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Brief Communication

Aspects of dietary carbohydrate intake are not related to risk of colorectal polyps in the Tennessee Colorectal Polyp Study.

Authors:

Helen G Coleman [1], Reid M Ness [2,3], Walter E. Smalley [2,3], Wei Zheng [3-5], and Martha J Shrubsole [3-5].

Affiliations of authors:

[1]Cancer Epidemiology & Health Services Research Group, Centre for Public Health, Queens University Belfast, Northern Ireland.

[2]Division of Gastroenterology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

[3]Veterans Affairs Tennessee Valley Geriatric Research, Education and Clinical Center, Nashville, TN, USA.

[4]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, TN, USA.

[5]Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA.

Corresponding author:

Martha J. Shrubsole, PhD.

Vanderbilt Epidemiology Center and Vanderbilt, Ingram Cancer Center

2525 West End Avenue, Suite 800

Nashville, TN 37203-1738

Phone: 615-936-0812 Fax: 615-936-8241

martha.shrubsole@vanderbilt.edu

Short title: Carbohydrate intake & colorectal polyp risk

Abstract

Purpose: High digestible carbohydrate intakes can induce hyperglycemia and hyperinsulinemia, and collectively have been implicated in colorectal tumor development. Our aim was to explore the association between aspects of dietary carbohydrate intake and risk of colorectal adenomas and hyperplastic polyps in a large case-control study.

Methods: Colorectal polyp cases (*n*=1,315 adenomas only, *n*=566 hyperplastic polyps only and *n*=394 both) and controls (*n*=3,184) undergoing colonoscopy were recruited between 2003 and 2010 in Tennessee, USA. Dietary intakes were estimated by a 108-item food frequency questionnaire. Unconditional logistic regression analysis was applied to determine odds ratios (OR) and corresponding 95% confidence intervals (CI) for colorectal polyps according to dietary carbohydrate intakes, after adjustment for potential confounders.

Results: No significant associations were detected for risk of colorectal adenomas when comparing the highest versus lowest quartiles of intake for total sugars (OR 1.03; 95% CI 0.84-1.26), starch (OR 1.01; 95% CI 0.81-1.26), total or available carbohydrate intakes. Similar null associations were observed between dietary carbohydrate intakes and risk of hyperplastic polyps, or concurrent adenomas and hyperplastic polyps.

Conclusion: In this US population, digestible carbohydrate intakes were not associated with risk of colorectal polyps, suggesting that dietary carbohydrate does not have an etiological role in the early stages of colorectal carcinogenesis.

Keywords: diet; carbohydrate; starch; sugars; colorectal adenomas; hyperplastic polyps; colorectal polyps.

Introduction

Elevated circulating insulin and glucose levels have been strongly associated with colonic carcinogenesis, and an increased risk of colorectal adenomas [1, 2]. Hyperglycemia may induce chronic inflammation and tissue damage via excess oxidative stress and the liberation of pro-inflammatory cytokines, both of which may be implicated in carcinogenesis [3, 4]. In addition, meta-analyses have illustrated that colorectal cancer risk is positively associated with high levels of circulating insulin and C-peptide, a marker of insulin secretion [5]. Insulin itself conveys mitogenic properties *in vitro* that promote tumor cell growth but also acting indirectly through the actions of insulin-like growth factors (IGFs) and associated binding proteins [6]. Two comprehensive systematic reviews have identified a direct association between circulating IGF-1 concentrations and risk of colorectal cancer [7, 8].

Digestible carbohydrate intakes are a key determinant of blood glucose and insulin responses, therefore, it is plausible that available carbohydrate intakes may be related to colorectal cancer and polyp risk [2, 9]. Despite the biological mechanisms potentially linking available carbohydrate, i.e. sugars and starch, intakes with colorectal neoplasm development, relatively few studies have examined this relationship. Indeed, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Continuous Update Project report on colorectal cancer published in 2011 was unable to make a 'convincing' or 'probable' judgement on the association between digestible carbohydrate intakes and colorectal cancer risk [10]. This has led to calls for further research on starch, sugars and colorectal health in order to provide clarification of the relationship and make appropriate public health recommendations [11].

