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# Type 2 diabetes mellitus and colorectal neoplasia risk in Hispanics: a case–control study

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ABSTRACT

*Aims:* There is inconclusive evidence regarding the potential link between diabetes mellitus (DM) and colorectal cancer (CRC). Associations between type 2 DM and colorectal neoplasia (CRN; colorectal cancer and/or adenomas) have not been well studied in Hispanics, an ethnic minority at high risk for type 2 DM. This study aims to assess the association between type 2 DM and CRN in Hispanics.
*Methods:* Hispanics with incident CRN and colonoscopy-negative controls from 2005 to 2009 were evaluated. Diagnosis of type 2 DM was established by previous medical diagnosis and/or use of DM treatments. Unconditional logistic regression was performed to estimate odds ratios for the association between type 2 DM and CRN.
*Results:* A total of 451 participants (mean age 61.1 ± 11.9 years, 59.6 % men) were evaluated (218 with incident CRC, 77 with colorectal adenomas, and 156 colonoscopy-negative controls). The prevalence of type 2 DM in this study was 25.1%. After adjusting for potential confounding variables, women with type 2 DM were 2.74 (95% CI: 0.94–7.99) times more likely to have CRN and 4.83 times more likely to present with proximal colonic CRN (95% CI: 1.25–18.58) than women without type 2 DM. No statistically significant associations were found between type 2 DM and CRN among men.
*Conclusions:* An increased odds for CRN and proximal location of CRN was observed among Hispanic women with type 2 DM. Since DM is a highly prevalent disease in this population, adherence to routine CRC screening is of outmost importance.



## 1. Introduction

Colorectal cancer (CRC) is the 2nd leading cause of cancer death in the United States (US) (SEER, 2014). In Puerto Rico (PR), it is the 2nd most commonly diagnosed cancer and the leading cause of cancer death among men and women. During 2006–2010, the age-adjusted CRC incidence rate was 52.0 and 34.8 per 100,000 men and women, respectively (Tortolero-Luna, Zavala-Zegarra, Pérez-Ríos, et al., 2013). Age-adjusted mortality rates during this period were 21.0 per 100,000 men and 13.0 per 100,000 women (Tortolero-Luna et al., 2013). Diabetes mellitus (DM) is a common cause of morbidity and mortality in both the US and PR. According to the Behavioral Risk Factor Surveillance System (BRFSS), the prevalence of DM in the US during 2010 was 8.7% (9.0% in men and 8.7% in women) (CDC, 2010). However, the prevalence of DM in PR during the same year was 12.8% (12.1% in men and 13.4% in women) showing that there is a higher burden of this disease among Puerto Rican Hispanics (PRH) (CDC, 2010).

Studies have reported inconclusive results on the association between DM and CRC (Khaw et al., 2004; Larsson, Orsini, & Wolk, 2005; Limburg, Anderson, Johnson, et al., 2005; Limburg, Vierkant, Fredericksen, et al., 2006). Individuals with DM have been reported to have a 30–60% increased risk of developing CRC compared to people

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Precis for use in the Table of Contents: A significant increased risk for colorectal neoplasia (CRN) and proximal location of CRN was observed among Hispanic women with type 2 DM. Since DM is a highly prevalent disease among Hispanics, adherence to routine colorectal cancer screening are of outmost importance.

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without DM (Limburg et al., 2006; Will, Galuska, Vinicor, & Calle, 1998). A possible explanation for the observed association between DM and CRC may be related to dietary patterns and sedentary lifestyles resulting in increased insulin levels, which may in turn stimulate the growth of colorectal malignancies (Bowers, Albanes, Limburg, et al., 2006; Nilsen & Vatten, 2001). Type 2 DM and CRC share multiple modifiable risk factors including: high-energy intake, high animal fat intake, elevated consumption of refined carbohydrates, and elevated body mass index (BMI). These factors have also been associated with insulin resistance and hyperinsulinemia (Giovannucci, Harlan, Archer, et al., 2010). Hyperinsulinemia can occur either endogenously, due to insulin resistance during the early stages of DM, or exogenously as a result of insulin administration or insulin secretagogues (Giovannucci et al., 2010).

