Dietary Sugar and Colon Cancer[1]

Martha L. Slattery,[2] Joan Benson, T. Dennis Berry, Debra Duncan, Sandra L. Edwards, Bette J. Caan, and John D. Potter

Department of Oncological Sciences, University of Utah, Salt Lake City, Utah 84108 [M. L. S., J. B., T. D. B., S. L. E.]; Division of Research, Kaiser Permanente Medical Care Program, Oakland, California 94611 [D. D., B. J. C.]; and Fred Hutchinson Cancer Research Center, Seattle, Washington 98104 [J. D. P.]

Abstract

It has been hypothesized that levels of triglycerides, glucose, and insulin are associated with risk of colon cancer and that diets high in simple sugars increase risk of colon cancer because of their impact on these factors. Limited epidemiological evidence supports the association between simple carbohydrates and risk of colon cancer. Using data from a population-based case-control study (n = 1993 cases and 2410 controls), we examined the associations between dietary sugars, foods containing high levels of sugars, and dietary glycemic index (GI) and colon cancer. A dietary GI was developed to estimate metabolic response to a diet that may increase plasma glucose levels. Dietary data were obtained using a validated diet history questionnaire. High levels of sucrose intake were associated with increased risk of colon cancer among younger men [odds ratio (OR) for highest quintile relative to lowest, 1.59; 95% confidence interval (CI), 1.07–2.37]. There was also a trend of increasing colon cancer risk associated with a higher sucrose:dietary fiber ratio for proximal tumors in both men and women. Individuals with proximal tumors who consumed a diet ranked as having a high GI were at increased risk (for men, comparing highest quintile to lowest quintile: OR, 1.58; 95% CI, 1.06–2.36; P trend, 0.04; for women: OR, 1.72; 95% CI, 1.11–2.67; P trend, 0.04). Those at greatest risk from a high dietary GI were those who were sedentary (for men, relative to those who were most active and had a low-GI diet: OR, 3.46; 95% CI, 1.78–6.70; for women: OR, 2.00; 95% CI, 0.98–4.07). We also observed that people who had a high sucrose:dietary fiber ratio and who also were sedentary and had a large body mass index were at increased risk (OR, 4.58; 95% CI, 2.33–8.98) relative to those who had a low sucrose:dietary fiber ratio, were active, and had low body mass indices. These findings support previous reports that dietary sugars, especially diets high in simple carbohydrates relative to complex carbohydrates, increase risk of colon cancer, possibly through their impact on plasma glucose levels.

Introduction

As early as 1916, Higgins (1) concluded that there was a "fundamental and distinct difference in the metabolism of the various sugars in man." Since then, controlled studies have shown that glucose from sucrose is absorbed more rapidly than galactose or fructose (2); that diets high in sucrose appear to increase triglyceride levels to a greater extent than other forms of dietary sugars (3); that sucrose is the only carbohydrate associated with a significant increase in fasting triglyceride levels (4); and that diets high in simple carbohydrates (mono- and disaccharides) and low in fiber increase serum triglycerides and plasma glucose. The associations between serum triglycerides, plasma glucose, and insulin resistance and cancer are not well understood, although McKeown-Eyssen (5) has hypothesized that these metabolic characteristics might be risk factors for colorectal cancer, thus providing a unifying biological link for several previously identified risk factors, including the following: intense physical activity, which reduces serum triglycerides and improves glucose tolerance (6); obesity, which increases serum triglycerides and blood glucose (7); a diet high in plant foods, which tends to be associated with lower blood glucose levels (8); and a diet high in energy, which tends to increase triglyceride levels (9).

The purpose of this study was to evaluate dietary factors that may influence triglycerides and blood glucose levels. As reviewed by Bostick *et al.* (10), most studies that have attempted to assess the association between sucrose and colon cancer have studied isolated foods, such as desserts, as an indicator of total sucrose intake (11–14), have been hospital-based case-control studies (15–19), or have had few study participants to examine associations by age at diagnosis or tumor site in the colon in both men and women (10–21). In this study, we examined colon cancer associations with sugars, with sucrose:dietary fiber ratio, and with foods high in simple sugar content in a large population-based study. To further test the hypothesis that dietary sugars increase risk of colon cancer through their systemic effect on blood glucose levels, we estimated a dietary GI.[3] The GI originally was developed to better describe the plasma glucose response to consumption of various foods and also describes the rates of digestion and absorption of energy-providing nutrients, especially of carbohydrates (22, 23). Some foods, such as legumes, have a low GI, whereas other foods, such as those high in simple carbohydrates, have a

Received 12/2/96; revised 3/18/97; accepted 3/21/97.
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[1] This study was funded by Grant RO1 CA48998 (to M. L. S.). Case identification and verification was supported by the Utah Cancer Registry, the Northern California Cancer Registry, the Sacramento Tumor Registry, and the Minnesota Cancer Surveillance System.
[2] To whom requests for reprints should be addressed, at Department of Oncological Sciences, University of Utah, 546 Chipeta Way, Suite 1100, Salt Lake City, UT 84108.

