

Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women¹⁻³

Martin Lajous, Marie-Christine Boutron-Ruault, Alban Fabre, Françoise Clavel-Chapelon, and Isabelle Romieu

ABSTRACT

Background: Diets high in carbohydrates may result in chronically elevated insulin concentrations and may affect breast cancer risk by stimulation of insulin receptors or through insulin-like growth factor I (IGF-I)-mediated mitogenesis. Insulin response to carbohydrate intake is increased in insulin-resistant states such as obesity.

Objective: We sought to evaluate carbohydrate intake, glycemic index (GI), and glycemic load (GL) and subsequent overall and hormone-receptor-defined breast cancer risk among postmenopausal women.

Design: A prospective cohort analysis of dietary carbohydrate and fiber intakes was conducted among 62 739 postmenopausal women from the E3N French study who had completed a validated dietary history questionnaire in 1993. During a 9-y period, 1812 cases of pathology-confirmed breast cancer were documented through follow-up questionnaires. Nutrients were categorized into quartiles and energy-adjusted with the regression-residual method. Cox model-derived relative risks (RRs) were adjusted for known determinants in breast cancer.

Results: Dietary carbohydrate and fiber intakes were not associated with overall breast cancer risk. Among overweight women, we observed an association between GI and breast cancer (RR_{Q1-Q4} : 1.35; 95% CI: 1.00, 1.82; P for trend = 0.04). For women in the highest category of waist circumference, the RR_{Q1-Q4} was 1.28 (95% CI: 0.98, 1.67; P for trend = 0.10) for carbohydrates, 1.35 (95% CI: 1.04, 1.75; P for trend = 0.01) for GI, and 1.37 (95% CI: 1.05, 1.77; P for trend = 0.003) for GL. We also observed a direct association between carbohydrate intake, GL, and estrogen receptor-negative breast cancer risk.

Conclusions: Rapidly absorbed carbohydrates are associated with postmenopausal breast cancer risk among overweight women and women with large waist circumference. Carbohydrate intake may also be associated with estrogen receptor-negative breast cancer. *Am J Clin Nutr* 2008;87:1384–91.

INTRODUCTION

The plasma insulin response to carbohydrate intake is increased in insulin-resistant states such as obesity (1). Elevated circulating insulin may affect breast cancer risk either directly, by stimulating insulin receptors in breast tissue, or indirectly, through the mitogenic effects of insulin-like growth factor I (IGF-I) (2). Although most prospective epidemiologic studies show little evidence of a role of dietary carbohydrates in breast cancer risk (3–9), this association may be of particular relevance

in populations with a high prevalence of underlying insulin resistance (10). Results from a large prospective study in primarily premenopausal women lend some support to this hypothesis. In the Nurses' Health Study II, dietary carbohydrates were associated with increased breast cancer risk only among women who were overweight (9). Fiber intake may also play a role in breast cancer by lowering circulating concentrations of estrogens and increasing serum concentrations of insulin-like growth factor binding protein 3 (IGFBP-3), the main protein carrier for IGF-I (11, 12). However, most prospective studies of fiber intake and breast cancer risk have found little evidence for this association (4, 8, 9, 13).

Breast cancer categorized by hormone receptor status may represent distinct phenotypes that possibly have different risk factors (14). Results from prior studies showed that dietary factors are associated primarily with estrogen receptor-negative (ER[−]) breast cancer (15, 16). Currently, information is limited on the association of carbohydrate and fiber intakes with hormone receptor-defined breast cancer.

We therefore conducted a prospective analysis of a large sample of postmenopausal French women to evaluate carbohydrate intake, glycemic index (GI), glycemic load (GL), and fiber intake and the subsequent risk of overall and hormone receptor-defined breast cancer. For dietary carbohydrate, we sought to examine these associations at different levels of anthropometric markers of insulin resistance.

SUBJECTS AND METHODS

The E3N study cohort

The E3N [Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale (MGEN)] study

¹ From the INSERM (Institut National de la Santé et de la Recherche Médicale), ERI 20, EA 4045, and Institut Gustave Roussy, Villejuif, France (ML, M-CB-R, AF, and FC-C); the Center for Population Health Research, National Institute of Public Health, Cuernavaca, Mexico (ML and IR); the Department of Epidemiology, Harvard School of Public Health, Boston, MA (ML).

² Supported by the National Council of Science and Technology of Mexico (CONACYT) and by the Cabot Family Charitable Trust (ML).

³ Reprints not available. Address correspondence to I Romieu, Instituto Nacional de Salud Publica, Av Universidad # 655, Col Santa Maria Ahuacatitlan, Cuernavaca Morelos 62508, México. E-mail: iromieu@correo.insp.mx.

Received September 1, 2007.

Accepted for publication December 12, 2007.

was established in 1990–1991 when 98 995 women born between 1925 and 1950 and insured with the MGEN, a French health insurance scheme primarily covering teachers, completed a mailed questionnaire on their lifestyle and medical history (17). The E3N cohort represents the French component of the European Prospective Investigation into Cancer and Nutrition (18). Follow-up questionnaires were sent in 1992, 1993, 1994, 1997, 2000, and 2002 to update reproductive and lifestyle information and to ascertain newly diagnosed diseases, including breast cancer.