Most of the studies that have evaluated the association between type 2 DM and CRC have been performed in Caucasian and Asian populations. There is limited data available on Hispanic populations, including PRH. We hypothesized that individuals with type 2 DM have increased odds of colorectal neoplasia (adenomas and CRC; CRN) compared to those without type 2 DM. In this study, we pooled data from three studies to assess the association between type 2 DM and CRN and to examine this association by neoplasia subsite while controlling for potential confounding factors. Confirmation of DM as a risk factor for CRN may have important implications for CRC screening strategies, especially in PR where the prevalence of DM is high and adherence to CRC screening is low.

## 2. Materials and methods

### 2.1. Study population

This analysis was based on pooled data from three IRB-approved studies in two study centers: the VA Caribbean Healthcare System and the Puerto Rico Medical Center facilities. Data from the following studies were included in our analysis: *Type 2 DM and CRN Risk in Hispanics: A Case–Control Study* (51 cases and 78 controls), *Epidemiology of Loss of Imprinting (LOI) in Colorectal Cancer* (164 cases and 77 controls), and *Familial Colorectal Cancer in Puerto Rico: A Feasibility Study* (80 cases and 1 control). Study participants included in this study were individuals with medical and pathological information up to October 11, 2011. Informed consent was obtained from all participants.

Study participants visited the designated study centers for colonoscopies due to routine screening, symptoms, and/or referrals by gastroenterologists and colorectal surgeons. A total of 1045 participants older than 21 years were recruited; 451 subjects were included in the study (156 controls, 77 adenomas, and 218 CRC) and 594 were excluded. Cases must have had a CRN diagnosis confirmed by biopsy during the study period from January 1, 2005 to December 31, 2009. Control subjects were individuals without a personal history of CRN and a normal result in the colonoscopy and/or surgery reports. CRN was defined as cancer or adenomas of any size with serrated, tubular, villous, or tubulovillous features.

Cases and controls were recruited consecutively using convenience sampling. All participants included in this analysis were Hispanics as defined by the participant's self-reported heritage, lineage, or place of birth. We excluded the following participants: diagnosis date outside of the 2005–2009 study period (n = 119); recruitment colonoscopy date outside the 2005–2009 study period (n = 15); genetic syndrome diagnosis (including relatives) (n = 77); possible genetic syndrome diagnosis (including relatives) (n = 93); diagnosed with other cancers (n = 82); incomplete data and/or no pathological documentation (n = 186); incomplete colonoscopy (n = 10); colitis (n = 3); non-Hispanic origin (n = 3); no information on DM (n = 4); and age at diagnosis of DM (<25 years) (n = 2). Epidat 3.1 (Xunta de Galicia, Pan American Health Organization and World Health Organization) was used to estimate the sample size needed (n = 520) for a case–control study to detect the association using the following parameters: a 1:1 control:case ratio, an estimated odds ratio (OR) of 2.0 (Larsson et al., 2005; Limburg et al., 2005), an estimated prevalence of DM in the control group of 12.4% (CDC, 2008), a significance level of 5%, and a statistical power of 80%.

### 2.2. Variables

Medical history, colonoscopy, and pathology reports were obtained from medical records. Colonoscopy reports provided information regarding the presence of colorectal polyps and/or cancer (size, number, location, and appearance), completeness to cecum, and bowel preparation at the time of the procedure. Information regarding CRN location and histological type was obtained from pathology reports. For this analysis, CRN locations were classified as proximal colon (cecum, ascending colon, hepatic flexure, and transverse colon) or distal colon (splenic flexure, descending colon, sigmoid colon, recto-sigmoid junction, and rectum). Diagnosis of type 2 DM was established by previous medical diagnosis and/or use of DM treatments. Similar to Flood et al. (Flood, Strayer, Schairer, & Schatzkin, 2010), diagnosis of DM before age 25 was considered type 1 DM and all others type 2 DM.

The Collaborative Family Registries for Colorectal Cancer (Colon CFR) questionnaire was used to obtain sociodemographic and clinical data from study participants (Newcomb, Baron, Cotterchio, et al., 2007). The following variables were analyzed: gender (male vs. female), median age (<61 years vs. ≥61 years), education (<12 years vs. ≥12 years), health insurance (public vs. private/Medicare), marital status (married vs. unmarried), type 2 DM diagnosis (yes vs. no), family history of DM (yes vs. no), and family history of CRC (yes vs. no). The lifestyle characteristics analyzed included: fruit intake (≤1 time/week, 2–4 times/week, and ≥5 times/week), dark green leafy vegetable intake (≤1 time/week, 2–4 times/week, and ