Carbohydrates and the Risk of Breast Cancer among Mexican Women

Isabelle Romieu,[1] Eduardo Lazcano-Ponce,[1] Luisa Maria Sanchez-Zamorano,[1] Walter Willett,[2] and Mauricio Hernandez-Avila[1]

[1]Instituto Nacional de Salud Publica, Cuernavaca, Morelos, Mexico and [2]Departments of Nutrition and Epidemiology, Harvard School of Public Health and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

Abstract

Objective: High carbohydrate intake has been hypothesized to be a risk factor for breast cancer, possibly mediated by elevated levels of free insulin, estrogens, and insulin-like growth factor-1. Therefore, we conducted a population-based case-control study among a Mexican population characterized by relatively low fat and high carbohydrate intakes. Methods: Women ages 20 to 75 years, identified through six hospitals in Mexico City (n = 475), were interviewed to obtain data relating to diet (using a food frequency questionnaire) and breast cancer risk factors. Controls (n = 1,391) were selected from the Mexico City population using a national sampling frame. Results: Carbohydrate intake was positively associated with breast cancer risk. Compared with women in the lowest quartile of total carbohydrate intake, the relative risk of breast cancer for women in the highest quartile was 2.22 [95% confidence interval (95% CI) 1.63-3.04], adjusting for total energy and potential confounding variables (P for trend < 0.0001). This association was present in premenopausal and postmenopausal women (for highest versus lowest quartile, odds ratio 2.31, 95% CI 1.36-3.91 in premenopausal women and odds ratio 2.22, 95% CI 1.49-3.30 in postmenopausal women). Among carbohydrate components, the strongest associations were observed for sucrose and fructose. No association was observed with total fat intake. Discussion: In this population, a high percentage of calories from carbohydrate, but not from fat, was associated with increased breast cancer risk. This relation deserves to be investigated further, particularly in populations highly susceptible to insulin resistance. (Cancer Epidemiol Biomarkers Prev 2004;13(8):1283–9)

Introduction

Diet has been prominent among the hypothesized determinants of breast cancer, but few, if any, constituents of the diet are definitely associated with the disease (1). If dietary factors are involved in the etiology of breast cancer, this is important to establish because these are potentially modifiable, whereas most known risk factors for breast cancer are not.

Breast cancer is the most frequent malignancy among women in Western countries, and the incidence is still increasing (2). Rates in most parts of Asia, South America, and Africa have been only one fifth as high as in the United States; however, in almost all these regions, rates of breast cancer are also increasing. In Mexico, the incidence of breast cancer is estimated to be 38.4 cases per 100,000 women (3), and age-standardized mortality has increased during the last 20 years from 6.4 deaths per 100,000 women in 1979 to 12.2 deaths per 100,000 women in 2000 (3, 4). This increase in mortality, while treatment has improved, reflects an increase in incidence linked in part to changes in women's lifestyles, such as later age at first pregnancy, decreasing duration of lactation, and more sedentary lifestyle (4). Whereas carbohydrate intake has remained high (64% of energy), the prevalence of obesity in Mexican women has greatly increased, raising the risk for diabetes and other chronic diseases (5). Recently, insulin and insulin-like growth factor (IGF) have been implicated in the regulation of sex hormone binding globulin, which modifies the availability of estrogens (6). Further, the elevation in plasma insulin level that follows carbohydrate consumption is greatly exaggerated in the presence of insulin resistance (7). Given the high prevalence of type 2 diabetes mellitus reflecting underlying insulin resistance in the Mexican population, high carbohydrate intake might adversely affect the risk of breast cancer among Mexican women.

To examine further the relationships between dietary factors, particularly carbohydrate intake and breast cancer, we conducted a case-control study among women living in Mexico City, an area with dietary patterns distinct from those of affluent Western countries because of higher intake of carbohydrates and lower intake of fat and animal protein. In this article, we report the associations of dietary carbohydrate and fats with the risk of breast cancer.

Received 6/20/03; revised 2/23/04; accepted 3/23/04.

Grant support: American Institute for Cancer Research, Ministry of Health of Mexico, and National Center for Environmental Health, Centers for Disease Control and Prevention (Atlanta, GA).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Isabelle Romieu, Instituto Nacional de Salud Publica, Avenida Universidad 655, Colonia Santa Maria Ahuacatitlan, Cuernavaca, Morelos 62508, Mexico. Phone: 52-777-101-2935; Fax: 52-777-311-1148. E-mail: iromieu@correo.insp.mx

Materials and Methods

Study Population. Participants in this study were enrolled in a population-based case-control study to assess the relationships of dietary and reproductive factors with breast cancer risk among residents of Mexico City (8). Cases who had been resident for at least 1 year in metropolitan Mexico City were recruited using a network of six hospitals that are part of the two major health care providers in Mexico City, the Social Security System and the Ministry of Health. These hospitals provided medical care to 80% of breast cancer cases reported to the Mexico City Tumor Registry. From 1990 to 1995, incident histologically confirmed breast cancer cases without previous treatment were identified among women ages 20 to 75 years attending gynecologic clinics for the biopsy of a breast lump. Only women whose biopsy confirmed the diagnosis of breast cancer were included in the study; a total of 537 cases were identified. Of those, 88% (n = 475) agreed to participate and provided dietary information. Controls were an age-stratified random sample of metropolitan Mexico City residents. Households were first randomly selected using the National Household Sampling Frame. Study personnel ascertained whether the selected units contained a woman in the intended age group and then visited these households and determined willingness to be interviewed and to provide a blood sample. If willing, an interview was arranged at the control's home. If not, the procedure was repeated. Only one eligible control was included per household. From 1,534 eligible controls, 90% (n = 1,391) agreed to participate in the study.