To our knowledge, only one prior study has explored the role of dietary carbohydrate on risk of colorectal polyps [12]. In that study, conducted within the US Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, the highest intakes of dietary carbohydrate was associated with a 29% reduced risk of adenoma in men, but this was not seen in women [12]. Further, the risk of adenoma according to sugars and starch intake separately was not investigated in the PLCO analysis. Previous research from our group has demonstrated that well-established lifestyle factors for colorectal cancer can also influence risk of pre-malignant adenoma and hyperplastic polyp development [13]. Therefore, our aim was to explore the association between aspects of dietary carbohydrate intake and risk of colorectal adenomas and hyperplastic polyps in a large case-control study.

Materials and Methods

Study design

The Tennessee Colorectal Polyp Study is a case-control study conducted in Nashville, Tennessee, USA. A detailed study design has been described elsewhere [14]. Briefly, eligible participants aged 40-75 years were recruited from patients undergoing colonoscopy at the Vanderbilt Gastroenterology Clinic between February 2003 and October 2010, and the Veterans Affairs Tennessee Valley Health System Nashville Campus between August 2003 and May 2007. Individuals were excluded if they had genetic colorectal cancer syndromes, a prior history of inflammatory bowel disease, adenomatous polyps, or cancer (except non-melanoma skin cancer). The study was approved by the Vanderbilt University Institutional Review Board, the Veterans Affairs Institutional Review Board, and the Veterans Affairs Research and Development Committee.

Study participants

Among 12,585 eligible individuals, 7,621 participated (61% response rate). Following colonoscopy and pathology review, 7,487 participants were classified as polyp-free controls (who had a complete colonoscopy reaching the cecum), or cases with adenomas(s) only, hyperplastic polyp(s) only, or both.

Data collection

Standardized telephone interviews following colonoscopy were conducted to collect information on demographics, medication use, medical history, family history, reproductive factors, anthropometry and lifestyle. Dietary intake was assessed using a semi-quantitative 108-item food frequency questionnaire (FFQ), developed to capture diet in the Southeastern US [15, 16]. Among participants, 5,495 (73%) completed both the telephone interview and FFQ. Telephone interview and FFQ responders did not differ from non-responders with regards to most characteristics, including case-control status, sex, smoking (pack-years) or exercise undertaken in the past 10 years, after accounting for study site. Telephone interview and FFQ responders were, on average 2-3 years older than non-responders.

Statistical analysis

Participants were excluded from analysis if they had daily energy intakes ≤600 kcal/day (n=36). Available carbohydrate intake was derived by subtracting dietary fiber from total carbohydrate intakes. Analysis of total sugars intake represents the sum of all monosaccharides and disaccharides, in accordance with standard classifications [17].

Characteristics and mean nutrient intakes were compared between groups using general linear models and Mantel-Haenszel chi-squared tests with additional adjustment for age and sex when appropriate. Unconditional logistic regression analysis was conducted to generate odds ratios (OR) and corresponding 95% confidence intervals (CI) for polyps, according to quartiles of intake. Multivariate analyses were adjusted for energy intake (via the residuals method [18]), age, sex, study site, colonoscopy indication, race, BMI, smoking status, alcohol consumption, exercise and intakes of red meat, calcium and dietary folate equivalents. Other potential confounders outlined in Table 1 were not significantly associated with both intake and case status. Quartiles of carbohydrate intake were entered into regression models as continuous variables to test for trend. Statistical power calculations are shown in Table 2.

Sub-group analyses were conducted, grouping individuals with any adenoma diagnosis (with or without a concurrent hyperplastic polyp), and by number of adenomas, location of adenomas, advanced adenomas, sessile serrated adenomas, sex, BMI categories, smoking status, multivitamin use and prior history of hyperplastic polyps. All statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

Results

Descriptive characteristics and daily nutrient intakes for all case groups and controls are shown in Table 1. All polyp cases were more likely to be male, smoke tobacco, consume alcohol, and were less likely to take multivitamins or regular exercise compared with controls. Adenoma, but not hyperplastic polyp, cases were older, less likely to be White or use non-steroidal anti-inflammatory drugs, and had higher BMIs compared with controls.