[3] The abbreviations used are: GI, glycemic index; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; CI, confidence interval.

Table 1 Description of dietary sugar and sugar-containing foods in the study population

	Men			Women		
	Cases, n = 1099, mean (SD)	Controls, n = 1290, mean (SD)	P	Cases, n = 894, mean (SD)	Controls, n = 1120, mean (SD)	P
Nutrients (intake/day)						
Total energy (kcal)	2752 (1218)	2651 (1197)	0.04	2066 (913)	1991 (858)	0.06
Total carbohydrates (g)	336 (144)	330 (139)	0.35	270 (117)	263 (111)	0.22
Carbohydrate (g/1000 kcal)	124 (22)	127 (22)	<0.01	132 (22)	134 (22)	0.09
Sucrose (g)	54 (33)	53 (33)	0.34	46 (29)	44 (28)	0.16
Sucrose (g/1000 kcal)	20 (8.0)	20 (8.6)	0.46	22 (8.7)	22 (8.8)	0.92
Glucose (g)	37 (23)	36 (20)	0.09	31 (18)	29 (17)	0.07
Glucose (g/1000 kcal)	14 (6.1)	14 (5.6)	0.63	15 (6.1)	15 (6.5)	0.92
Fructose (g)	37 (25)	36 (22)	0.21	31 (19)	30 (18)	0.10
Fructose (g/1000 kcal)	14 (7.1)	14 (6.6)	0.42	16 (6.9)	16 (7.1)	0.94
Sucrose/dietary fiber (g)	2.1 (1.2)	2.0 (1.1)	0.03	2.1 (1.2)	2.0 (1.1)	0.14
Foods (servings/week)						
Added sugar	9.3 (11)	8.9 (11)	0.37	6.0 (7.0)	5.3 (6.5)	0.04
High-sugar dairy	4.6 (5.9)	4.4 (6.7)	0.55	2.8 (3.7)	2.7 (3.8)	0.51
Other high-sugar foods	7.8 (8.7)	7.3 (8.9)	0.16	6.1 (8.0)	5.8 (8.0)	0.49
High-sugar drinks	5.0 (8.3)	4.5 (7.5)	0.14	3.4 (5.9)	3.1 (6.1)	0.16

food items. The GI for specific sugars was developed so that dietary carbohydrates could be weighed by their metabolic effect; this measure was very easy to calculate and was not dependent on imputing values for specific food items. The GI from food items was developed in an attempt to estimate a total dietary GI, although there are limitations to the method, in that the GI for a given food may vary because of other foods eaten at the same time. Unfortunately, we did not have detailed meal composition data from the diet history questionnaire.

Other Data. Other data obtained and used in these analyses were age at the time of diagnosis or selection; BMI (weight/height^2 for men; weight/height$^{1.5}$ for women) reported for the referent year; presence or absence of first-degree relatives with colorectal cancer; use of aspirin and/or other NSAIDs on a regular basis; and long-term vigorous leisure-time activity (26). Physical activity, performed at home and at leisure, was ascertained using an adaptation of the validated CARDIA physical activity history (37, 38). The BMI of weight/height$^{1.5}$ was used for women because it has been shown to be more independent of height than weight/height^2 (39). A family history of colorectal cancer was used rather than a family history of colon cancer because there are data to suggest that recall of tumor site within the large intestine is questionable (40). Tumor site within the colon was classified as proximal (cecum through transverse colon) or distal (splenic flexure, descending, and sigmoid colon).

Statistical Methods. Population demographics have been previously reported (26). The population is described in terms of types and sources of sugar in the diet as well as a sucrose (g):dietary fiber (g) ratio (5). Age-specific analyses used the median age of the controls, 67 years, as the cutpoint. Dietary data were categorized into quintiles based upon the distribution of the control population for men and for women separately. Sugars were evaluated using the density method, in which they are expressed as the average grams of sugar per 1000 kcal per day. We have shown that this method yields results similar to those obtained from the residual method, and results appear to be independent of energy (41). In addition, it is based on units of measurement that are easy to interpret. To determine the associations between sugars and colon cancer, ORs and 95% CIs were calculated from unconditional logistic regression models. In these analyses, energy intake was adjusted along with other covariates that were associated with both dietary energy and colon cancer in this study (41). These variables include age at selection; BMI; family history of colorectal cancer; long-term vigorous physical activity; dietary cholesterol, calcium, and fiber; and use of aspirin and/or other NSAIDs. Sugars (g/1000 kcal per day) were categorized into quintiles, and total energy and other covariates were entered into the model as continuous variables. In models evaluating the GI, we adjusted for noncarbohydrate energy in logistic regression models to better evaluate the associations with GI, taking into account other dietary components of fat and protein. We evaluated associations of levels of dietary sugars with family history of colorectal cancer, physical activity, and BMI by testing for the overall improved fit of the model with an interaction term. This was calculated by taking -2 times the difference in the log-likelihood of those models with and without the cross-product term (42). Statistical testing for differences in effect by age at diagnosis and sex was estimated from the cross-product term for each dietary sugar with age and with sex in logistic regression models. To determine whether differences existed by tumor site within the colon, we conducted polychotomous logistic regression.