Interviewers administered a questionnaire about sociodemographic variables and potential risk factors for breast cancer including reproductive and lactation history and diet. Cases were interviewed at the gynecologic clinics of the study hospitals before breast cancer was confirmed; controls were interviewed in their homes. Self-reported height and weight have proven unreliable in this population, and we had to send women to a health center to obtain actual measurements. These were available only for 226 cases (48% of all cases) and 669 controls (50% of all controls) who attended the health center.

Semiquantitative Food Frequency Questionnaires. We used a dietary questionnaire developed by Willett (9) and adapted to the Mexican population (10). This questionnaire included 116 items and 10 multiple choice frequency categories of consumption: ≥6 per day, 4 to 5 per day, 2 to 3 per day, 1 per day, 5 to 6 per week, 2 to 4 per week, 1 per week, 2 to 3 per month, ≤1 per month, and never. For each food in the questionnaire, a commonly used unit or portion size (specified serving size: slice, glass, or natural unit such as one apple) was specified, and women were asked how often on average over the previous year they had consumed that amount of each food. Nutrient intakes were computed by multiplying the frequency response by the nutrient content of specified portion sizes using a program developed at the National Institute of Public Health in Mexico. The database for calculating the nutrient intakes used information from the U.S. Department of Agriculture food composition tables (11) complemented when necessary by a nutrient database developed by the Mexican National Institute of Nutrition (12). This questionnaire has been validated against sixteen 24-hour recalls among a sample of 134 women in Mexico City comparable with our present population and was shown to perform well. Correlations between the food frequency questionnaire and dietary records for total energy carbohydrate, protein, and total fat intakes were 0.52, 0.57, 0.32, and 0.63, respectively (10).

Statistical Analysis. Our main goals were to assess the relationships between carbohydrate and fat intake with the risk of breast cancer. We calculated nutrient densities for carbohydrate, protein, and fat intakes (as percentage of total energy intake; ref. 13). These variables were categorized as quartiles based on the distribution among the control group, and relative risks of breast cancer were determined by comparison with the lowest quartile. An index of socioeconomic status (SES) was developed as suggested by Bronfman et al. (14) by combining the following variables: number of persons living in the house, number of rooms in the house (excluding the kitchen and bathroom), availability of drinking water, sanitary conditions, and education of the head of the family. To control for the influence of potential confounding factors, we included the following variables in our multivariate logistic regression in models (15): age (in 5-year groups), SES (low, medium, or high), age at first birth (<20, 20 to 29, or >29 years), parity (0, 1 to 2, 3 to 4, or ≥5), and family history of breast cancer (yes or no) defined as the diagnosis of breast cancer in the mother, sister, or grandmother. All models were also adjusted for total energy intake (13). We did separate analyses for premenopausal and postmenopausal breast cancer, because postmenopausal breast cancer is thought to be more susceptible to environmental exposures (2). Information on type of menopause (natural or surgical) was obtained by questionnaire. Natural menopause was defined as 12 consecutive months of amenorrhea without an obvious cause. We tested for linear trends in relative risks with increasing exposure using the likelihood ratio test (15, 16). To evaluate the relationships between total and specific types carbohydrates (as a percentage of energy) and breast cancer risk, other macronutrients (fat and protein) were not included in the models; therefore, differences in the percentage of energy from carbohydrate represent substitution for a similar percentage of energy from both fat and protein. To evaluate the relationships between total and specific types of fat (as a percentage of energy) and breast cancer risk, we included dietary fat and protein (as a percentage of energy) in the model; the comparison was therefore the same percentage of calories from carbohydrate (13).

Because body mass index [BMI = weight (kg)/height $(m)^2$] is a predictor of breast cancer (2), analyses were repeated in the subsample of women who had BMI data, controlling for BMI and the variables previously mentioned and compared with the results obtained in the full study. Nutritional data were log transformed to perform t tests because of their skewed distributions. We did all statistical analyses with Stata statistical software, release 5.0 (Stata Corporation, College Station, TX).

Results

Cases (n = 475) were histologically confirmed as having breast cancer. Among them, 189 occurred in premenopausal women and 286 occurred in postmenopausal women. Controls (n = 1,391) frequency matched on 5-year age strata participated in the study.

The associations of known breast cancer risk factors, including SES, family history of breast cancer, age at first birth, and parity, with breast cancer risk in this study are presented in Table 1 for all women and for premenopausal and postmenopausal cases. These are consistent with known relationships.

Mean nutrient intakes as percentage of total energy intake are presented in Table 2 for cases and controls. In our population, 57% of total energy intake were provided by carbohydrate intake, 27.6% by fat, and 15.4% by protein. Cases reported a significantly higher intake of total calories, proteins, carbohydrates, sucrose, and fructose. In contrast, significantly lower intake was observed for total fat and polyunsaturated fat, starch, and insoluble dietary fiber.

Table 3 presents the associations between quartiles of carbohydrate intakes and the risk of breast cancer among all women and for premenopausal and postmenopausal women. Total carbohydrate was positively and significantly related to the risk of breast cancer. After adjusting for age, total energy intake, SES, family history of breast cancer, and parity, the risk of breast cancer was 2.2 times higher in women in the highest quartile of total carbohydrate (as a percentage of energy; P for trend < 0.0001). We also observed significant increases in risks of breast cancer for sucrose [odds ratio (OR) 2.00, 95% confidence interval (CI) 1.47-2.71] and fructose (OR 1.36, 95% CI 1.00-1.86).

Among premenopausal women, risks of breast cancer increased with consumption of total carbohydrate (OR 2.31 95% CI 1.36-3.91) and sucrose (OR 2.51, 95% CI 1.47-4.26), with significant trends for both. Similarly, among postmenopausal women, the risk of breast cancer was 2.2 times higher among women in the highest quartile of total carbohydrate intake when compared with women in the lowest quartile (OR 2.22, 95% CI 1.49-3.30), with a highly significant trend. Sucrose intake was significantly related to the risk of breast cancer (OR 1.84, 95% CI 1.26-2.71). Slightly increased risks were also observed for glucose and fructose intake, but these trends did not reach significance (Table 3).

We repeated these analyses in the subsample of our study population for which we had information on height and weight. The associations between carbohydrate intake and breast cancer risk were similar in this subgroup compared with the total population and did not change appreciably when BMI was added to the model (for total carbohydrate, OR (95% CI) values for quartile 4 versus quartile 1 are 2.21 (1.62-3.02) in the full data set and 2.86 (1.77-4.63) in the subset with BMI) after adjusting for age, total energy intake, SES, family history of breast cancer, parity, menopausal status, BMI, and an interaction term for BMI and menopausal status. Stratification by BMI (median) led to a similar association between carbohydrate and breast cancer risk in both

Table 1. Risk for breast cancer and socioeconomic and reproductive variables in Mexican women

Risk factor	All women (n = 1,866)			Premenopausal women (n = 875)			Postmenopausal women (n = 991)		
	Control (n = 1,391)	Cases (n = 475)	OR* (95% CI)	Control (n = 699)	Cases (n = 226)	OR* (95% CI)	Control (n = 692)	Cases (n = 249)	OR* (95% CI)
SES									
Low	423	130	1.00	191	69	1.00	232	61	1.00
Middle	695	201	0.89 (0.69-1.15)	356	67	0.49 (0.33-0.74)	339	134	1.39 (0.98-1.98)
High	273	144	1.58 (1.17-2.12)	139	53	1.04 (0.66-1.66)	134	91	2.22 (1.48-3.31)
P for trend			0.005			0.503			0.000
Familial breast cancer									
No	1,365	456	1.00	677	178	1.00	688	278	1.00
Yes	26	19	1.95 (1.05-3.63)	9	11	4.18 (1.60-10.90)	17	8	1.07 (0.43-2.62)
Menopausal status									
Premenopausal	686	189	1.00						
Postmenopausal	705	286	0.71 (0.49-1.03)						
Age (y) at first birth†									
<20	541	139	1.00	268	62	1.00	273	77	1.00
20-29	613	219	1.35 (1.05-1.73)	336	89	1.10 (0.75-1.60)	277	130	1.58 (1.13-2.21)
>29	67	82	1.61 (1.01-2.56)	29	9	0.95 (0.41-2.20)	38	26	2.01 (1.13-3.58)
Nulliparous	161	81	1.64 (1.17-2.30)	48	29	2.26 (1.28-3.96)	113	52	1.48 (0.96-2.26)
Missing	9	1	—	5	0	—	4	1	—
P for trend			0.11			0.48			0.02
Parity									
0	161	81	1.00	48	29	1.00	113	52	1.00
1-2	265	103	0.93 (0.64-1.36)	189	50	0.58 (0.32-1.06)	76	53	1.39 (0.85-2.29)
3-4	399	132	0.83 (0.59-1.19)	263	60	0.44 (0.25-0.77)	136	72	1.18 (0.75-1.86)
≥5	566	159	0.61 (0.44-0.85)	186	50	0.40 (0.22-0.73)	380	109	0.69 (0.46-1.03)
P for trend			<0.001			<0.001			<0.001

*Adjusted by other variables and age, except age at first birth (colinearity).
†Adjusted by other variables and age, except parity (colinearity).

