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Association between calcium intake and colorectal neoplasia in Puerto Rican Hispanics

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SUMMARY. Epidemiological studies show that a high calcium intake reduces the risk of colon cancer. The objective was to study the association between calcium intake and colorectal neoplasia in a clinic-based sample of Hispanics adults from Puerto Rico. As part of this cross-sectional study, a total of 433 subjects were recruited from surgery and gastroenterology clinics at the University of Puerto Rico. Calcium intake was estimated using a food frequency questionnaire (FFQ) of calcium rich foods. Socio-demographics, health history and colonoscopy results were obtained from the primary study. Chi square and odds ratios (OR) for colorectal neoplasia (adenomas and/or adenocarcinoma) were calculated for total calcium, dietary calcium and for calcium supplement use. In total, 312 (72%) from 433 participants completed the FFQ and had available colonoscopy results; from these, 196 (62.5%) were free of neoplasia and 117 (37.5%) had colorectal neoplasia. Colorectal neoplasia subjects were older, a lower proportion were females and less educated than those without neoplasia ($p<0.01$). Total calcium intake (median 1180 mg/d) was greater in those free of neoplasia compared to colorectal neoplasia subjects (median 1036 mg/d; $p<0.05$). A high total calcium intake and the use of calcium supplements significantly reduced the OR (crude and age adjusted) for colorectal neoplasia; although these associations lost statistical significance after additionally adjusting for gender and educational level. In conclusion, a high calcium intake and the use of calcium supplements may be protective against colorectal neoplasia, although a greater sample may be required to observe significant associations in a multivariate model.
Key words: Calcium intake, dietary calcium, calcium supplements, adenomas, colorectal neoplasia.

RESUMEN. Asociación entre el consume de calico y la neoplasia colorectal en hispanos puertorriqueños. Los estudios muestran que un alto consumo de calcio reduce el riesgo de cáncer de colon. El objetivo del presente estudio fue estudiar la asociación entre el consumo de calcio y la neoplasia colorrectal en una muestra de hispanos adultos en Puerto Rico. Un total de 433 sujetos fueron reclutados de las clínicas de cirugía y gastroenterología de la Universidad de Puerto Rico. El consumo de calcio fue estimado usando un cuestionario de frecuencia de consumo (CFC) de alimentos ricos en calcio. Los datos socio-demográficos y la colonoscopia se obtuvieron del estudio principal. Se calculó el Ji^2 y la razón de productos cruzados de neoplasia colorrectal por el consumo total, dietético y uso de suplementos de calcio. Un total de 312 (72%) de 433 participantes completaron el estudio; de éstos, 196 (62.5%) estaban libres de neoplasia y 117 (37.5%) tenían neoplasia colorrectal, los cuales eran de mayor edad, con menor proporción de mujeres y menos educados que aquellos sin neoplasia ($p<0.01$). El consumo total de calcio (mediana 1180 mg/d) fue mayor en sujetos sin neoplasia que los sujetos con neoplasia (mediana 1036 mg/d; $p<0.05$). Un alto consumo total de calcio y el uso de suplementos de calcio redujo significativamente la posibilidad (crudo y ajustado por edad) de neoplasia colorrectal; aunque no fue significativo cuando se ajusto también por género y educación. En conclusión, un alto consumo de calcio y el uso de suplementos de calcio pueden proteger contra la neoplasia colorrectal, aunque se requieren más sujetos para ver asociaciones significativas en el modelo multivariado.
Palabras clave: Consumo de calcio, calcio dietético, suplementos de calcio, adenomas, neoplasia colorrectal.

INTRODUCTION

Cancer is the third leading cause of death worldwide. It is estimated that there are 24.6 million people alive who have received a diagnosis of cancer in the last five years (1). Colon cancer is the third most common cause of death from cancer worldwide accounting for an estimated 1,023,256 new cancer cases and 529,026 cancer deaths per year (1). In the United States, it is also the third most commonly diagnosed cancer in both men and women and is the second leading cause of death from cancer (2). In Puerto Rico, colorectal cancer is the second most commonly diagnosed cancer and incidence trends have been shown to be on an increase in recent decades (3).