Results

The mean level of sugar intake in the population is shown in Table 1. Of the sugars assessed, the mean sucrose:dietary fiber ratio intake was significantly different between cases and controls among men. Among women, mean levels of dietary intake were not different between cases and controls. For both men and women, cases consumed a higher mean level of added sugars and of drinks containing high levels of sugar, although the differences were not statistically significant.

There was a slight increase in risk of colon cancer associated with higher sucrose intake and the ratio of sucrose:dietary fiber ratio in the diet among younger men (OR, 1.59; Table 2; P = 0.05 for interaction between age and sucrose:dietary fiber ratio). The sucrose:dietary fiber ratio also was associated significantly with colon cancer for all men, as well as those with proximal tumors (P = 0.06 for difference in association between proximal and distal tumor sites). High levels of fructose or glucose intake were not associated with

Table 2 Associations between sugars and colon cancer in men[a]

	OR	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P* trend
Sucrose (g/1000 kcal/day)						
	<13.1	13.1–17.2	17.3–20.6	20.7–26.0	>26.0	
n, all cases	218	232	197	240	208	
All subjects	1.00	1.13 (0.87–1.46)	1.00 (0.76–1.31)	1.26 (0.97–1.65)	1.14 (0.87–1.51)	0.21
<67	1.00	1.30 (0.92–1.84)	0.89 (0.61–1.29)	1.33 (0.92–1.92)	1.59 (1.07–2.37)	0.05
≥67	1.00	0.95 (0.63–1.43)	1.06 (0.71–1.58)	1.18 (0.80–1.76)	0.90 (0.60–1.34)	0.96
Proximal	1.00	1.23 (0.88–1.72)	1.18 (0.84–1.67)	1.37 (0.98–1.92)	1.18 (0.83–1.69)	0.26
Distal	1.00	1.01 (0.73–1.40)	0.90 (0.64–1.26)	1.17 (0.84–1.61)	1.10 (0.78–1.54)	0.39
Sucrose:dietary-fiber ratio (g)						
	<1.2	1.2–1.6	1.7–2.0	2.1–2.7	>2.7	
n, all cases	180	204	238	230	243	
All subjects	1.00	1.15 (0.87–1.51)	1.39 (1.06–1.82)	1.31 (1.00–1.72)	1.37 (1.04–1.79)	0.02
<67 years	1.00	0.99 (0.68–1.44)	1.35 (0.92–1.96)	1.03 (0.71–1.51)	1.51 (1.05–2.19)	0.04
≥67 years	1.00	1.35 (0.90–2.03)	1.46 (0.98–2.16)	1.63 (1.09–2.42)	1.28 (0.85–1.92)	0.19
Proximal	1.00	1.32 (0.92–1.87)	1.66 (1.18–2.35)	1.51 (1.07–2.15)	1.51 (1.06–2.14)	0.02
Distal	1.00	0.99 (0.70–1.39)	1.20 (0.86–1.68)	1.18 (0.85–1.65)	1.23 (0.88–1.72)	0.12
Glucose (g/1000 kcal/day)						
	<9.0	9.0–11.8	11.9–14.6	14.7–18.1	>18.1	
n, all cases	218	239	259	173	206	
All subjects	1.00	1.17 (0.90–1.52)	1.36 (1.05–1.76)	0.91 (0.69–1.20)	1.07 (0.82–1.41)	0.77
<67	1.00	1.12 (0.79–1.59)	1.06 (0.75–1.51)	0.78 (0.52–1.15)	0.94 (0.64–1.39)	0.32
≥67	1.00	1.28 (0.86–1.89)	1.86 (1.26–2.76)	1.14 (0.76–1.72)	1.32 (0.89–1.98)	0.44
Proximal	1.00	1.26 (0.90–1.76)	1.55 (1.11–2.16)	1.06 (0.74–1.51)	1.26 (0.89–1.79)	0.45
Distal	1.00	1.08 (0.79–1.48)	1.23 (0.90–1.68)	0.77 (0.54–1.09)	0.86 (0.61–1.22)	0.14
Fructose (g/1000 kcal/day)						
	<8.4	8.5–11.5	11.6–15.0	15.1–18.6	>18.6	
n, all cases	224	237	252	180	202	
All subjects	1.00	1.18 (0.91–1.53)	1.30 (1.00–1.70)	0.97 (0.73–1.27)	1.06 (0.80–1.41)	0.80
<67	1.00	1.13 (0.79–1.62)	1.07 (0.75–1.54)	0.86 (0.58–1.27)	0.98 (0.66–1.46)	0.52
≥67	1.00	1.22 (0.83–1.81)	1.64 (1.11–2.44)	1.12 (0.75–1.68)	1.22 (0.81–1.84)	0.66
Proximal	1.00	1.27 (0.91–1.77)	1.34 (0.96–1.88)	1.12 (0.79–1.60)	1.15 (0.80–1.64)	0.74
Distal	1.00	1.10 (0.80–1.51)	1.20 (0.87–1.66)	0.82 (0.60–1.16)	0.93 (0.66–1.32)	0.29