Table 2. General characteristics of the study population and among women with and without information on BMI

Factors	All women		With BMI information		Without BMI information	
	Controls (n = 1,391), Median	Cases (n = 475), Median	Controls (n = 699), Median	Cases (n = 226), Median	Controls (n = 692), Median	Cases (n = 249), Median
Nutritional (per day)						
Total energy intake (kcal)	1,564	1,696*	1,680	1,826	1,498	1,598
Total protein (%)†	14.5	16.3*	16.9	19.1*	17.9	16.6*
Total fat (%)†	27.9	26.5*	28.4	26.6*	27.6	26.5*
Saturated fat (%)†	11.3	10.6	10.7	10.7	11.2	10.4
Monounsaturated fat (%)†	9.3	9.0	9.4	9.3	9.3	8.9
Polyunsaturated fat (%)†	3.1	2.3*	3.0	2.9*	3.2	2.3*
Carbohydrates (%)†	56.6	58.6*	57.3	58.8*	56.2	58.6*
Sucrose (%)†	6.7	7.8*	7.1	7.9*	6.5	7.6*
Fructose (%)†	7.0	7.6*	7.0	8.1	7.0	7.1*
Lactose (%)†	6.3	6.0	5.8	6.1	6.6	6.0
Starch (%)†	14.4	13.6*	13.1	12.6	15.2	14.0
Glucose (%)†	6.3	6.8	6.1	7.1	6.4	6.2*
Insoluble dietary fiber (g)	22.2	15.8*	17.9	15.8*	22.6	15.8*
Reproductive						
Parity (live birth)	4	3*	4	3*	4	3*
Breast-feeding (mo)	24	16*	24	16*	27	15*
Age (y)	49	53*	45	53	53	53
BMI (kg/m^2)			26.7	26.5		

*$P < 0.05$ (Mann-Whitney test).
†Median intake, % of energy.

groups. Similarly, when data were stratified by menopausal status, including BMI in the models, this did not substantially modify the estimates. Thus, in this population, BMI did not seem to confound or modify the association between carbohydrate intake and the risk of breast cancer. The prevalence of diabetes in this population (11%) did not allow stratification by these variables.

Fiber intake may modulate the absorption of carbohydrates and can influence the glycemic response (17); therefore, we examined the relation of carbohydrate intake and breast cancer risk stratified by tertiles of insoluble fiber intake. The strength of the association between sucrose intake and risk for breast cancer was lower among women in the highest tertile of insoluble fiber intake when compared with women in the lowest tertile of insoluble fiber intake. The relative risk (95% CI) of breast cancer in the highest quartile of sucrose intake was 2.37 (1.58-3.55) among women who consumed low levels of insoluble fibers (≤22.2 g/d) and was 1.07 (0.65-1.77) among women who consumed high levels of insoluble fibers (>22 g/d). The interaction term between high sucrose intake and fiber intake was marginally significant (P = 0.09). Similar results were observed for fructose and glucose intakes.

In a multivariate nutrient density model including total fat, total protein, and total energy intakes as well as other nondietary covariates, total fat intake (substituted for a similar percentage of energy from carbohydrate) was not significantly associated with the risk of breast cancer. When we replaced total fat with specific types of fat, we observed that saturated and monounsaturated fat intakes were not associated with the risk for breast cancer (Table 4). In contrast, polyunsaturated fat intake was inversely related to the overall risk of breast cancer, particularly among postmenopausal women.

Discussion

In this population-based case-control study, we observed a positive association between carbohydrate intake and the risk of breast cancer. The strongest association was observed for sucrose intake, and this was stronger among postmenopausal women. Polyunsaturated fat was inversely associated with risk of breast cancer, particularly among postmenopausal women.

Few epidemiologic studies have investigated intake of carbohydrate in relation to the risk of breast cancer, and results are inconsistent. In a case-control study conducted in southeast England, no association was reported between sugar intake and breast cancer risk (18), but the consumption of carbohydrates was lower than that observed in our population. In a large Italian case-control study, greater carbohydrate consumption was significantly associated with higher risk of breast cancer; starch was the main contributor to the increase, and no increased risk was observed for sugar (19). Witte et al. (20) reported that carbohydrate intake (and sweetened beverages) was associated with the risk of premenopausal bilateral breast cancer. In accordance with our results, a recent case-control study suggests an association between sweet intake, expressed as a percentage of calories, and the risk of breast cancer among premenopausal women. No association was observed with fat intake (21).

One hypothesis suggesting that carbohydrate intake may increase the risk of breast cancer is related to the insulin pathway. The ingestion of carbohydrates as starch or sucrose leads to a rapid rise in blood glucose and provokes insulin secretion. Elevated insulin levels reduce plasma and tissue levels of IGF binding proteins 1 and 2, which may increase the availability of IGF-I (6). IGF-I can increase cell proliferation and thus influence carcinogenesis (22). Recent studies have shown a relation

between IGF-I and the risk of premenopausal breast cancer (23, 24). In addition, 90% of breast tumors are insulin receptor positive and overexpress IGF-I; apparently, insulin is more directly involved in the development or the progression of breast tumor (25, 26). Insulin and IGF-I also inhibit the hepatic synthesis of the sex hormone binding globulin, leading to higher circulating levels of free estrogens and androgens (27, 28). Insulin and IGF-I both stimulate the ovarian synthesis of sex steroids. Several studies have reported a positive association between measures of glucose intolerance and breast cancer risk (29-31), but this has not been seen consistently (32). Similarly, recent works have reported an association between glycemic index and glycemic load and breast cancer in populations with high carbohydrate intake (33, 34), but this was not observed in one U.S. population (35). Unfortunately, we did not have the necessary data basis to calculate the glycemic index and could not explore the association of glycemic index and breast cancer in our population.