This analysis was based on women who responded to a dietary history questionnaire sent in 1993 to participants who had responded to the 2 previous nondietary questionnaires ($n = 95\,644$). After 2 reminders for nonrespondents, 77 613 dietary questionnaires were collected between June 1993 and July 1997 (81.1% response rate). Of these questionnaires, 2104 were excluded because of miscoding and 985 because respondents did not give their consent to follow-up by the health insurer (MGEN) in case of dropout. We excluded questionnaires with an unreasonable report of total energy intake, as defined by the 1st and 99th percentile of the ratio of energy intake to basal metabolic rate computed on the basis of age, height, and weight at the time of the dietary survey (19). Of the remaining 73 034 subjects with valid questionnaires, 4500 who had reported cancer diagnosis before responding to the dietary questionnaire and 901 with unavailable follow-up information after this questionnaire were excluded. Menopausal status was updated after each follow-up questionnaire. We restricted the analysis to postmenopausal women, because postmenopausal breast cancer is considered to be more strongly associated with environmental exposure (20). Thus, the final number of women included in the analysis was 62 739.

All study subjects provided written informed consent in accord with the rules of the French National Commission on Computer Data and Individual Freedom. Approval for the study was provided by the same commission.

Dietary assessment

A food-frequency questionnaire with 208 items was used to assess usual dietary intake during the past year (21). The questionnaire consisted of 2 parts: the first part was divided into 8 sections for each meal (including regular meals such as breakfast and between-meal snacks), and women were asked about the frequency of consumption of a given list of foods and food groups (eg, fruit, meat, cheese). Eleven categories of frequency of consumption were available, ranging from “never or less than once a month” to “7 times a week.” The amount of specific food consumed was assessed with the use of either natural units or portion sizes illustrated in a booklet with colored photographs that was sent along with the questionnaire (22). The second part of the questionnaire contained qualitative questions about consumption frequency of specific food items within one of the generic food groups used in the first part (eg, different fruit for generic fruit consumption).

Nutrient intakes were calculated with the use of a food composition table derived from the updated French national database (23). The GI of foods is a measure of the relative postprandial blood glucose response per gram of carbohydrate. GI values were obtained from international tables (24), and values reported from French studies were preferred when available. These values were extracted from the international tables by an experienced French

dietitian to ensure comparability between the foods reported in the tables and the foods included in our questionnaire. The dietary GL was calculated by summing, for all foods, the GI value for that food multiplied by the quantity of carbohydrates consumed from that food. Therefore, each unit of GL represents the equivalent of 1 g carbohydrate from a glucose solution. The overall GI for each participant was estimated by dividing the dietary GL by the total amount of carbohydrates consumed. GI represents a weighted average of the GI value of the foods consumed and is an indicator of the average GI of the carbohydrates consumed.

The validity and reproducibility of our dietary assessment questionnaire was previously described (21). Briefly, in 1990 a sample of 119 women similar to participants in the E3N study were asked to complete 2 food-frequency questionnaires at the beginning and end of the 1-y study period. Both questionnaires were then compared with twelve 24-h dietary recalls carried out monthly throughout the study period. High correlations between the first food-frequency questionnaire and the 24-h dietary recalls for proteins ($r = 0.56$), carbohydrates ($r = 0.64$), fat ($r = 0.49$), and alcohol ($r = 0.71$) were observed (21).

Ascertainment of breast cancer cases

Incidental cases of breast cancer were initially identified by self-report on the 1994, 1997, 2000, and 2002 questionnaires. The final questionnaire was sent in 2 batches, one for postmenopausal women (July 4) and one that included additional questions on menopause for premenopausal women and women of uncertain menopausal status (August 28). Deaths in the cohort were identified by reports from family members, the postal service, and the MGEN health insurance database. Cause of death was obtained from the French National Service of Deaths. Participants who reported cancer diagnosis were asked to provide their physician's address for confirmation. Physicians were individually contacted to obtain pathology reports and information on estrogen receptor (ER) and progesterone receptor (PR) status. Overall, a total of 2323 cases of breast cancer were identified between 1993 and 2002; 96.6% of them were confirmed by pathology reports. Because the number of false positives was <5%, all cases were included. Menopausal status was updated after each follow-up questionnaire.

Other variables

Information on educational level, reproductive history, history of benign breast diseases, familial history of breast cancer, and hormonal treatments was obtained from the 2 questionnaires preceding the dietary assessment in 1993. Height and weight were obtained from a follow-up questionnaire that accompanied the dietary assessment. When missing, information on preceding questionnaires was used. Body mass index (BMI; in kg/m^2) was calculated. Waist circumference from the questionnaire after the dietary questionnaire was available for 54 914 (87.5%) of the analytic sample. Self-reported anthropometry in the E3N study cohort was validated for 152 study participants who were asked to complete a questionnaire the day before their appointment. A trained technician repeated the same anthropometric measurements with the use of standardized equipment. The correlation coefficient for BMI was 0.92; for waist circumference it was 0.79 (25). A metabolic equivalent score of total physical activity based on walking, light and vigorous household activity, and

moderate and vigorous physical activity was estimated based on responses to the 1993 questionnaire.