[a] OR and 95% CI estimated from logistic regression models that included age at diagnosis, BMI, long-term vigorous physical activity, use of aspirin and/or other NSAIDs, family history of colorectal cancer, energy intake, dietary calcium, fiber, and cholesterol.

risk consistently across categories nor was there a significant linear trend. Among women, the sucrose:dietary fiber ratio was associated with a significant trend toward increased risk for proximal tumors (Table 3; $P = 0.07$ for difference between proximal and distal tumor sites). There were not significant interactions between dietary sugar consumption and age among women. Whereas the magnitude of the associations differed slightly by sex, only dietary sucrose was of borderline significance when evaluating interaction between sex and sugar consumption ($P = 0.08$).

There was no significant associations between colon cancer and consumption of high-sugar foods from all sources. However, there was some variation in risk between various types of high-sugar foods consumed (data not shown in Table 3). The strongest and most consistent associations for both men and women were from high intakes of sugars that were added at the table to other foods (OR for upper quintile of intake relative to lowest quintile of intake for men was 1.30; 95% CI, 0.98–1.72; OR for women, 1.48; 95% CI, 1.09–1.99).

A high dietary GI was associated with increased risk of colon cancer. Associations were generally stronger among younger individuals (Table 4), although an increase in risk also was observed with high-GI diets among older women ($P = 0.06$ for interaction between dietary GI and age in both men and women). Proximal tumors were more consistently associated with increased risk with increasing dietary GI than were distal tumors. This difference in association by tumor site was statistically significantly among men ($P = 0.05$) but not among women.

We evaluated two-way associations between dietary sugars and GI on the one hand and physical activity and BMI on the other. We did not observe any significant two-way interactions between dietary sugars and either physical activity or BMI. However, individuals who were sedentary and had a high GI were at higher risk than those who were active and had a high GI or those who were sedentary and had a low GI (Table 5). This association was most marked among younger men, in whom risk estimates were 6.55 (OR, 2.39–18.0), 2.43 (95% CI, 1.05–5.63), and 1.00, respectively. Similar patterns were observed for most subgroups except for individuals who were older than 66 years of age at the time of diagnosis.

We further evaluated the three-way associations among sucrose, sucrose:dietary fiber ratio, and GI with physical activity and BMI. Of these factors, the most marked associations were observed for sucrose:dietary fiber ratio as it related to physical activity and BMI. We observed that as the level of physical activity decreased and the levels of BMI and sucrose:dietary fiber-ratio increased, risk of colon cancer increased (Table 6). Associations were seen for both men and women, although associations were stronger for men (OR, 5.90; 95% CI, 2.23–15.6 for the group with the highest sucrose:dietary fiber ratio, lowest physical activity, and highest BMI relative to the group with the lowest sucrose:dietary fiber ratio, highest physical activity, and lowest BMI) than for women (OR, 3.45; 95% CI, 1.29–9.23).

We assessed the association between family history of colorectal cancer and dietary sugar intake and GI (data not shown). Only among older women did there appear to be a

Table 3 Associations between sugars and colon cancer in women[a]