BMI has been associated with the risk of breast cancer (36) and is also related to caloric intake; however, in our study, the relation of carbohydrate intake and the risk of breast cancer remained after accounting for BMI in addition to other potential confounding factors. Therefore, it is unlikely that the effect observed in our total population is biased by not adjusting for BMI in all subjects. In addition, when we stratified data by the median BMI, results were similar in both groups, suggesting that BMI did not modify the association of carbohydrate intake and breast cancer. However, our capacity to further evaluate the potential impact of a high BMI on this association is limited by missing data. The lack of a significant overall association between total fat intake and breast cancer risk in this study is consistent with the analysis of prospective studies of diet and cancer (37). In the 14-year follow-up of the Nurses' Health Study (38) that used repeated measures of diet, a weak but statistically significant inverse association with polyunsaturated fat was observed. Polyunsaturated fat intake in the group of Mexican women (mean 3.1% of energy) was only half that of the U.S. population at present. Low intake of polyunsaturated fatty acids per se or of antioxidants such as vitamin E that are abundant

Table 3. Carbohydrates (% calories) intake and risk of breast cancer in Mexican women

Range of intake (% Calories)	All women (n = 1,866)				Premenopausal women (n = 875)			Postmenopausal women (n = 991)		
	Control	Cases	OR Age adjusted (95% CI)	OR* (95% CI)	Controls	Cases	OR* (95% CI)	Controls	Cases	OR* (95% CI)
Carbohydrates										
≤52	347	89	1.00	1.00	147	26	1.00	200	63	1.00
53-57	348	100	1.62 (0.83-1.60)	1.13 (0.81-1.57)	155	46	1.75 (1.01-3.05)	193	54	0.83 (0.54-1.27)
58-62	348	113	1.40 (1.02-1.94)	1.39 (1.00-1.93)	196	49	1.60 (0.93-2.77)	152	64	1.36 (0.89-2.07)
>62	348	173	2.15 (1.59-2.91)	2.22 (1.63-3.04)	188	68	2.31 (1.36-3.91)	160	105	2.22 (1.49-3.30)
P for trend			<0.001	0.000			0.004			0.000
Sucrose										
≤5.2	347	100	1.00	1.00	136	26	1.00	211	74	1.00
5.3-6.7	349	78	0.84 (0.60-1.17)	0.81 (0.57-1.14)	170	31	0.96 (0.53-1.75)	179	47	0.67 (0.43-1.04)
6.8-8.5	347	121	1.40 (1.02-1.91)	1.34 (0.97-1.85)	185	58	2.05 (1.19-3.53)	162	63	1.03 (0.68-1.56)
>8.5	348	176	2.04 (1.52-2.74)	2.00 (1.47-2.71)	195	74	2.51 (1.47-4.26)	153	102	1.84 (1.26-2.71)
P for trend			<0.001	0.000			0.000			0.000
Fructose										
≤4.3	348	111	1.00	1.00	136	32	1.00	212	79	1.00
4.4-7.0	348	105	1.02 (0.75-1.39)	0.95 (0.69-1.30)	164	49	1.32 (0.78-2.22)	184	56	0.71 (0.47-1.08)
7.1-10.1	348	108	1.07 (0.79-1.46)	0.90 (0.65-1.24)	189	48	1.12 (0.66-1.89)	159	60	0.77 (0.51-1.16)
>10.1	347	151	1.56 (1.16-2.09)	1.36 (1.00-1.86)	197	60	1.40 (0.83-2.34)	150	91	1.32 (0.88-1.97)
P for trend			0.003	0.058			0.325			0.184
Lactose										
≤3.2	348	107	1.00	1.00	172	42	1.00	176	65	1.00
3.3-6.3	348	136	1.34 (1.00-1.81)	1.20 (0.88-1.63)	207	72	1.45 (0.91-2.30)	141	64	0.95 (0.61-1.47)
6.4-8.4	348	87	0.76 (0.55-1.06)	0.66 (0.48-0.93)	162	38	0.84 (0.50-1.41)	186	49	0.52 (0.33-0.82)
>8.4	347	145	1.25 (0.93-1.68)	1.06 (0.78-1.45)	145	37	1.08 (0.64-1.82)	202	108	1.00 (0.67-1.48)
P for trend			0.673	0.515			0.575			0.649
Starch										
≤11.2	348	159	1.00	1.00	182	49	1.00	166	110	1.00
11.3-14.3	348	114	0.72 (0.54-0.96)	0.79 (0.59-1.07)	180	47	1.08 (0.67-1.75)	168	67	0.70 (0.47-1.03)
14.4-17.5	347	79	0.48 (0.35-0.65)	0.54 (0.39-0.75)	166	33	0.65 (0.38-1.10)	181	46	0.48 (0.31-0.74)
>17.5	348	123	0.75 (0.57-1.00)	1.04 (0.76-1.44)	158	60	1.51 (0.90-2.51)	190	63	0.85 (0.56-1.30)
P for trend			0.008	0.531			0.359			0.136
Glucose										
≤3.4	348	109	1.00	1.00	137	33	1.00	211	76	1.00
3.5-6.3	348	111	1.09 (0.80-1.48)	1.02 (0.74-1.39)	159	50	1.34 (0.80-2.25)	189	61	0.81 (0.54-1.21)
6.4-9.2	348	113	1.15 (0.85-1.57)	0.97 (0.70-1.34)	197	49	1.12 (0.66-1.89)	151	64	0.89 (0.59-1.35)
>9.2	347	142	1.47 (1.09-1.98)	1.28 (0.94-1.75)	193	57	1.30 (0.77-2.19)	154	85	1.20 (0.80-1.80)
P for trend			0.010	0.140			0.505			0.328