Several large prospective studies have shown that high intakes of calcium rich foods result in a low relative risk of colon cancer (4-8), large colorectal adenomas (9,10) and recurrent colon cancer (10) in subjects with or without colon cancer history. Pooled analysis of cohort studies, with more than 500,000 subjects followed for up to 16 years, also found that those with the highest intake of calcium and milk had significantly reduced risk of colon cancer (11). However, others have not found a relationship between calcium intake and colon cancer risk (12).

There is scarce data on the association between calcium intake and colorectal neoplasia in Hispanics, particularly in Puerto Ricans. Therefore, the objective of the present analysis was to study the association of calcium intake with colorectal neoplasia in Puerto Rican Hispanic adults.

MATERIALS AND METHODS

Study design and study population

This cross-sectional study recruited subjects from an ongoing clinic-based study of colorectal cancer. Subjects were recruited prospectively from the University of Puerto Rico Comprehensive Cancer Center (UPRCCC) from September 2005-until November 2009. Recruitment for all subjects was performed at the time of colonoscopic examination for several medical indications (screening or evaluation of symptoms) and surgery for colorectal cancer at the UPRCCC. Eligibility criteria of this study included: (1) having a colonoscopy at the UPRCCC for any medical indication, and (2) being 21 years of age or older. Subjects that used intravenous anticoagulation were excluded from the study. This study was approved by the IRB of the Medical Sciences Campus, University of Puerto Rico.

Data collection procedures

A demographic questionnaire was administered to patients at the UPRCCC clinics before performing the colonoscopy. The questionnaire obtained sociodemographic data such as age, sex, education, smoking habits, physical activity, weight, height, history of cancer, family history of cancer and diabetes, among other conditions. Body mass index (BMI) (kg/m^2) was calculated using the reported weight and height of each patient.

Assessment of colorectal neoplasia

Colorectal neoplasia was defined as colorectal adenomas, tubullovillous adenoma and/or colorectal adenocarcinoma. Diagnosis of colorectal neoplasia was obtained from the official colonoscopy report, and histologic confirmation was obtained from the pathology report. Individuals with a normal colon and those with hyperplastic polyps, inflammation and colitis from the colonoscopy results were combined in another category as non-neoplasia and used as the comparison group.

Assessment of dietary intake and supplement use

Data for calcium intake was collected using a self-reported semi-quantitative Food Frequency Questionnaire (FFQ) of foods and beverages rich in calcium, validated in a sample of Puerto Ricans adults (13). This FFQ was mailed out to the subjects, along with pre-paid mailing envelopes. The total daily calcium intake was calculated from the self-administered FFQ of foods rich in calcium. The FFQ consisted of a list of 26 items identified from the baseline food records and from other typical Puerto Rican foods rich in calcium. The FFQ was divided into 3 sections: (1) dairy products and other calcium rich foods, (2) prepared foods rich in calcium and (3) supplements. Each food item included a fixed commonly used portion size. The frequency of each food item was assessed for the previous 6 months, and included 8 frequency responses, ranging from "3 or more servings per day" to "rarely or never". Calcium consumption was summed into three categories: dietary calcium, supplemental calcium and total calcium. Dietary calcium intake was obtained for each subject by multiplying the amount reported for each food, by the response frequency (for example, 2 to 3 times a week = [((2+3)/2)/7] x amount of calcium (mg) for that food). To calculate the calcium content of each of the foods included in the FFQ, the US Department of Agriculture food composition table (USDA Nutrient Data Laboratory and HealthTec Inc) and the Nutritionist Pro analysis (Ayxxa Systems 2008, Stafford, TX) software were used. Calcium intake from supplements was calculated using the same frequency formula as for the dietary calcium intake, but the amount of calcium was taken individually from the manufacture of each supplement. Total calcium was computed by adding the dietary calcium and the calcium from supplements. The FFQ were scanned and processed using the Remark Office OMR® software (Gravic Inc, Malvern, PA).