This measure of physical activity was used to assess the relation between physical activity and breast cancer and was shown to perform well (26). Information on total physical activity was not available for 8698 subjects (13.9% of the total). In addition to indicators for quartiles of physical activity, an indicator for women with missing values for physical activity was included in the models. Menopausal status and age at menopause were determined with information on last menstruation, hot flushes, hysterectomy, ovariectomy, and hormonal treatments recorded in each follow-up questionnaire. Regular mammography was defined as report of a recent mammogram in 1990, 1992, and 1993.

Statistical analysis

Person-years were calculated from the date of returning the 1993 dietary questionnaire if postmenopausal at that time, date of menopause to date of cancer diagnosis, date of the last questionnaire returned for nonrespondents, and deaths or mailing date of the last follow-up questionnaire in 2002, whichever occurred first. Relative risk (RR) estimates and 95% CIs were obtained with the use of Cox's proportional hazards model stratified by 5-y interval birth cohorts with the women's age as the time scale. Nutrients, GI, and GL were adjusted for total energy intake with the use of the regression-residual method and were categorized as quartiles based on distribution (27). RRs of breast cancer were determined by comparison with the lowest quartile.

In multivariate analyses, we adjusted simultaneously for age, 2-y follow-up period, region of residence, education, family history of breast cancer, history of benign breast disease, age at menarche, parity, breastfeeding, years since last use of oral contraceptives, age at menopause, years of hormone replacement therapy use, regular mammographic evaluation, height, physical activity, BMI, vitamin supplement use, and intakes of calories, folate, and alcohol. Carbohydrate models were additionally adjusted for total fiber intake, whereas models evaluating fiber were adjusted for carbohydrate intake. To test for trend, the median value for each quartile was used as a continuous variable. We evaluated the consistency of our results by examining the association of specific foods that were important contributors of dietary factors of interest and breast cancer risk in both age-adjusted and multivariable models. We repeated the analyses, restricting the outcome to invasive cases only. To evaluate whether the association of carbohydrate intake, GI, and GL differed in markers of underlying insulin resistance, we stratified our analyses by BMI (<25 , ≥ 25) as well as waist circumference (in tertiles) when information was available. To test for interaction we included a cross-product term of the median value of intake for each quartile of carbohydrate intake, GI, and GL as a continuous variable and the prespecified categories of stratification. Log-likelihood tests were used to evaluate these possible interactions. All P values were 2-tailed. We used the SAS statistical software (version 9.02; SAS Institute Inc, Cary, NC) for data analysis.

RESULTS

We documented 1812 cases of incident postmenopausal breast cancer during the 9 y of follow-up (410 314 person-years) of 62 739 postmenopausal women, for whom 1595 were invasive and 217 in situ. The age range of participants at baseline was

42–72 y ($\bar{x} \pm \text{SD}$: 53 ± 7 y), and the age range at breast cancer diagnosis was 46–76 ($\bar{x} \pm \text{SD}$: 60 ± 6 y). The distribution of known risk factors for breast cancer by quartiles of energy-adjusted carbohydrate intake is shown in **Table 1**. Women with a higher carbohydrate intake were less likely to have a university degree and to use hormone replacement therapy. These women were also more likely to have had a history of benign breast disease, to have breastfed for ≥ 12 mo, and to use vitamin supplements. Women with a higher intake of carbohydrates had a higher mean age at first pregnancy, consumed more fiber, were more physically active, had a lower waist circumference, and drank less alcohol.

Median carbohydrate intake was 223 g/d (10th–90th percentile range: 141–327 g/d), and median intakes in energy-adjusted quartiles ranged from 177 to 267 g/d. Median overall GI was 56 (10th–90th percentile range: 43–67), whereas median dietary GL was 122 (10th–90th percentile range: 67–200). Carbohydrate intake, GI, and GL were not associated with overall postmenopausal breast cancer risk (**Table 2**). The multivariate-adjusted RRs that compared the first and fourth quartiles of intake were 1.05 (95% CI: 0.90, 1.22; P for trend = 0.64) for carbohydrates, 1.14 (95% CI: 0.99, 1.32; P for trend = 0.06) for GI, and 1.11 (95% CI: 0.96, 1.29; P for trend = 0.14) for GL. We also examined the association of breast cancer risk with quartiles of the main food contributors of dietary carbohydrates in the population one at a time. We did not find any specific association between baguette (white bread), potatoes, *pain de campagne* (semi-whole-meal bread), marmalade, added sugar, pasta or rice, and breast cancer risk. We repeated these analyses, excluding in situ breast cancer cases, and results remained essentially unchanged.

Because adiposity and, in particular, central adiposity are important determinants of insulin resistance, we hypothesized that the relation between these nutritional factors and breast cancer risk could differ by BMI and waist circumference. The association between GI and breast cancer among overweight women (BMI ≥ 25) was statistically significant (RR_{Q1–Q4}: 1.35; 95% CI: 1.00, 1.82; P for trend = 0.04), whereas the association was absent among women with a BMI < 25 . The test for an interaction between GI and overweight (BMI ≥ 25) was borderline significant ($P = 0.054$). We further explored this association among overweight women by increasing the cutoffs for obesity. Results were similar but nonsignificant for women whose BMI was ≥ 26 . Evaluation of further cutoffs led to insufficient statistical power because women with a BMI ≥ 27 represented only 10.8% of the population.