*Adjusted for age, total energy intake, SES, family breast cancer, menopausal status, and parity.

Table 4. Fat intakes and total specific types of fat (% calories) and risk for breast cancer in Mexican women

Range of intake (% Calories)	All women (n = 1,866)				Premenopausal women (n = 875)			Postmenopausal women (n = 991)		
	Control	Cases	OR Age Adjusted (95% CI)	OR* (95% CI)	Controls	Cases	OR* (95% CI)	Controls	Cases	OR* (95% CI)
Total fat										
≤24.1	348	171	1.00	1.00	181	64	1.00	167	107	1.00
2.2-27.9	347	102	0.57 (0.43-0.76)	0.70 (0.51-0.95)	168	42	0.91 (0.56-1.48)	179	60	0.58 (0.38-0.89)
28.0-32.1	348	98	0.57 (0.43-0.77)	0.73 (0.53-1.02)	172	43	1.04 (0.63-1.70)	176	55	0.55 (0.35-0.87)
>32.1	348	104	0.59 (0.44-0.78)	0.83 (0.59-1.16)	165	40	1.03 (0.61-1.74)	183	64	0.71 (0.45-1.12)
P for trend			0.000	0.361			0.784			0.171
Saturated fat†										
≤8.5	347	144	1.00	1.00	181	62	1.00	166	82	1.00
8.6-11.2	349	109	0.80 (0.58-1.11)	0.96 (0.68-1.36)	196	51	1.05 (0.62-1.80)	153	53	0.82 (0.51-1.31)
11.3-13.2	348	84	0.64 (0.43-0.96)	0.87 (0.56-1.34)	157	38	1.23 (0.63-2.41)	191	46	0.62 (0.34-1.11)
>13.2	347	138	0.89 (0.57-1.39)	1.37 (0.83-2.25)	152	38	1.34 (0.59-3.01)	195	100	1.15 (0.60-2.20)
P for trend			0.272	0.372			0.511			0.852
Monounsaturated fat†										
≤8.1	348	164	1.00	1.00	178	70	1.00	170	94	1.00
8.2-9.3	347	96	0.77 (0.54-1.09)	0.81 (0.56-1.17)	182	40	0.63 (0.35-1.11)	165	56	1.01 (0.61-1.66)
9.4-10.6	349	109	0.97 (0.64-1.48)	1.00 (0.65-1.55)	171	41	0.80 (0.41-1.55)	178	68	1.38 (0.75-2.53)
>10.6	347	106	1.05 (0.63-1.75)	1.13 (0.67-1.91)	155	38	0.88 (0.39-2.00)	192	68	1.56 (0.77-3.15)
P for trend			0.413	0.319			0.985			0.085
Polyunsaturated fat†										
≤2.7	348	176	1.00	1.00	196	62	1.00	152	114	1.00
2.8-3.1	347	131	0.78 (0.58-1.05)	0.86 (0.63-1.18)	169	50	1.02 (0.62-1.68)	178	81	0.71 (0.47-1.08)
3.2-3.6	349	97	0.57 (0.41-0.79)	0.68 (0.47-0.98)	168	46	0.87 (0.50-1.52)	181	51	0.51 (0.31-0.85)
>3.6	347	71	0.38 (0.26-0.56)	0.47 (0.31-0.72)	153	31	0.68 (0.36-1.30)	194	40	0.37 (0.20-0.66)
P for trend			0.000	<0.001			0.181			<0.001

*Adjusted for age, total energy intake, protein intake (% calories), SES, family breast cancer, menopausal status, and parity.
†Saturated fat, monounsaturated fat, and polyunsaturated fat are all in the same models without total fat.

in vegetable oils could explain our findings. Polyunsaturated fat intake seems to reduce insulin resistance (39) and thus could partially mitigate the adverse effects of high carbohydrate intake.

Bias and confounding must be considered as possible explanations for the observed results. The documentation of established breast cancer risk factors in this study argues against serious bias. Recall bias is always a concern in case-control studies, but lack of awareness among women in this population of any links between carbohydrate intake and the risk for breast cancer should minimize this problem. Recall of the diet before the disease onset could be biased toward current dietary intake, which may change due to the disease (40, 41). We aimed to limit this bias by recruiting incident cases before they knew their diagnosis and at an early state of their disease, thus reducing the likelihood of dietary changes resulting from the diagnosis of cancer. The use of oral contraceptive or hormone replacement therapy was very low in our population (<3%) and similar among cases and controls; in addition, most of the women (95%) were involved only in housekeeping as physical activity. These variables are therefore unlikely to bias our results.