	OR	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P* trend
Sucrose (g/1000 kcal/day)						
	<15.0	15.0–19.1	19.2–22.8	22.9–28.5	>28.5	
n, all cases	169	196	180	184	159	
All subjects	1.00	1.19 (0.90–1.58)	1.10 (0.82–1.47)	1.14 (0.85–1.52)	1.02 (0.75–1.39)	0.99
<67 years	1.00	1.02 (0.69–1.49)	0.86 (0.58–1.28)	1.08 (0.72–1.62)	0.99 (0.63–1.55)	0.98
≥67 years	1.00	1.48 (0.96–2.28)	1.47 (0.95–2.29)	1.32 (0.85–2.04)	1.18 (0.76–1.81)	0.85
Proximal	1.00	1.28 (0.89–1.83)	1.28 (0.89–1.84)	1.17 (0.81–1.70)	1.11 (0.76–1.63)	0.79
Distal	1.00	1.15 (0.81–1.65)	0.98 (0.68–1.42)	1.14 (0.79–1.64)	0.97 (0.65–1.43)	0.87
Sucrose:dietary-fiber ratio (g)						
	<1.2	1.3–1.6	1.7–2.0	2.1–2.6	>2.6	
n, all cases	142	174	184	205	183	
All subjects	1.00	1.25 (0.93–1.68)	1.31 (0.98–1.76)	1.40 (1.04–1.87)	1.24 (0.92–1.68)	0.12
<67 years	1.00	1.13 (0.75–1.70)	1.10 (0.73–1.66)	1.34 (0.89–2.02)	1.32 (0.87–2.01)	0.13
≥67 years	1.00	1.44 (0.94–2.22)	1.69 (1.10–2.59)	1.59 (1.04–2.44)	1.27 (0.82–1.97)	0.31
Proximal	1.00	1.25 (0.86–1.82)	1.28 (0.88–1.86)	1.53 (1.06–2.21)	1.38 (0.95–2.02)	0.05
Distal	1.00	1.23 (0.85–1.79)	1.32 (0.91–1.91)	1.27 (0.88–1.84)	1.11 (0.76–1.63)	0.59
Glucose (g/1000 kcal/day)						
	<10.0	10.0–12.7	12.8–15.7	15.8–19.8	>19.8	
n, all cases	173	162	198	193	162	
All subjects	1.00	1.00 (0.74–1.34)	1.34 (1.01–1.79)	1.25 (0.93–1.68)	1.15 (0.85–1.58)	0.15
<67 years	1.00	0.74 (0.50–1.09)	1.04 (0.71–1.55)	1.10 (0.73–1.66)	1.07 (0.69–1.69)	0.32
≥67 years	1.00	1.55 (0.98–2.46)	1.97 (1.27–3.08)	1.57 (1.01–2.45)	1.45 (0.92–2.30)	0.27
Proximal	1.00	1.18 (0.82–1.70)	1.42 (0.98–2.05)	1.47 (1.02–2.13)	1.15 (0.77–1.71)	0.24
Distal	1.00	0.83 (0.57–1.21)	1.26 (0.88–1.81)	1.09 (0.75–1.59)	1.20 (0.82–1.78)	0.16
Fructose (g/1000 kcal/day)						
	<9.6	9.6–12.7	12.8–16.4	16.5–20.7	>20.7	
n, all cases	165	175	197	185	166	
All subjects	1.00	1.13 (0.84–1.51)	1.40 (1.05–1.88)	1.34 (0.99–1.80)	1.26 (0.92–1.73)	0.08
<67	1.00	1.07 (0.73–1.58)	1.20 (0.80–1.80)	1.29 (0.84–1.96)	1.09 (0.70–1.71)	0.43
≥67	1.00	1.19 (0.76–1.87)	1.71 (1.11–2.63)	1.42 (0.91–2.21)	1.46 (0.93–2.31)	0.10
Proximal	1.00	1.59 (1.11–2.29)	1.47 (1.01–2.15)	1.59 (1.08–2.34)	1.39 (0.93–2.08)	0.18
Distal	1.00	0.77 (0.53–1.13)	1.31 (0.91–1.88)	1.21 (0.83–1.76)	1.21 (0.82–1.79)	0.09

[a] OR and 95% CI estimated from logistic regression models that included age at diagnosis, BMI, long-term vigorous physical activity, use of aspirin and/or other NSAIDs, family history of colorectal cancer, energy intake, dietary calcium, fiber, and cholesterol.

significant interaction between the sucrose:dietary fiber ratio and family history (P = 0.03 for overall improved fit of the model). The subgroup of women with a family history of colorectal cancer had over a 3-fold increase in risk (OR, 3.52; 95% CI, 1.60–7.75) if they had a high sucrose:dietary fiber ratio. This compares with a risk of 2.32 (95% CI, 1.08–4.99) for family history only and an OR of 1.10 (95% CI, 0.82–1.49) for high sucrose:dietary fiber ratio without a family history of colorectal cancer. We observed no significant interactions between other dietary sugars or GI and a family history of colorectal cancer.

Discussion

There is considerable evidence that diet is involved in the etiology of colon cancer. Whereas research has focused on components of a western-style diet, such as fat and protein, in conjunction with colon cancer, dietary carbohydrates have received much less attention. However, it is recognized that levels of simple sugar consumption vary from country to country and also may typify a western-style diet. It is possible that high levels of consumption of simple sugars result in increased triglyceride and plasma glucose levels, especially among those who are insulin resistant; insulin resistance is a possible risk factor for colon cancer that has generally been unexplored.

Many of the studies that have attempted to examine an association with sugars have examined foods containing high levels of sucrose (10–15). We observed that foods most dense in simple sugar (such as sugars added to other foods, including sugar, honey, and jam) were most consistently associated with colon cancer. Bostick *et al.* (10) observed that sucrose-containing foods showed stronger associations than sucrose itself; the strongest associations were observed for non-dairy product foods. Others have shown associations for specific foods (11, 14), although the association with foods containing high levels of sugar is not universal (12, 13, 15), and food items with a high-sugar content, such as desserts or dairy products, contain fat and calcium which may account for observed associations with colon cancer. Consistent with the findings by Bostick *et al.* (10), we observed that the strongest associations were among older women. Studies are mixed in their findings of an association reported for sucrose itself (15–21). Of the studies reported, only two found a significant association between sucrose and colon or colorectal cancer (14, 16). Some of these differences could be accounted for by the age of the study participants. No previous studies have had an adequate sample to examine tumor site-specific associations by sex.