We also found a positive association between GI and GL and breast cancer risk among women in the highest tertile of waist circumference (**Table 3**). The RR for the highest compared with the lowest quartile in the highest category of waist circumference was 1.28 (95% CI: 0.98, 1.67; P for trend = 0.10) for carbohydrates, 1.35 (95% CI: 1.04, 1.75; P for trend = 0.01) for GI, and 1.37 (95% CI: 1.05, 1.77; P for trend = 0.003) for GL. The P for interaction with tertiles of waist circumference was 0.03 for carbohydrates, 0.08 for GI, and 0.008 for GL. To better characterize these associations, we conducted 2 additional analyses: we dichotomized waist circumference into abdominal obesity (> 88 cm), and we calculated tertiles of waist-to-hip ratio. The associations between dietary carbohydrates, GI, and GL and breast cancer were in the same direction, but they were nonsignificant for abdominal obesity and absent for all dietary factors in the waist-to-hip ratio subgroups.

We conducted analyses to determine whether dietary carbohydrates, GL, and GI were associated with ER and PR status. ER

TABLE 1

Baseline characteristics by quartile (Q) of energy-adjusted carbohydrate intake in 1993 for 62 739 postmenopausal women from the French Etude Epidémiologique auprès des femmes de la Mutuelle Générale de l'Education Nationale study¹

	Carbohydrate intake				<i>P</i> for trend ²
	Q1 (181 ± 74 g/d)	Q2 (222 ± 66 g/d)	Q3 (243 ± 63 g/d)	Q4 (273 ± 62 g/d)	
Characteristics					
Age (y)	52.8 ± 6.3 ³	52.9 ± 6.4	53.2 ± 6.6	54.3 ± 6.8	<0.0001
University degree (%)	19.1	17.4	16.8	16.4	<0.0001
First-degree relative with breast cancer (%)	11.8	11.6	11.6	11.6	<0.0001
History of benign breast disease (%)	38.7	39.3	39.4	40.2	<0.0001
Mean age at menarche (y)	12.7 ± 1.4	12.7 ± 1.4	12.8 ± 1.4	12.9 ± 1.4	<0.0001
Mean age at first pregnancy (y)	24.6 ± 4.0	24.7 ± 3.9	24.9 ± 3.9	25.0 ± 4.0	<0.0001
≥12 mo of breastfeeding (%)	4.6	4.6	5.5	5.7	<0.0001
Oral contraceptive use (%)	37.1	38.8	40.8	45.8	<0.0001
Mean age at menopause (y)	50.2 ± 3.7	50.3 ± 3.6	50.4 ± 3.7	50.3 ± 3.7	<0.0001
Hormone replacement therapy use (%)	66.7	66.1	66.5	64.8	<0.0001
Regular mammography (%) ⁴	35.6	35.0	34.4	34.6	<0.0001
Physical activity (MET/d) ⁵	44.9 ± 29.9	46.1 ± 30.5	46.5 ± 30.2	48.3 ± 31.1	<0.0001
Mean BMI (kg/m ²)	23.7 ± 3.6	23.3 ± 3.4	22.9 ± 3.1	22.3 ± 3.0	<0.0001
Waist circumference (cm) ⁶	77.9 ± 12.1	76.8 ± 13.5	76.1 ± 17.1	74.6 ± 12.5	<0.0001
Dietary intake ⁷					
Total energy (kcal/d)	2 161 ± 728	2 193 ± 580	2 167 ± 511	2 134 ± 437	<0.0001
Overall glycemic index	50.5 ± 9.3	54.2 ± 8.5	56.3 ± 8.3	59.6 ± 8.7	<0.0001
Dietary glycemic load	86.8 ± 21.2	114.1 ± 18.7	132.9 ± 20.3	162.7 ± 29.0	<0.0001
Carbohydrate intake (g/d)	170.8 ± 22.5	210.5 ± 7.6	235.8 ± 7.4	272.1 ± 19.6	<0.0001
Folate intake (μg/d)	414.5 ± 101.8	408.2 ± 90.6	399.9 ± 87.1	391.3 ± 87.3	<0.0001
Total fiber intake (g/d)	21.6 ± 5.5	23.8 ± 5.4	24.9 ± 5.5	26.5 ± 6.1	<0.0001
Alcohol intake (g/d)	18.9 ± 20.1	11.8 ± 12.4	8.6 ± 9.8	5.6 ± 7.3	<0.0001
Vitamin supplement use (%)	23.2	23.8	24.6	25.5	<0.0001

¹ MET, metabolic equivalent. *n* = 15 699, 15 593, 15 646, and 15 831 for Q1, Q2, Q3, and Q4, respectively.

² Based on ordinal variables containing median variables for each quartile, with the exception of age at menarche and at first pregnancy, when the mean value was used.