Study variables

Colorectal neoplasia was categorized as yes or no. Total calcium and dietary calcium were divided into two categories, based on the median calcium consumption. For total calcium intake, median calcium consumption was 1165 mg/d and for dietary calcium intake, median calcium consumption was 971 mg/d. Due to an insufficient range of calcium intake from supplements, it was calculated as use or no use of calcium supplements. Age was categorized as $\leq$ or > than 60 years, which was the median age; educational level was categorized as $\leq$ or > than high school diploma. BMI was categorized as normal if < 25 kg/m^2, overweight if $\geq$ 25 and <29.9 25 kg/m^2 and obese if $\geq$ 30 kg/m^2.

Statistical analysis

Median and 25^{th} and 75^{th} percentile range were computed for all the continuous variables. Wilcoxon and chi-square statistics were used to compare the characteristics of subjects with or without colorectal neoplasia. The Chi-square statistic was used to compare the three calcium consumption variables (total calcium intake, dietary calcium intake and calcium supplement use) by colorectal neoplasia status. For the variables total calcium intake and dietary calcium intake, the reference group was those consuming less than the median baseline amount in each category; for the variable calcium supplements use, those not using calcium supplements were defined as the reference group. Through the use of logistic regression models, crude and adjusted odds ratios (OR) and their 95% confidence intervals (CIs) were calculated to study the magnitude of the association between calcium consumption and colorectal neoplasia. The multivariate models were

adjusted for the significant potentially confounding variables identified in the bivariate analysis, which were age, gender and education. Interaction terms within each model were tested with the likelihood ratio test (14). Analyses were performed using the SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

From the total sample size of 433 subjects in the main study, 321 (74%) mailed back the FFQ, of whom 9 did not have a diagnosis report from the colonoscopy. Therefore, a sample size of 312 subjects was used in this analysis. Of these, 195 (62.5%) were free of colorectal neoplasia and 117 (37.5%) had colorectal neoplasia. Table 1 compares the baseline characteristics of subjects with and without colorectal neoplasia. Subjects with colorectal neoplasia were older ($p<0.01$), with a lower proportion of female participants ($p<0.001$), and with a greater proportion having an educational level of high school diploma or lower ($p<0.01$). The majority of the sample was overweight or obese (43-46% were overweight and 29-32% were obese), sedentary (46-51%) and were non smokers (93%); these results were similar among subjects with and without colorectal neoplasia. Median calcium intake was close to the National Dietary Reference Intake (DRI) of 1000-1200 mg/d recommended for age groups >50 years (15) in subjects free of neoplasia but lower in those with colorectal neoplasia; these differences were statistical significant ($p<0.05$). In addition, those free of neoplasia had a higher use of calcium supplements compared to those with colorectal neoplasia ($p=0.06$). Calcium intake from foods was similar among both groups ($p>0.05$).

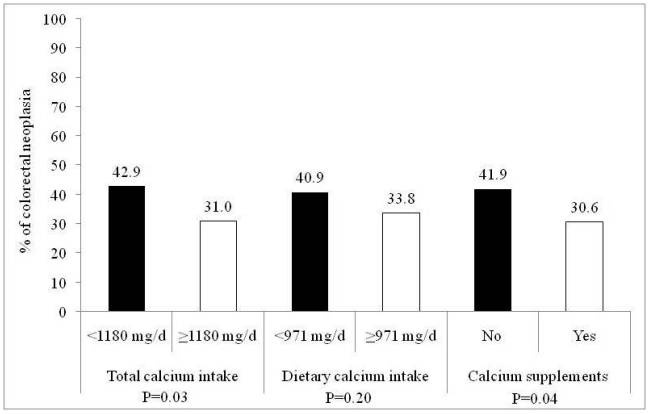
TABLE 1
Study sample characteristics (n=312)