Although studies have focused on sugars and foods high in simple and complex carbohydrates, no attempts have been made to estimate a metabolic response based on consumption of foods. Variation in reported risk estimates between studies for high-sugar foods and/or sugar may be the result of different metabolic response to specific foods. The GI was developed to provide an indication of plasma glucose response to diet (22, 23). However, the literature is unclear regarding the impact of mixed meals on GI for a given food; some studies report no difference in GI in a mixed-meal test situation, and others report

Table 4 Association between estimated dietary GI and colon cancer in men and women[a]

	OR (Low rank)	OR (95% CI) (rank 2)	OR (95% CI) (rank 3)	OR (95% CI) (rank 4)	OR (95% CI) (high rank)	*P* trend
Men						
GI from dietary sugars: sucrose, glucose, and fructose						
All subjects	1.00	1.11 (0.85–1.46)	1.35 (1.03–1.78)	1.23 (0.93–1.65)	1.55 (1.12–2.13)	0.02
<67	1.00	1.10 (0.74–1.62)	1.39 (0.93–2.06)	1.16 (0.77–1.74)	1.87 (1.20–2.91)	0.02
≥67	1.00	1.14 (0.78–1.66)	1.32 (0.90–1.93)	1.33 (0.88–2.03)	1.26 (0.78–2.02)	0.20
Proximal	1.00	1.16 (0.83–1.62)	1.35 (0.95–1.90)	1.30 (0.91–1.87)	1.58 (1.06–2.36)	0.04
Distal	1.00	1.04 (0.74–1.46)	1.29 (0.92–1.82)	1.10 (0.77–1.58)	1.48 (1.00–2.19)	0.08
GI from foods						
All subjects	1.00	1.18 (0.90–1.56)	1.33 (1.02–1.75)	1.41 (1.07–1.85)	1.37 (1.04–1.82)	0.02
<67	1.00	1.34 (0.90–1.99)	1.19 (0.80–1.78)	1.48 (1.01–2.18)	1.39 (0.93–2.07)	0.10
≥67	1.00	1.08 (0.74–1.58)	1.49 (1.02–2.16)	1.35 (0.92–1.99)	1.33 (0.89–1.99)	0.08
Proximal	1.00	1.48 (1.04–2.10)	1.51 (1.06–2.14)	1.84 (1.30–2.60)	1.59 (1.10–2.29)	0.02
Distal	1.00	0.98 (0.70–1.38)	1.18 (0.85–1.65)	1.18 (0.84–1.65)	1.23 (0.88–1.74)	0.14
Women						
GI from dietary sugars: sucrose, glucose, and fructose						
All subjects	1.00	1.05 (0.79–1.40)	0.98 (0.73–1.33)	1.01 (0.73–1.38)	1.51 (1.06–2.14)	0.08
<67	1.00	1.05 (0.69–1.59)	1.06 (0.69–1.63)	1.15 (0.73–1.81)	1.69 (1.02–2.79)	0.06
≥67	1.00	1.06 (0.70–1.59)	0.95 (0.62–1.45)	0.95 (0.60–1.49)	1.49 (0.90–2.47)	0.28
Proximal	1.00	1.07 (0.75–1.52)	0.92 (0.63–1.35)	1.18 (0.79–1.74)	1.72 (1.11–2.67)	0.04
Distal	1.00	1.08 (0.75–1.57)	1.07 (0.73–1.57)	0.90 (0.60–1.35)	1.42 (0.92–2.21)	0.06
GI from foods						
All subjects	1.00	0.95 (0.71–1.27)	0.98 (0.73–1.31)	0.96 (0.71–1.29)	1.34 (1.00–1.81)	0.08
<67	1.00	1.04 (0.67–1.62)	0.87 (0.55–1.35)	0.95 (0.61–1.46)	1.16 (0.76–1.78)	0.60
≥67	1.00	0.86 (0.58–1.29)	1.10 (0.74–1.63)	1.00 (0.66–1.52)	1.66 (1.09–2.53)	0.04
Proximal	1.00	0.91 (0.63–1.32)	1.02 (0.71–1.47)	0.99 (0.68–1.43)	1.39 (0.96–2.01)	0.08
Distal	1.00	0.97 (0.68–1.41)	0.94 (0.65–1.37)	0.94 (0.65–1.37)	1.22 (0.84–1.78)	0.36

[a] OR and 95% CI estimated from logistic regression models that included age, BMI, long-term vigorous physical activity, use of aspirin and/or other NSAIDs, family history of colorectal cancer, non-carbohydrate energy intake, dietary calcium and fiber.

differences in food-specific GI when consumed as part of a meal (43, 44). A limitation of this study is our lack of detailed information on meal composition because dietary data were obtained primarily from a diet history questionnaire. We have adjusted for energy from fat and protein in an attempt to correct for the mixed meal situation, but the underlying assumption of this analysis is that overall patterns of intake, whether measured as GI or as fat and protein, are useful predictors of what may be short-term meal-to-meal variability in true metabolic glycemic response. It does seem likely, however, that deriving a GI for an individual diet rather than a 24-h intrinsic study period is likely to underestimate rather than overestimate the true metabolic response and possibly smooth out the higher degree of variability that would be observed over shorter time periods.