³ $\bar{x} \pm SD$ (all such values).

⁴ Report of a recent mammogram in 1990, 1992, and 1993 questionnaires.

⁵ Information not available for 8698 women.

⁶ Information not available for 7764 women.

⁷ All nutrients except alcohol intake were adjusted for total energy intake with the use of the residual method.

status was available for 1362 (75.2%) cases; 1083 (59.8%) were ER⁺ and 279 (15.4%) were ER⁻. For 1325 (73.1%) cases, PR status was available: 814 (44.9%) were PR⁺ and 511 (28.2%) were PR⁻. Carbohydrate intake and GL were associated with ER⁻ cancers (**Table 4**). The RR for extreme quartiles of carbohydrate intake in ER⁻ cancers was 1.78 (95% CI: 1.20, 2.64; *P* for trend = 0.003), the RR_{Q1-Q4} for GI was 0.91 (95% CI: 0.63, 1.32; *P* for trend = 0.98), and the RR_{Q1-Q4} for GL was 1.55 (95% CI: 1.07, 2.25; *P* for trend = 0.03). For ER⁺ tumors, the RRs for extreme quartiles were 0.89 (95% CI: 0.73, 1.08; *P* for trend = 0.21) for carbohydrates, 1.05 (95% CI: 0.88, 1.27; *P* for trend = 0.59) for GI, and 0.91 (95% CI: 0.75, 1.11; *P* for trend = 0.37) for GL. None of these dietary factors were associated with the risk of developing a PR⁺ or PR⁻ breast tumor. We repeated these analyses, cross-classifying breast cancers by ER and PR status. We were limited in this approach because there were only 46 ER⁻/PR⁺ cases; however, we observed a fairly strong association between ER⁻/PR⁻ tumors for carbohydrate intake (RR_{Q1-Q4}: 2.12; 95% CI: 1.37, 3.28; *P* for trend = 0.0006) and GL (RR_{Q1-Q4}: 1.71; 95% CI: 1.13, 2.57; *P* for trend = 0.01).

Median intake of total fiber was 23.7 g/d (10th–90th percentile range: 15.4–35.2 g/d). For soluble fibers and insoluble fibers, the

median intake was 5.0 g/d (10th–90th percentile range: 3.2–7.3 g/d) and 18.7 g/d (10th–90th percentile range: 12.1–28.0 g/d), respectively. No associations were observed between total fiber and its fractions and breast cancer risk. The multivariable RR for the highest quartile compared with the lowest quartile of intake was 0.99 (95% CI: 0.85, 1.16; *P* for trend = 0.94) for total fiber, 1.05 (95% CI: 0.89, 1.23; *P* for trend = 0.88) for soluble fiber, and 0.99 (95% CI: 0.85, 1.16; *P* for trend = 0.58) for insoluble fiber. The RR for extreme quartiles of total fiber intake in ER⁻ cancers was 0.84 (95% CI: 0.57, 1.25; *P* for trend = 0.65), the RR_{Q1-Q4} for soluble fiber was 1.23 (95% CI: 0.82, 1.85; *P* for trend = 0.51), and the RR_{Q1-Q4} for insoluble fiber was 0.85 (95% CI: 0.58, 1.25; *P* for trend = 0.65). Additional analyses for hormone-receptor-defined breast cancers yielded similar null results.

DISCUSSION

In this prospective cohort, we did not observe a direct association between carbohydrate intake, GI, and GL and overall postmenopausal breast cancer. However, these associations appeared to differ in anthropometric markers of insulin resistance. GL and

TABLE 2

Relative risk (RR) (and 95% CI) of postmenopausal breast cancer according to quartile (Q) of energy-adjusted carbohydrate intake, glycemic index (GI), and glycemic load (GL) overall and stratified by BMI ($n = 62\ 739$)

	Median intake ¹	Cases	Age-adjusted	Multivariate ²	BMI < 25 kg/m ²³		BMI ≥ 25 kg/m ²³		<i>P</i> for interaction ⁴
			RR (95% CI)	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	
	<i>g/d</i>	<i>n</i>			<i>n</i>		<i>n</i>		
Carbohydrate intake									0.58
Q1	177	431	1.00	1.00	318	1.00	113	1.00	
Q2	211	462	1.08 (0.94, 1.23)	1.08 (0.94, 1.24)	342	1.02 (0.88, 1.20)	120	1.27 (0.97, 1.66)	
Q3	236	454	1.04 (0.91, 1.19)	1.05 (0.91, 1.21)	364	1.03 (0.88, 1.21)	90	1.12 (0.83, 1.50)	
Q4	267	465	1.02 (0.89, 1.16)	1.05 (0.90, 1.22)	393	1.04 (0.89, 1.20)	72	1.07 (0.77, 1.49)	
<i>P</i> for trend ⁵			0.89	0.64		0.68		0.72	
Overall GI									0.054
Q1	44.3	414	1.00	1.00	322	1.00	92	1.0	
Q2	52.4	444	1.08 (0.94, 1.23)	1.07 (0.93, 1.23)	348	1.07 (0.91, 1.25)	96	1.08 (0.80, 1.44)	
Q3	58.5	468	1.12 (0.98, 1.27)	1.11 (0.97, 1.28)	369	1.10 (0.94, 1.28)	99	1.18 (0.88, 1.59)	
Q4	65.6	486	1.12 (0.98, 1.28)	1.14 (0.99, 1.32)	378	1.09 (0.93, 1.28)	108	1.35 (1.00, 1.82)	
<i>P</i> for trend ⁵			0.07	0.06		0.28		0.04	
Dietary GL									0.10
Q1	84	418	1.00	1.00	312	1.00	106	1.00	
Q2	111	444	1.06 (0.93, 1.21)	1.05 (0.92, 1.21)	348	1.05 (0.90, 1.22)	96	1.05 (0.79, 1.38)	
Q3	134	470	1.10 (0.96, 1.25)	1.11 (0.96, 1.27)	362	1.04 (0.88, 1.22)	108	1.37 (1.03, 1.82)	
Q4	165	480	1.08 (0.95, 1.23)	1.11 (0.96, 1.29)	395	1.08 (0.92, 1.28)	85	1.22 (0.90, 1.67)	
<i>P</i> for trend ⁵			0.24	0.14		0.38		0.09	