Variable	Free of neoplasia (n=195)[1]	Colorectal neoplasia (n=117)	P value*
Age (y) [2]	59 (48-65)	61 (53-69)	0.01
Gender			
Females	80.0%	56.4%	<0.001
Males	20.0%	43.6%	
Education			
High school diploma or less	48.72%	66.67%	<0.01
Higher than high school diploma	51.28%	33.33%	
BMI (kg/m ^{2}) [2]	28.3 (25.5-31.2)	28.1 (24.7-30.7)	0.54
Normal[3]	21.88%	27.43%	
Overweight[4]	45.83%	43.36%	
Obese[5]	32.29%	29.20%	
Physical activity:			
Sedentary	50.54%	46.15%	0.45
Medium/intense	49.46%	53.85%	
Smoking, current	6.56%	7.53%	0.76
Diabetes	20.10%	25.60%	0.25
Calcium intake			
Total calcium intake[2]	1180 (793-1779)	1036 (672-1515)	0.02
Dietary calcium intake[2]	971 (656-1323)	896 (613-1318)	0.30
Use of calcium supplements	43.50%	31.40%	0.03

[1]Free of neoplasia group included those with inflammation or colitis (n=14), hyperplastic polyps (n=4) and normal colon (n=177)
[2]Median (25th and 75th percentile)
[3]Normal was defined as BMI <25 kg/m^2
[4]Overweight was defined as BMI 25-29.9 kg/m^2
[5]Obese was defined as BMI ≥30 kg/m^2
*Chi-square was performed for categorial variables and student t test for continuous variables

Persons consuming a total calcium intake below the median (<1180 mg/day) had a greater percentage of colorectal neoplasia compared to those consuming an intake equal or above 1165 mg/day (42.9% vs 31.0%, p<0.05) (Figure 1).

FIGURE 1
Diagnosed colorectal neoplasia by calcium intake (n=117). Non adjusted bivariate analysis shows that those with a higher calcium intake have a lower percentage of colorectal neoplasia



Similarly, those consuming a dietary calcium intake below the median (<971 mg/day) also had a greater percentage of colorectal neoplasia (40.9%) compared to those with a dietary calcium intake equal or above 971 mg/d (33.8%), although this difference was not significantly different (p=0.2). Those not using calcium supplements also had higher percentage of colorectal neoplasia (41.9%) in comparison to those using any level of calcium from supplements (30.6%, p<0.05).

Table 2 shows the crude and adjusted ORs (and their 95% CIs) of the association between calcium intake and colorectal neoplasia. Although dietary calcium was not associated to colorectal neoplasia (p>0.05), persons with a high total calcium intake (OR=0.60, 95% CI: 0.37-0.95) and those who used calcium supplements (OR=0.61, 95% CI: 0.38-0.99) were less likely to have colorectal neoplasia (p<0.05). Similar results were observed in age-adjusted analyses. However, after adjusting for age, gender and educational level, which were significant in the bivariate analysis, the associations between total calcium intake and use of calcium supplements were reduced to marginal significance (p=0.10 for total calcium intake and p=0.088 for use of calcium supplements). No significant interactions were observed in the models (p>0.05).

TABLE 2
Association between calcium intake and colorectal neoplasia (n=312)

	Crude		Age adjusted		Multivariate*	
	OR	95% CI	OR	95% CI	OR	95% CI
Total Calcium						
<1180 mg/d	1.00		1.00		1.00	
>1180 mg/d	0.6	(0.37, 0.95)	0.58	(0.37, 0.94)	0.67	(0.41, 1.09)
Dietary Calcium						
<971 mg/d	1.00		1.00		1.00	
>971 mg/d	0.74	(0.47, 1.17)	0.74	(0.47, 1.18)	0.83	(0.51, 1.13)
Supplemental Calcium						
No	1.00		1.00		1.00	
Yes	0.61	(0.38, 0.99)	0.59	(0.36, 0.96)	0.64	(0.39, 1.07)