Strengths of this study include a range of carbohydrate intake that has not been possible to evaluate in most Western populations. In a validation study of our questionnaire conducted in a population similar to that in this study, we observed a correlation of 0.57 between the intakes of carbohydrate estimated by the food frequency questionnaire and the 24-hour recalls, signifying that validity is reasonable (10). Although measurement error remains, this would tend to attenuate associations and cannot explain our findings. A source of bias that is difficult to exclude is that the cases may not be fully representative of the population from which they are derived. The minimal effect on the relative risk due to control for SES provides some reassurance that selection bias is not serious. However, confirmation of our findings in a prospective study of Mexican women will be important.

Carbohydrates are the major source of calories in the Mexican population. In the recent National Nutritional Survey, women ages 12 to 49 years residing in urban areas reported a mean daily carbohydrate intake of 357 g/d corresponding to 64% of total caloric intake (5). In addition, BMI has been increasing among the urban Mexican population so that 31% of women ages 12 to 49 years are overweight (BMI 25 to 29 kg/m^2) and 22.6% are obese (BMI $\geq$ 30 kg/m^2; ref. 5). In addition, the traditional reproductive pattern that protected against breast cancer is rapidly changing in Mexico: women are having later first pregnancies, fewer children, and shorter lactation periods (4). Moreover, type 2 diabetes mellitus is highly prevalent among populations with American Indian ancestry and has been related to a genetic susceptibility to insulin resistance (42-45). This is of particular concern because the adverse effects of high carbohydrate intake on hyperinsulinemia and glucose and lipid metabolism are strongly exaggerated in the presence of underlying insulin resistance (7, 46). All these factors would be expected to increase the incidence of breast cancer in Mexican women. Thus, the relation between macronutrient intake and breast cancer among Mexican women deserves further evaluation.