¹ Energy-adjusted by using the residual method.

² Adjusted for age, 2-y follow-up period, region of residence, years of education (<12, 12–15, or ≥15), family breast cancer (0, 1, or >1 first-degree relative), history of benign breast disease (yes or no), age at menarche (<12, 12, 13, or ≥14 y), parity (0, ≤2, age at first birth ≤30 y, ≥3 and age at first birth ≤30 or age at first birth >30 y), breastfeeding (none or <7, 7–12, or ≥12 mo), years since last use of oral contraceptives (never, unknown date of last use, or <25, 25–29, or ≥30 y), age at menopause (<45, 45–49, 50–54, or ≥55 y), years of hormone replacement therapy use (never, unknown duration, or <3, 3–5.9, or ≥6 y), regular mammographic evaluation (yes or no) that was defined as a report in 1990, 1992, and 1993 of a recent mammogram, height (in cm), BMI (in quartiles), vitamin supplement use (yes or no), total energy intake (in quartiles), folate intake (in quartiles), fiber intake (in quartiles), alcohol intake (0, <5, or ≥15 g/d), and physical activity (in quartiles).

³ Adjusted for all previous variables and BMI as a continuous variable.

⁴ Log-likelihood ratio test.

⁵ Test for linear trend used median quartile values as a continuous variable.

GI are measures that evaluate different aspects of carbohydrate intake. Although GI is a measure of overall carbohydrate quality in the diet that is independent of quantity, GL incorporates both quality and quantity of carbohydrates, thus reflecting a more general effect of dietary carbohydrates. The GI and breast cancer association was statistically significant only among overweight women, and GI and GL appeared to increase breast cancer risk among women with a large waist circumference. In the subset of women with ER[−] breast cancer, we observed a direct association between carbohydrate intake and GL and breast cancer risk. Fiber intake was not associated with breast cancer risk in this population.

Results from 2 case-control studies and an analysis of adolescent diet and subsequent risk of breast cancer suggest an association between carbohydrate intake, GI, and GL and breast cancer risk (10, 28, 29). However, several large prospective studies found no overall association between carbohydrate intake and breast cancer, although their results suggested that this relation may differ by lifestyle and menopausal status (4, 6, 7, 9). One prospective cohort study observed a significant interaction between carbohydrate intake and BMI; the RR for premenopausal overweight women when comparing extreme quintiles of carbohydrate intake was 1.47 [95% CI: 0.84, 2.59; *P* for trend = 0.14; *P* for interaction = 0.02 (9)]. These results suggest that dietary carbohydrate intake may be of relevance to breast cancer risk

among women with underlying insulin resistance. In our study, we observed that women with a BMI ≥ 25 had an increased risk of breast cancer with increasing amounts of rapidly absorbed carbohydrates. Furthermore, the association between GI and GL and breast cancer was strongest among women with the highest category of waist circumference, a better predictor of insulin resistance than BMI (30). However, our results contrast with a nested case-control study that found that elevated concentrations of glycated hemoglobin, a marker for average prior glucose concentration over 6–8 wk, were not associated with increased risk of breast cancer (31).

Data are scant on the relation between carbohydrate intake, GI, and GL and hormone-receptor-defined breast cancer. A Danish prospective study observed a RR of 1.46 (95% CI: 1.01, 2.11) for an increase of 10 units/d of GI only in ER[−] cases (3). Another study found no significant association by subtype of breast cancer in an analysis of 245 cases, 52 of which were ER[−]/PR[−] (8). On the basis of 279 ER[−] breast cancers and after adjustment for several potential confounders, we observed a significant association between carbohydrate intake and GL and ER[−] breast cancer risk.