Although we do not have information on meal patterns, we do have information from the diet history questionnaire on over 800 specific food items, such as types of cereal consumed, so that we were able to give various GIs to individual food items rather than to food items that represented groups of food (*i.e.*, corn flakes and bran flakes instead of dry cereal). Additionally, most estimates of GI for specific foods that are reported in the literature have been based on estimates from small samples of people with non-insulin-dependent diabetes and healthy populations. Thus, our GI is a very crude measure, which we used to rank individuals rather than report any given GI that may be associated with cancer. Despite the limitations of the GI, it does suggest that the increased risk associated with diets high in foods that have a high glycemic effect, many of which are also high in sucrose and low in fiber, may be the result of metabolic factors such as elevated plasma glucose levels.

Although dietary fats are thought to have their primary effects on the lumen of the large intestine, associations between colon cancer and dietary carbohydrates may be the result of their metabolic properties and have a systemic effect. For instance, it has been shown that rats given boluses of fat have increased colonic epithelial proliferation associated with the columnar cells of normal epithelium being replaced with less mature, cuboidal cells (45). On the other hand, boluses of sucrose did not lead to histological changes to the surface colonic epithelium. It has been hypothesized that cell proliferation associated with sucrose is not the result of direct injury to the colon but rather is the result of changes in carbohydrate metabolic pathways that release gut hormones and stimulate epithelial proliferation (46, 47). If the mode of action involves hormones, a stronger association with proximal tumors could be expected because it has been suggested that endogenous factors may be associated with proximal rather than distal tumors (48).

We believe that our data lend indirect support to the hypothesis that increased serum triglycerides and plasma glucose levels and insulin resistance, as seen in Syndrome X, are associated with colon cancer. Those at highest risk were those who were sedentary, had a high BMI, and consumed a diet with a high ratio of simple to complex carbohydrates (sucrose: dietary fiber ratio). This suggest a possible mechanistic interaction in that one's level of physical activity, body size, and dietary intake of sucrose and fiber may alter the individual associations of the other factors in the expression of insulin resistance. All of these factors have been shown to independently elevate serum triglycerides and plasma glucose (49–51). The increased risk was present after adjusting for energy intake and was not consistently observed for other components of energy intake, such as protein or total carbohydrates; a similar trend was observed for total fat intake, although the magnitude of the association was less (OR, 3.26 and 95% CI, 1.75–6.07 for the highest percentage of calories from fat, low physical

Table 5 Association between dietary sugar GI and physical activity[a]

Physical activity	GI for men			GI for women		
	Low, OR (95% CI)	Intermediate, OR (95% CI)	High, OR (95% CI)	Low, OR (95% CI)	Intermediate, OR (95% CI)	High, OR (95% CI)
All Subjects[b]						
High	29/58[c]	137/233	158/90	21/28	79/128	45/68
Intermediate	118/139	379/415	141/137	86/129	226/343	107/104
Low	55/63	127/123	51/30	69/66	187/197	68/51
All Subjects						
High	1.00	1.26 (0.75–2.10)	1.40 (0.77–2.56)	1.00	0.88 (0.46–1.67)	1.08 (0.52–2.23)
Intermediate	1.57 (0.93–2.65)	1.84 (1.13–2.97)	2.13 (1.23–3.68)	0.89 (0.47–1.69)	0.95 (0.52–1.75)	1.56 (0.80–3.04)
Low	1.54 (0.85–2.77)	1.90 (1.12–3.22)	3.46 (1.78–6.70)	1.38 (0.71–2.71)	1.35 (0.73–2.50)	2.00 (0.98–4.07)
<67 yr						
High	1.00	1.84 (0.88–3.86)	2.43 (1.05–5.63)	1.00	1.12 (0.50–2.50)	1.48 (0.59–3.70)
Intermediate	2.42 (1.14–5.15)	2.52 (1.25–5.08)	3.75 (1.73–8.13)	1.20 (0.54–2.67)	1.24 (0.58–2.64)	2.18 (0.92–5.13)
Low	2.19 (0.89–5.43)	2.55 (1.15–5.65)	6.55 (2.39–18.0)	1.58 (0.64–3.90)	1.80 (0.81–3.98)	2.45 (0.93–6.41)
≥67 yr						
High	1.00	0.83 (0.40–1.73)	0.74 (0.30–1.81)	1.00	0.52 (0.16–1.63)	0.58 (0.16–2.07)
Intermediate	0.98 (0.46–2.06)	1.28 (0.64–2.54)	1.09 (0.49–2.44)	0.47 (0.16–1.44)	0.55 (0.19–1.61)	0.86 (0.27–2.69)
Low	1.03 (0.46–2.29)	1.31 (0.63–2.73)	1.88 (0.76–4.65)	0.87 (0.28–2.66)	0.80 (0.27–2.32)	1.36 (0.42–4.40)
Proximal						
High	1.00	1.48 (0.74–2.97)	1.42 (0.62–3.23)	1.00	0.87 (0.39–1.96)	1.15 (0.45–2.92)
Intermediate	1.77 (0.87–3.59)	2.14 (1.10–4.15)	2.61 (1.25–5.44)	0.92 (0.42–2.02)	0.93 (0.44–1.96)	1.77 (0.78–4.04)
Low	2.05 (0.95–4.44)	2.26 (1.11–4.60)	3.96 (1.69–9.26)	1.28 (0.56–2.90)	1.44 (0.67–3.08)	2.00 (0.83–4.86)
Distal						
High	1.00	1.03 (0.55–1.93)	1.35 (0.65–2.80)	1.00	0.96 (0.41–2.23)	1.11 (0.43–2.83)
Intermediate	1.40 (0.74–2.63)	1.51 (0.84–2.71)	1.68 (0.87–3.26)	0.92 (0.40–2.14)	1.03 (0.46–2.28)	1.50 (0.63–3.60)
Low	1.17 (0.56–2.43)	1.58 (0.83–3.00)	3.02 (1.38–6.63)	1.51 (0.62–3.63)	1.38 (0.61–3.12)	2.22 (0.90–5.49)