*Adjusted for age, gender and education

DISCUSSION

In this cross-sectional study, we are the first to show an inverse association between total calcium intake and the use of calcium supplements with colorectal neoplasia in adult Hispanic Puerto Ricans. These associations were significant after adjusting for age, and remained marginally significant after additional adjustment by gender and education. Our results are consistent with several epidemiological studies that have also shown an inverse association between calcium intake and adenomas and colorectal cancer in subjects with or without colon cancer history (5-10,16-18). The study by Flood et al (5) found a significant reduction in the risk of colon cancer with the highest quintile of calcium intake (831 mg/d) compared to the lowest quintile (412 mg/d) in women (RR 0.74, 95% C.I. 0.56-0.98). Similarly, Kampman et al (16) also found a significant reduction in colon cancer risk with the highest quintile of dietary calcium intake (1700 mg/d in men and 1330 mg/d in women) compared to the lowest quintile (681 mg/d in men and 546 mg/d in women) in predominantly white individuals (RR: 0.7, 95% C.I. 0.5-0.9 in men and RR: 0.6, 95% C.I. 0.4-0.9 in women). Furthermore, Peters et al

(18) also found in predominantly non-Hispanic Whites, that the highest quintile of total calcium intake (>1767 mg/d), reduced the risk of adenoma by 12% compared to those in the lowest quintile (<731 mg/d) (OR: 0.88; 95% CI: 0.76, 1.02; P for trend <0.04). In the present study, we show similar results in a group of Hispanics men and women, whereas those consuming the highest calcium intake (=1180 mg/d) had a 42% reduced risk of colorectal neoplasia (age-adjusted OR: 0.58, 95% CI 0.37-0.94). Also, similar to our study, a pooled analysis of 10 cohort studies found that a total calcium intake (>800 mg/d) significantly reduced the risk of colorectal cancer compared to a low calcium intake (500 mg/d) (11). However, this was not found in predominantly white women from the Nurses' Health study (19).

Studies have found that combining calcium intake from dietary sources as well as from supplements reduces even more the risk of colon cancer. Flood et al (5) showed that a high intake of calcium from dietary sources plus calcium from supplements resulted in even further risk reduction (RR = 0.54, 95% CI, 0.37-0.79) compared with low consumption of both sources of calcium. Similarly, Kearney et al (17) also found a lower colon cancer risk with the highest quintile of total calcium intake (age and energy adjusted RR: 0.58, 95% CI, 0.39-0.87) compared to the highest quintile of dietary calcium intake (age and energy adjusted RR: 0.61, 95% CI, 0.40-0.91). In the present study, we found a similar risk reduction of colorectal neoplasia when calcium intakes were pooled from dietary sources and supplements (age-adjusted OR: 0.58, 95% CI 0.37-0.94) compared to dietary sources only (age-adjusted OR 0.74, 95% CI 0.47-1.18).

The beneficial effect of calcium on colorectal cancer has been found to be more effective from calcium rich foods as opposed to calcium from dietary supplements (20). Other investigators have found that both sources reduce the risk of colorectal cancer (5,21). In the present study, the magnitude of the reduction in the age adjusted OR for colorectal neoplasia was greater and statistically significant for the use of calcium supplements compared to calcium intake from foods, which was not significant. Similar findings were reported by Peters et al (18), whereas those using calcium supplements (>1200 mg/d) had a 27% decrease in adenoma risk than for nonusers of supplements (OR: 0.73; 95% CI: 0.56-0.91).