Several large prospective studies have evaluated the relation between fiber and breast cancer and, with the exception of one study performed in Sweden (32), results have been consistently null (4, 8, 9, 13, 33). Our results are in accordance with most of

TABLE 3

Relative risk (RR) (and 95% CI) of postmenopausal breast cancer among 54 914 women according to quartile (Q) of energy-adjusted carbohydrate intake, glycemic index (GI), and glycemic load (GL) stratified by tertile (T) of median waist circumference¹

	Waist circumference						<i>P</i> for interaction ²
	T1 (68 cm)		T2 (75 cm)		T3 (84 cm)		
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	
	<i>n</i>		<i>n</i>		<i>n</i>		
Carbohydrate intake							0.03
Q1	109	1.00	131	1.00	147	1.00	
Q2	117	0.89 (0.68, 1.16)	153	1.08 (0.85, 1.37)	145	1.15 (0.91, 1.46)	
Q3	114	0.74 (0.56, 0.99)	167	1.13 (0.88, 1.45)	128	1.11 (0.86, 1.43)	
Q4	154	0.80 (0.60, 1.07)	139	0.90 (0.68, 1.18)	126	1.28 (0.98, 1.67)	
<i>P</i> for trend ³		0.10		0.47		0.10	
Overall GI							0.08
Q1	108	1.00	140	1.00	120	1.00	
Q2	124	1.12 (0.86, 1.45)	156	1.05 (0.83, 1.32)	127	1.09 (0.85, 1.41)	
Q3	132	1.12 (0.86, 1.47)	145	0.94 (0.74, 1.20)	148	1.28 (0.99, 1.64)	
Q4	130	1.03 (0.78, 1.36)	149	0.97 (0.76, 1.25)	151	1.35 (1.04, 1.75)	
<i>P</i> for trend ³		0.87		0.66		0.01	
Dietary GL							0.008
Q1	95	1.00	139	1.00	135	1.00	
Q2	142	1.28 (0.98, 1.67)	144	0.97 (0.76, 1.23)	120	0.96 (0.75, 1.24)	
Q3	114	0.90 (0.68, 1.20)	161	1.00 (0.78, 1.27)	153	1.37 (1.07, 1.74)	
Q4	143	0.99 (0.74, 1.33)	146	0.89 (0.69, 1.16)	138	1.37 (1.05, 1.77)	
<i>P</i> for trend ³		0.39		0.42		0.003	

¹ Adjusted for age, 2-y follow-up period, region of residence, years of education (<12, 12–15, or ≥15), family breast cancer (0, 1, or >1 first-degree relative), history of benign breast disease (yes or no), age at menarche (<12, 12, 13, or ≥14 y), parity (0, ≤2 and age at first birth ≤30 y, ≥3 and age at first birth ≤30 y or age at first birth >30 y), breastfeeding (none, <7, 7–12, or ≥12 mo), years since last use of oral contraceptives (never, unknown date of last use, or <25, 25–29, or ≥30 y), age at menopause (<45, 45–49, 50–54, or ≥55 y), years of hormone replacement therapy use (never, unknown duration, or <3, 3–5.9, or ≥6 y), regular mammographic evaluation (yes or no) that was defined as a report in 1990, 1992, and 1993 of a recent mammogram, height (in cm), vitamin supplement use (yes or no), total energy intake (in quartiles), folate intake (in quartiles), fiber intake (in quartiles), alcohol intake (0, ≤15, or ≥15 g/d), and physical activity (in quartiles).

² Log-likelihood ratio test.

³ Test for linear trend used median quartile values as a continuous variable.

the literature and may be relevant because the distribution of fiber intake in our population is much higher than that of other evaluated populations. The mean intake of total fiber in a large prospective study in the United States was 18.1 ± 5.5 g/d (4); our population's mean intake was 24.2 ± 5.9 g/d.

Plasma C-peptide, a marker of insulin secretion, is directly associated with dietary GL, and insulin stimulates potent proliferative effects in normal and cancer cells (34–36). High insulin concentrations increase circulating IGF-I by down-regulating its carrier, the IGFBP-3 (37). In experimental settings, IGF-I showed strong proliferative and antiapoptotic effects on human mammary cells; however, results from observational studies have not yielded equally strong evidence to support this association (38–41). IGF-I concentrations are markedly elevated in type 2 diabetes, and persons with diabetes were shown to be at a higher risk of breast cancer (42, 43). However, other IGF-I-independent metabolic pathways may be involved. Among persons with diabetes, high-GL diets lowered adiponectin, an adipocyte-produced insulin sensitizer (44). This protein is inversely associated with obesity, and decreased concentrations of adiponectin were related to an increase in postmenopausal breast cancer risk independently of IGF-I and IGFBP-3 concentrations (45, 46).

The prospective design of this study and the small number of women lost to follow-up limits the possibility of recall bias and

selection bias as explanations for our results. Although residual confounding may be present, the minimal effect observed in our estimates after adjustment for several recognized risk factors for breast cancer reduces this possibility. In this study, both dietary and anthropometric assessment tools were validated in similar populations and were shown to be reliable. Nevertheless, this study is limited by a single dietary assessment. It is still possible that some participants may have changed their diets through follow-up and that some misclassification of exposure may be present. This nondifferential misclassification would have weakened the observed associations. Another limitation of this study was the lack of information about waist circumference in a subset of women. This is unlikely to have drastically affected our results, because women for whom waist circumference was not available had similar baseline weights and were thus equally likely to be overweight compared with women for whom information was complete. An important concern may be that women with available hormone receptor status may differ from those for whom this was not the case. We observed no differences in demographic characteristics and nutritional intake between the 24.8% of cases without ER status compared with cases in which information was available.