[a] OR and 95% CI calculated from logistic regression models that adjusted for age, BMI, noncarbohydrate energy intake, calcium and dietary fiber intake, family history of colorectal cancer, and use of aspirin and/or other NSAIDs.
[b] Numbers for cases and controls are for all subjects; approximately 1/2 of these numbers are in the cells for age and tumor site analysis.
[c] No. of cases/controls.

Table 6 Interaction of physical activity with BMI and sucrose:dietary fiber ratio (all subjects combined)

Sucrose:dietary fiber ratio	Physical activity	BMI		
		Low	Intermediate	High
No. of cases/controls				
Low	High	20/47	20/42	26/39
	Intermediate	44/81	49/86	91/82
	Low	16/28	22/39	36/34
Intermediate	High	87/141	70/104	79/126
	Intermediate	172/249	211/257	266/251
	Low	96/106	113/97	149/120
High	High	28/39	21/35	20/31
	Intermediate	67/93	74/88	89/84
	Low	34/40	26/36	67/35
OR (95% CI)[a]				
Low	High	1.00	1.06 (0.50–2.25)	1.55 (0.75–3.22)
	Intermediate	1.26 (0.66–2.40)	1.29 (0.68–2.44)	2.57 (1.40–4.74)
	Low	1.33 (0.59–3.01)	1.34 (0.63–2.84)	2.40 (1.17–4.89)
Intermediate	High	1.37 (0.76–2.48)	1.51 (0.82–2.79)	1.40 (0.77–2.56)
	Intermediate	1.55 (0.88–2.73)	1.88 (1.07–3.30)	2.50 (1.43–4.37)
	Low	2.10 (1.15–3.83)	2.65 (1.45–4.82)	2.89 (1.61–5.19)
High	High	1.49 (0.72–3.07)	1.41 (0.66–3.01)	1.55 (0.71–3.37)
	Intermediate	1.66 (0.89–3.08)	1.79 (0.97–3.32)	2.45 (1.33–4.51)
	Low	1.88 (0.93–3.80)	1.55 (0.74–3.23)	4.58 (2.33–8.98)

[a] Adjusted for age, presence or absence of a first degree relative with colorectal cancer, noncarbohydrate energy, calcium, and use of aspirin and/or other NSAIDs.

activity, and high BMI compared to people who consumed the lowest percentage compared to OR, 4.58 and 95% CI, 2.33–8.98 for sucrose:fiber ratio). This suggests that although total energy intake is potentially an important contributor to risk, associations may vary by the source of energy. Of the dietary sources of energy evaluated, sucrose appears to have the greatest impact on risk. Furthermore, the data suggest that diets low in fiber may contribute to a dietary pattern associated with increased risk of colon cancer. These data also suggest that physical activity may be working through metabolic pathways; in controlled settings, vigorous physical activity has been shown to improve insulin resistance (6).

There are other possible mechanisms whereby sucrose could be associated with colon cancer, beyond or in addition to an association with Syndrome X. In rats, uncooked sucrose has been shown to increase colonic epithelial cell proliferation and aberrant crypt foci formation (52). Cooked sucrose contains compounds that can be genotoxic (53, 54) and can increase microadenoma formation (55). In humans, high-sucrose diets increase overall mouth-to-anus transit time, although mouth-to-cecum transit time is decreased (56). Diets high in sucrose also have been shown to increase fecal concentration of bile acids (56).

In summary, we believe that our sucrose data corroborate those reported elsewhere and that a diet that increases glycemic response is involved in the etiology of colon cancer. These associations appear to be more related to proximal tumors, possibly because of their effect on hormonal regulation. Although there are many possible explanations for our results, we believe that they lend indirect support to the hypothesis that insulin resistance is associated with colon cancer.

Acknowledgments

We acknowledge the contributions and support of Dr. Richard Kerber, Dr. Kristin Anderson, and Khe-Ni Ma to the data collection, study supervision, and analysis.

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Cancer Epidemiol Biomarkers Prev 1997;6:677-685.