Northern Italy, enrolled in the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study).

Inclusion Criteria:

Healthy women aged 34 to 70 years who were residents of the province of Varese in Northern Italy and recruited into the prospective ORDET Study.

Exclusion Criteria:

Women who:

- Were taking hormone therapy (HRT) in the three months before recruitment
- Had a history of cancer
- Had current chronic or acute liver disease
- Had undergone bilateral ovariectomy.

Description of Study Protocol:

Recruitment

- Between June 1987 and June 1992, 10,786 healthy women aged 34 to 70 years who were residents of the province of Varese in Northern Italy were recruited to the prospective ORDET Study

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- The women were volunteers from the general population who had learned of the study at public meetings, through advertising or at breast cancer early-diagnosis units.

Design

Prospective cohort study.

Dietary Intake/Dietary Assessment Methodology

- Volunteers completed a semi-quantitative food-frequency questionnaire (FFQ), and anthropometric and lifestyle data were collected
- After compilation at recruitment, the FFQ was reviewed by a nurse with the volunteer to complete any missing items. The questionnaire consisted of 107 items; it was designed to ascertain in detail the quantities and kinds of foods consumed over the previous year by using illustrations of two or three sample dishes of definite sizes or by reference to standard portion sizes. The frequency of consumption of items could be specified by day, week or month. Questions on seasoning and food preparation were also included. From the FFQ data, an average daily diet, consisting of food items and portion sizes, was calculated for each volunteer. The food groups included in the FFQ were vegetables (divided into cooked, raw vegetables, tomatoes, pulses, and so on), potatoes, fruit, cereals (categories of bread, pasta, rice and pizza), meat and meat products, fish, dairy products (categories of cheese, milk and yogurt), eggs, cakes, added fat and alcoholic beverages. Nutrient values for each food item were obtained from the Italian food composition tables. GIs of food items containing available carbohydrates were obtained from measurements of common Italian foods (F Brighenti et al, Italian glycemic index).

Statistical Analysis

- GLs and GIs were adjusted for the energy intake of each person by using the regression-residual method. They were then categorized into quintiles. Relative risks (RR) of breast cancer in relation to GI and GL were determined by multivariate Cox hazard modeling, which compared the highest quintile of GI or GL with the lowest quintile. Age at menarche, oral contraception use (yes or no), smoking status (smoker, never smoker or former smoker), height, weight, years of education, parity, alcohol intake and total energy intake were included as covariates. Additional models also included saturated fat and fiber intake as covariates. As a test for trend, a likelihood ratio test was used that compared models that included or omitted the variable whose value was the median of the quintile to which the subject belonged
- The effect on breast cancer of total carbohydrates, carbohydrates from high-GI foods and carbohydrates from low-GI foods was analyzed by using the energy partition method. This method is a non- isocaloric method that tests the effect of adding energy from a specific macronutrient, in this case carbohydrates, while keeping energy from other macronutrients constant. For total carbohydrates, high-GI carbohydrates and low-GI carbohydrates, RRs of breast cancer were calculated for a 5% increase of energy from each of these sources in turn, including age at menarche, oral contraception use (yes or no), smoking status (smoker, never smoker or former smoker), height, weight, years of education and parity as covariates
- The hypothesis was that the effect of high dietary GI and GL would be modified by factors associated with hormone status and insulin resistance. To explore this possibility, analyses performed were stratified by baseline menopausal status (pre-menopausal or post-menopausal) and body mass index [(BMI; in kg/m^2) less than 25 or 25 or more
- The authors examined whether associations for GI and GL differed according to BMI and menopausal status by employing product terms (zero and one for BMI less than 25 and

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25kg/m^2 or more, respectively, and also for pre-menopausal or post-menopausal status, respectively) and multiplying them by the median of the GI and GL quintile to which the subject belonged
- To assess the significance of interaction differences, a likelihood ratio test was used that compared the model that included the product term and the model that did not include it. In all Cox models, age at recruitment was the primary time variable. Spearman's rank correlation was used to assess relations between dietary GL and serum fructosamine and glucose concentrations.
- All analyses were performed with STATA software (version 7.0; Stata Corp, College Station, TX).

Data Collection Summary:

Timing of Measurements

- June 1987 to June 1992
- Mean follow-up of 11.5 years
- Cancer incidence information, available from the local cancer registry (Varese Cancer Registry) was linked to the ORDET Study file to identify incident breast cancer cases in the cohort up to December 2001. The Varese Cancer Registry is characterized by high-quality and completeness of the data; 2% of breast cancer cases are known to the registry by death certificate only and 96.3% of cases are confirmed histologically or cytologically. The ORDET Study file was also linked to the Varese residents' file to check vital status.

Dependent Variables

Breast cancer risk.

Independent Variables

- Glycemic index
- Glycemic load.

Description of Actual Data Sample:

- *Initial N:* 10,786 women
- *Attrition (final N):* 8,959 women
- *Age:* 34 to 70 years
- *Ethnicity:* Italian
- *Location:* Province of Varese in Northern Italy.

Summary of Results:

- RR for breast cancer in the highest quintiles of GI and GL was 1.57 (95% CI: 1.04 to 2.36, P=0.040) and 2.53 (95% CI: 1.54 to 4.16, P=0.001), respectively
- Total carbohydrate intake was not associated with greater breast cancer risk, but high carbohydrate from high GI foods was
- Increased risk associated with high GL was confined to women who were pre-menopausal and in women with normal BMI.

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Author Conclusion:

A high-GL diet may increase the risk of breast cancer in Italian women. The effect is particularly evident in pre-menopausal women and those with BMI over 25kg/m^2.

Reviewer Comments:

None.

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)	Yes
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)	Yes

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

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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)	Yes
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	N/A
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?	Yes
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?	???

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	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 interveningfactors 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?**		No
	7.1.	Were primary and secondary endpoints described and relevant to the question?	N/A
	7.2.	Were nutrition measures appropriate to question and outcomes of concern?	N/A
	7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	N/A
	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?	No
	7.6.	Were other factors accounted for (measured) that could affect outcomes?	N/A
	7.7.	Were the measurements conducted consistently across groups?	N/A
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

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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?	Yes
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?	N/A
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
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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