In fully adjusted models, no associations were identified for risk of colorectal adenomas when comparing the highest versus lowest quartiles of intake for total sugars (OR 1.03; 95% CI 0.84-1.26), starch (OR 1.01; 95% CI 0.81-1.26), total or available carbohydrate intakes (Table 2). Similarly, total carbohydrate, available carbohydrate, total sugars and starch intakes were not found to be related to risk of hyperplastic polyps. A non-significant reduced risk of concurrent adenomas and hyperplastic polyps was observed for individuals consuming the highest compared with the lowest intakes of starch (OR 0.73, 95%CI 0.49-1.08). Adjustment for dietary folate equivalents was the main confounder attenuating the relationship between starch and polyp risk. The null associations observed did not differ for risk of any adenoma, multiple adenomas, advanced adenomas, distal adenomas,

proximal adenomas, sessile serrated adenomas, sex, by multivitamin use, BMI categories or smoking status, or among individuals with no prior history of non-adenomatous polyps (data not shown).

Discussion

In this US population, no significant associations were detected between aspects of digestible dietary carbohydrate intake and colorectal adenoma or hyperplastic polyp risk.

Our results are the first to report on the association between these dietary exposures and hyperplastic polyp or sessile serrated adenoma risks, and this study is among the largest to report on colorectal adenoma risk. Our findings contrast with a previous report from the US PLCO cancer screening trial, which identified an inverse association between available carbohydrate intake and prevalent colorectal adenoma risk in men, but not women [12]. The lack of an association between digestible carbohydrate intake and colorectal polyp risk is perhaps surprising, since one of the main hypothesised mechanisms for this association is via hyperinsulinaemia, markers of which have been strongly linked with elevated colon cancer risk [5, 6]. However, glycemic index and glycemic load, which are alternative concepts to quantify the impact of carbohydrate-foods on postprandial glucose responses [19], have also been shown to be unrelated to colorectal cancer and adenoma risk in a systematic review [20]. Moreover, a recent US case-control study documented an unexpected inverse association between IGF-1 receptor levels and colorectal adenoma risk [21], thereby conflicting with earlier evidence of a direct association with colorectal cancer risk [7]. Collectively, the biological and epidemiological evidence to date appear to be contrasting. A global report could only determine that there is limited suggestive evidence that foods containing sugars increase colorectal cancer risk, while the association with other aspects of digestible carbohydrate intake remain unclear [10]. Findings from our study suggest that even if an association with colorectal cancer does exist, digestible carbohydrates do not appear to be of etiological importance in the initiation stages of colorectal tumour development for either the traditional adenoma-carcinoma or serrated polyp pathways.

Our analysis has several strengths, including adequate statistical power due to large size, the ability to account for other potential confounding, and thorough endoscopic investigation of participants at diagnosis minimising the potential for outcome misclassification. One potential limitation of our analyses was the reduced statistical power in subgroup analyses conducted. Further, it is possible that our method of dietary assessment was not

precise enough to detect an association between dietary carbohydrate intake and polyp risk, should one exist. This study was not able to assess glycemic index or glycemic load. As in all epidemiological case-control studies, there are potential limitations such as the possibility of selection bias, reverse causation or recall bias, whereby polyp cases may have altered their carbohydrate intake, or inadvertently contributed to dietary measurement error, resulting in falsely different intakes compared with controls. However, this is unlikely given the benign nature of colorectal polyps, and considering previous analyses of other dietary and lifestyle factors within this population (13) has been able to detect associations with adenoma and/or hyperplastic polyp risk.

In conclusion, results from our large US population-based study do not suggest an etiological role for dietary carbohydrate in early colorectal metaplastic or dysplastic changes.

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Conflicts of Interest

No author has any conflict to disclose.

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Table 1. Descriptive characteristics of individuals in the Tennessee Colorectal Polyp Study, 2003-2010.