References

1. Willett WC. Fat, energy and breast cancer. J Nutr 1997;127:921S-3S.
2. McPherson K, Steel C, Dixon J. Breast cancer epidemiology, risk factors, and genetics. Br J Nutr 2000;231:624-8.
3. Ferlay J, Bray F, Pisani P, Parkin DM. Cancer incidence, mortality and prevalence worldwide. Version 1.0. Globocan 2000. Lyon: IARC Press; 2001.
4. Lopez-Rios O, Lazcano-Ponce E, Tovar V, Hernandez M. La epidemiología de cáncer de mama en México. ¿Consecuencia de la transición demográfica? Salud Publica Mex 1997;39:259-65.
5. Rivera Dommarco J, Shamah Levy T, Villalpando Hernandez S, Gonzalez de Cossio T, Hernandez Prado B, Sepulveda J. Encuesta Nacional de Nutrición 1999. Estado nutricional de niños y mujeres en México. Cuernavaca, Morelos (México); Instituto Nacional de Salud Publica; 2001.
6. Kaaks R. Plasma insulin, IGF-I and breast cancer. Gynecol Obstet Fertil 2001;29:185-91.
7. Jeppesen J, Schaaf P, Jones G, Zhou MY, Chen YD, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr 1997; 65:1027-33.
8. Romieu I, Hernandez-Avila M, Lazcano-Ponce E, Weber JP, Dewailly E. Breast cancer, lactation history, and serum organochlorines. Am J Epidemiol 2000;152:363-70.
9. Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998.
10. Hernández-Avila M, Romieu I, Parra S, Hernández-Avila J, Madrigal H, Willett W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. Salud Publica Mex 1998;40:133-40.
11. Department of Agriculture. Composition of foods: raw, processed, prepared, 1963-1991. Agricultural handbook. Washington (DC): Government Printing Office; 1992.
12. Chavez N, Hernandez M, Roldan J, editors. Valor nutritivo de los alimentos de mayor consumo en México. Mexico City, Mexico: Comisión Nacional de Alimentación y Instituto Nacional de la Nutrición; 1992.
13. Willett W, Stampfer M. Implications of total energy intake for epidemiologic analysis. In: Willett W, editor. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998. p. 273-301.
14. Bronfman M, Guiscafre H, Castro V, et al. Estrategias para mejorar los patrones terapéuticos utilizados en diarrea aguda en unidades de atención medica primaria. II. Medición de la desigualdad: una estrategia metodologica, análisis de las características socioeconómicas de la muestra. Arch Invest Med (Mex) 1988;19:351-60.
15. Breslow NE, Day NE. Statistical methods in cancer research: the design and analysis of cohort studies. Lyon, France: IARC; 1987.
16. Woodward M. Epidemiology study design and data analysis. Text in statistical science. Florida: Chapman & Hall/CRC; 1999. p. 466-82.
17. Anderson JT. Nutrition management of diabetes mellitus. Modern nutrition in health and disease. 9th ed. Baltimore: Williams & Wilkins; 1998. p. 1365-418.
18. Cade J, Thomas E, Vail A. Case-control study of breast cancer in southeast England: nutritional factors. J Epidemiol Community Health 1998;52:105-10.
19. Franceschi S, Favero A, Decarli A. et al. Intake of macronutrients and risk of breast cancer. Lancet 1996;347:1351-6.
20. Witte J, Ursin G, Siemiatychi J, Thomson W, Paganini-Hill A, Haile R. Diet and premenopausal bilateral breast cancer: a case control study. Breast Cancer Res Treat 1997;42:243-51.
21. Potischman N, Coates RJ, Swanson CA, et al. Increased risk of early-stage breast cancer related to consumption of sweet foods among women less than age 45 in the United States. Cancer Causes & Control 2002;13:937-46.
22. Giovannucci E. Medical history and etiology of prostate cancer. Epidemiol Rev 2001;23:159-62.
23. Hankinson SE, Willett WC, Colditz GA, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 1998;351:1393-6.
24. Del-Guidice M, Fantus I, Ezzat S, McKewn-Essen G, Page D, Goodwin P. Insulin related factors in premenopausal breast cancer risk. Breast Cancer Res Treat 1998;47:111-20.
25. Quinn K, Treston A, Unsworth E, et al. Insulin-like growth factor expression in human cancer cell lines. J Biochem 1996;271:11477-83.
26. Cullen K, Yee D, Rosen N. Insulin-like growth factors in human malignancy. Cancer Invest 1991;9:443-54.
27. Lipworth L, Adami HO, Trichopoulos D, Carlestrom K, Mantzoros C. Serum steroid hormone levels, sex hormone binding globulin, and body mass index in the etiology of postmenopausal breast cancer. Epidemiology 1996;7:96-100.
28. Thomas D, Noonan E. Breast cancer and prolonged lactation. The WHO collaborative study of neoplasia and steroid contraceptives. Int J Epidemiol 1993;22:619-26.
29. Glicksman A, Myers W, Rawson R. Diabetes mellitus and carbohydrate metabolism in patients with cancer. Med Clin N Am 1956;40: 887-900.
30. de Waard F, de Laive J, Baanders-Vanhalewijn EA. On the bimodal age distribution of mammary carcinoma. Br J Cancer 1960;14:437-48.
31. Muck B, Trotnow S, Hommel G. Cancer of the breast, diabetes, and pathological glucose tolerance. Arch Gynakol 1975;220:73-81.
32. Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropology, blood pressure, blood lipids, and glucose metabolism: a prospective study within the Malmo Preventive Project. Eur J Cancer Prev 2001;10:33-42.
33. Levi F, Pasche C, Lucchini F, Bosetti C, La Vecchia C. Glycemic index, breast and colorectal cancer. Ann Oncol 2002;13:1688-9.
34. Augustin LS, Dal Maso L, La Vecchia C, et al. Dietary glycemic index and glycemic load, and breast cancer risk: a case-control study. Ann Oncol 2001 Nov;12:1507-9.
35. Jonas CR, McCullough ML, Teras LR, Walker-Thurmond KA, Thun MJ, Calle EE. Dietary glycemic index, glycemic load, and risk of incident breast cancer in postmenopausal women. Cancer Epidemiol Biomarkers & Prev 2003;12:573-7.
36. Willett WC. Diet and breast cancer. J Intern Med 2001;249:395-411.
37. Smith-Warner SA, Spiegelman D, Adami HO, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 2001;92:767-74.
38. Holmes MD, Hunter DJ, Colditz GA, et al. Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999; 281:914-20.
39. Salmeron J, Hu FB, Manson JE, et al. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019-26.
40. Giovannucci E, Stampfer MJ, Colditz GA, et al. A comparison of prospective and retrospective assessments of diet in the study of breast cancer. Am J Epidemiol 1993;137:502-11.
41. Friedenrich C, Howe G, Miller A. The effect of recall bias on the association of calorie providing nutrients and breast cancer. Epidemiology 1991;2:424-9.
42. Almind K, Inoue G, Pedersen O, Kahn C. A common amino acid polymorphism in insulin receptor substrate-1 causes impaired insulin signaling. J Clin Invest 1996;97:2596-975.
43. Clement K, Vaisse C, Manning B, et al. Genetic variation in the β3-adrenegic receptor and an increased capacity to gain weight in patients with morbid obesity. N Engl J Med 1995;333:352-4.
44. Mitchell B, Blangero J, Comuzzie A, et al. A paired sibling analysis of the β-3 adrenergic receptor and obesity in Mexican Americans. J Clin Invest 1995;101:584-7.
45. Walston J, Silver K, Bogardus C, et al. Time of onset of non-insulin-dependent diabetes mellitus and genetic variation in the β-3 adrenergic-receptor gene. N Engl J Med 1995;333:343-7.
46. Liu S, Manson JE, Stampfer MJ, et al. Dietary glycemic load assessed by food frequency questionnaire in relation to plasma high-density lipoprotein cholesterol and fasting triglycerides among postmenopausal women. Am J Clin Nutr 2001;73:560-6.