In conclusion, in this population of postmenopausal women we observed an association between rapidly absorbed carbohydrates and breast cancer risk among overweight women and

TABLE 4

Relative risk (RR) (and 95% CI) of postmenopausal breast cancer according to quartile (Q) of energy-adjusted carbohydrate intake, glycemic index (GI) and glycemic load (GL) by hormone receptor status ($n = 62\,739$)¹

	ER ⁺		ER ⁻		PR ⁺		PR ⁻	
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
	<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>	
Carbohydrate intake								
Q1	266	1.00	54	1.00	203	1.00	108	1.00
Q2	283	1.05 (0.88, 1.25)	66	1.34 (0.93, 1.94)	215	1.05 (0.86, 1.28)	123	1.19 (0.91, 1.55)
Q3	276	1.00 (0.83, 1.20)	79	1.69 (1.17, 2.45)	195	0.93 (0.75, 1.15)	151	1.48 (1.13, 1.93)
Q4	258	0.89 (0.73, 1.08)	80	1.78 (1.20, 2.64)	201	0.91 (0.73, 1.14)	129	1.26 (0.94, 1.68)
<i>P</i> for trend ²		0.21		0.003		0.29		0.07
Overall GI								
Q1	251	1.00	73	1.00	188	1.00	124	1.00
Q2	268	1.04 (0.87, 1.24)	61	0.86 (0.61, 1.21)	189	1.05 (0.86, 1.28)	130	1.04 (0.81, 1.33)
Q3	277	1.04 (0.87, 1.25)	82	1.16 (0.84, 1.62)	219	1.00 (0.81, 1.23)	132	1.03 (0.80, 1.34)
Q4	287	1.05 (0.88, 1.27)	63	0.91 (0.63, 1.32)	218	0.94 (0.75, 1.17)	125	0.97 (0.74, 1.27)
<i>P</i> for trend ²		0.59		0.98		0.29		0.83
Dietary GL								
Q1	260	1.00	60	1.00	195	1.00	115	1.00
Q2	273	1.01 (0.85, 1.20)	71	1.25 (0.88, 1.77)	211	1.05 (0.86, 1.28)	122	1.06 (0.82, 1.37)
Q3	286	1.0 (0.86, 1.22)	67	1.23 (0.85, 1.78)	207	1.00 (0.81, 1.23)	140	1.22 (0.94, 1.58)
Q4	264	0.91 (0.75, 1.11)	81	1.55 (1.07, 2.25)	201	0.94 (0.75, 1.17)	134	1.16 (0.88, 1.54)
<i>P</i> for trend ²		0.37		0.03		0.47		0.21

¹ ER, estrogen receptor; PR, progesterone receptor. Adjusted for age, 2-y follow-up period, region of residence, years of education (<12, 12–15, or ≥15), family breast cancer (0, 1, or >1 first-degree relative), history of benign breast disease (yes or no), age at menarche (<12, 12, 13, or ≥14 y), parity (0, ≤2 and age at first birth ≤30 y, ≥3 and age at first birth ≤30 y or age at first birth >30 y), breastfeeding (none, <7, 7–12, or ≥12 mo), years since last use of oral contraceptives (never, unknown date of last use, or <25, 25–29, or ≥30 y), age at menopause (<45, 45–49, 50–54, or ≥55 y), years of hormone replacement therapy use (never, unknown duration, or <3, 3–5.9, or ≥6 y), regular mammographic evaluation (yes or no) that was defined as a report in 1990, 1992, and 1993 of a recent mammogram, height (in cm), BMI (in quartiles), vitamin supplement use (yes or no), total energy intake (in quartiles), folate intake (in quartiles), fiber intake (in quartiles), alcohol intake (0, <15, or ≥15 g/d), and physical activity (in quartiles).

² Test for linear trend used median quartile values as a continuous variable.

women with large waist circumference. We also observed an increase in the risk of ER⁻ breast cancer with increasing carbohydrate and dietary GL intakes. These associations should be further explored in studies with a more precise characterization of metabolic and hormonal receptor status.

We thank the French League against Cancer, the European Community, the 3M Company, the Mutuelle Générale de l'Éducation Nationale, the Institut Gustave-Roussy, and the Institut National de la Santé et de la Recherche Médicale for their financial support of the E3N study. We thank Maryvonne Niravong for her advice on the creation of the glycemic index table. The E3N team is indebted to all participants for providing data used in this study, to their physicians for providing pathology reports, and to J Bram for linguistic revision of the manuscript.

The author's responsibilities were as follows—FC-C: obtained funding, collected the data, and revised the manuscript; ML: planned the analysis, analyzed the data, and drafted the manuscript; IR: planned the analysis, oversaw preliminary results, and critically reviewed and revised the manuscript; M-CB-R: critically reviewed the manuscript; AF: provided statistical support. All authors were responsible for study concept and design. None of the authors had a personal or financial conflict of interest.

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