		Polyp type			
	Controls	Adenoma only	Hyperplastic polyp only	Both [b]	
Characteristic [a]	*n*= 3,184	*n*= 1,315	*n*= 566	*n*= 394	*P*-value
Study site					
Vanderbilt University Medical Center	2,441 (76.7)	928 (70.6)	360 (63.6)	226 (57.4)	
VA, Tennessee Valley Health System	743 (23.3)	387 (29.4)	206 (36.4)	168 (42.6)	<0.001
Reason for colonoscopy					
Screening	1,838 (57.7)	786 (59.8)	321 (56.7)	216 (54.8)	
Family history	421 (13.2)	148 (11.3)	73 (12.9)	52 (13.2)	
Diagnostic/symptomatic/follow-up	671 (21.1)	275 (20.9)	114 (20.1)	73 (18.5)	
Other	254 (8.0)	106 (8.1)	58 (10.3)	53 (13.5)	0.02
Age, years	57.5 ± 7.6	59.2 ± 7.6	57.5 ± 7.0	58.8 ± 6.9	<0.001
Sex, Male	1,733 (54.4)	913 (69.4)	378 (66.8)	302 (76.7)	<0.001
Educational attainment					
High school or less	689 (21.7)	376 (28.7)	167 (29.7)	146 (37.1)	
Some college	875 (27.6)	330 (25.2)	165 (29.4)	136 (34.5)	
College graduate	710 (22.4)	296 (22.6)	117 (20.8)	60 (15.2)	
Graduate or professional education	897 (28.3)	308 (23.5)	113 (20.1)	52 (13.2)	<0.001
Race, White	2,928 (92.0)	1,179 (89.7)	520 (91.9)	367 (93.2)	0.04
Family history of colorectal cancer	9.1	9.8	8.5	11.3	0.10 [c]
BMI, kg/m^2	27.3	27.8	28.0	28.3	<0.001 [c]
Height, m	1.71	1.72	1.72	1.72	0.05 [c]
Smoking status					
Never	55.1	48.8	32.7	26.8	
Former	34.6	32.7	39.5	30.8	
Current	10.3	18.5	27.9	42.4	<0.001 [c]
Alcohol consumption status					
Never	60.5	57.0	54.4	55.8	
Former	19.8	22.2	22.9	23.9	
Current	19.7	20.8	22.8	20.3	0.01 [c]
Regular exercised in past 10 years	58.8	54.6	52.9	47.5	<0.001 [c]
Ever NSAID Use	51.5	45.7	52.2	49.2	0.009 [c]
Ever Multivitamin Use	55.9	47.3	50.5	47.4	<0.001 [c]
Ever HRT Use (women only)	62.0	59.2	61.5	57.4	0.49 [c]
Postmenopausal (women only)	73.8	73.3	78.2	86.3	0.02 [c]
Daily nutrient intakes					
Total energy (kcal)	1862	1930	1923	1929	0.02 [c]
Red meat (g)	44.0	52.0	55.1	60.5	<0.001 [c]
Total carbohydrate (g/1000kcal)	124.4	123.2	121.8	120.0	<0.001 [d]
Available carbohydrate (g/1000kcal)	114.7	113.9	112.6	111.3	0.006 [d]
Total sugars (g/1000kcal)	59.5	59.0	57.3	57.7	0.06 [d]
Starch (g/1000kcal)	55.1	54.9	55.3	53.6	0.10 [d]
Dietary fiber (g/1000kcal)	9.8	9.3	9.2	8.7	<0.001 [d]
Dietary calcium (mg/1000kcal)	479.9	454.8	448.4	445.7	<0.001 [d]
Dietary folate equivalents (µg/1000kcal)	320.0	305.3	298.0	291.1	<0.001 [d]

BMI: Body mass index; HRT: Hormone Replacement Therapy; NSAID: Non-steroidal anti-inflammatory drug; VA: Veterans Affairs.

[a] Categorical data presented as n (%), continuous data presented as mean ± SD.

[b] Synchronous adenomas and hyperplastic polyps.

[c] *P*-values adjusted for age (5-year categories) and sex. Data presented as least square mean of log transformed data (continuous) or frequencies standardized to age (5-year categories) and sex distribution of controls.

[d] *P*-values adjusted for age (5-year categories), sex and energy intake. Data presented as least square mean of log transformed data (continuous) or frequencies standardized to age (5-year categories) and sex distribution of controls.

Table 2. Aspects of dietary carbohydrate intake and colorectal polyp risk in the Tennessee Colorectal Polyp Study, 2003-2010.