A large body of evidence shows that calcium intake prevents colorectal neoplasia by several potential mechanisms. Calcium could protect against colon cancer by its role in cellular division and the regulation of cellular proliferation and differentiation, apoptosis, angiogenesis, and cell cycle regulation (22) mediated by the Ca-sensing receptor (23). In fact, clinical studies have shown a decrease in cell proliferation, differentiation, and apoptosis in colonic epithelia with calcium consumption (24,25). Low levels of ionized intracellular calcium promote colonic cellular proliferation but high levels have the opposite effect (26). Calcium intake (and vitamin D intake) increases the level of apoptosis in the colorectal epithelium, most significantly in those with adenomas (27). Alternatively, dietary calcium may also contribute by precipitating cytotoxic surfactants, such as secondary bile acids and fatty acids, in the colonic lumen (28). The insoluble salts of calcium are less toxic to the colonic mucosa. Calcium supplementation studies have found reduced bile acids in bile and feces in patients with resected adenocarcinoma (29), although others have not found this (30).

Studies of migrants indicate that colorectal cancer is especially sensitive to changes in the environment (31). Indeed, the risk of colorectal cancer is higher among first-generation Puerto Rican immigrants in the US compared to their native country (32). One environmental factor that has received much attention in relation to colorectal cancer is diet. Monroe et al (33) showed that Mexico-born subjects had a 7% higher mean calcium intake and a lower rate of colorectal cancer, compared to US born Mexican Americans. Although no studies have assessed the change in calcium intake in Puerto Ricans with adoption of a western diet, studies have shown that more acculturated Puerto Rican elders in the US have lower rice and beans consumption and higher intake of simple sugars (34). In addition, a systematic review of the relationship between acculturation and diet among Latinos in the United States also found that acculturation leads to a decrease in the consumption of fruit, rice, beans, and an increase in the consumption of sugar and sugar-sweetened beverages (35). More research is needed to study the dietary pattern changes associated with the high rates of colorectal cancer in Puerto Ricans living in Puerto Rico and in the United States.

This study had several limitations. The assessment of calcium intake was performed after the colonoscopy (about 1 year later), which may have changed calcium intake in this group and may have lead to alterations in the association if individuals with colorectal neoplasia were informed about the benefits of calcium consumption and/or modified their diet into a "healthier" diet which included calcium-rich products. However, the food questionnaire took into account the consumption of calcium during the preceding months, which should help to standardize acute changes in calcium dietary consumption. Nevertheless, it does not reflect long term calcium intake. Second, the study had a relatively small sample size, a fact that may have limited the power of our study to detect statistical significance in some of the associations evaluated. Nonetheless, we were able to identify statistically significant and marginally significant differences according to total and supplemental calcium consumption. Third, the FFQ was self-reported and sent by mail, which may have also affected the participants' response or understanding on how to complete the FFQ. However, we and others have experience with the use of self-reported calcium food questionnaires and

have shown a strong correlation between self-reported and actual nutrient consumption (r=0.5-0.9) (13,36). In addition, vegetable, fruit and fiber consumption were not assessed in the present study, and meta-analyses have shown that they may have a role in preventing against colorectal neoplasia (37,38). One of the strengths of the study is the use of a validated FFQ to estimate calcium intake (13), which has been shown to be a robust instrument to assess long term calcium intake in the population (39). An additional strength of this investigation was the assessment of colorectal neoplasia by colonoscopic evaluation to cecum.

In conclusion, a higher consumption of total calcium intake and the use of calcium supplements may reduce the risk of colorectal neoplasia among Puerto Rican Hispanics. This is of vital importance as colorectal cancer screening have been historically low for US and Puerto Rican Hispanics (38%), hence, dietary nutrients that may reduce the risk of colorectal neoplasia may have a high impact in decreasing the burden of disease among this minority population. Future studies should examine the protective role of dietary calcium as well as other nutrients in calcium rich foods, such as vitamin D on colorectal cancer in a larger sample size. Given the strong evidence of the protective effect of calcium intake on colorectal neoplasia from most epidemiologic, basic, and interventional studies, it is recommended that individuals meet the national recommended levels for calcium intake, which is 1200 mg/d for age groups >50 years.

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