		Polyp type					
	Controls	Adenoma only	Adjusted [a,b] OR (95% CI)	Hyperplastic polyp only	Adjusted [a,b] OR (95% CI)	Both	Adjusted [a,b] OR (95% CI)
Daily nutrient intake categories	*n* (%)	*n* (%)		*n* (%)		*n* (%)	
Total carbohydrate							
Quartile 1	796 (25.0)	362 (27.5)	1.00	161 (28.5)	1.00	133 (33.8)	1.00
Quartile 2	796 (25.0)	347 (26.4)	1.09 (0.90-1.32)	164 (29.0)	1.25 (0.95-1.57)	119 (30.2)	1.13 (0.84-1.52)
Quartile 3	796 (25.0)	309 (23.5)	1.03 (0.84-1.27)	134 (23.7)	1.13 (0.85-1.50)	71 (18.0)	0.75 (0.53-1.07)
Quartile 4	796 (25.0)	297 (22.6)	1.02 (0.82-1.27)	107 (18.9)	1.02 (0.74-1.40)	71 (18.0)	0.94 (0.64-1.36)
P for trend			0.99		0.99		0.32
Available carbohydrate							
Quartile 1	796 (25.0)	359 (27.3)	1.00	155 (27.4)	1.00	126 (32.0)	1.00
Quartile 2	796 (25.0)	345 (26.2)	1.12 (0.92-1.35)	167 (29.5)	1.35 (1.04-1.75)	114 (28.9)	1.14 (0.85-1.55)
Quartile 3	796 (25.0)	306 (23.3)	1.03 (0.84-1.26)	124 (21.9)	1.10 (0.83-1.47)	80 (20.3)	0.88 (0.63-1.24)
Quartile 4	796 (25.0)	305 (23.2)	1.06 (0.86-1.32)	120 (21.2)	1.18 (0.87-1.60)	74 (18.8)	1.01 (0.70-1.46)
P for trend			0.80		0.55		0.71
Total sugars							
Quartile 1	796 (25.0)	382 (29.1)	1.00	173 (30.6)	1.00	129 (32.7)	1.00
Quartile 2	796 (25.0)	312 (23.7)	0.96 (0.79-1.16)	152 (26.9)	1.12 (0.87-1.44)	101 (25.6)	1.07 (0.79-1.46)
Quartile 3	796 (25.0)	312 (23.7)	1.07 (0.87-1.30)	124 (21.9)	1.02 (0.77-1.34)	87 (22.1)	1.10 (0.79-1.53)
Quartile 4	796 (25.0)	309 (23.5)	1.03 (0.84-1.26)	117 (20.7)	0.97 (0.73-1.30)	77 (19.5)	1.00 (0.70-1.41)
P for trend			0.57		0.75		0.92
Starch							
Quartile 1	796 (25.0)	327 (24.9)	1.00	136 (24.0)	1.00	97 (24.6)	1.00
Quartile 2	796 (25.0)	303 (23.0)	0.89 (0.74-1.08)	136 (24.0)	1.01 (0.77-1.33)	115 (29.2)	1.12 (0.82-1.54)
Quartile 3	796 (25.0)	346 (26.3)	1.04 (0.86-1.27)	148 (26.2)	1.12 (0.84-1.48)	110 (27.9)	1.08 (0.77-1.51)
Quartile 4	796 (25.0)	339 (25.8)	1.01 (0.81-1.26)	146 (25.8)	1.18 (0.87-1.60)	72 (18.3)	0.73 (0.49-1.08)
P for trend			0.58		0.24		0.15

[a] Adjusted for energy intake (residuals method and entering log kcal/day into the model), age, sex, study site (Vanderbilt University Medical Centre/VA Tennessee Valley Health System), colonoscopy indication (screening/family history/symptomatic/other), race (White/other), BMI (kg/m^2), smoking status (never/former/current), alcohol consumption (never/former/current), exercise (regular exercise in past 10 years), energy-adjusted dietary calcium intake (mg/d), dietary folate equivalents and red meat intake(g/d).

[b] We had 80% statistical power to detect a significant inverse/direct association in the magnitude of OR 0.80/ OR 1.23 for adenoma only analysis, OR 0.73/ OR1.33 for hyperplastic polyp only analysis, and OR 0.69/ OR 1.43 for both polyp types analysis.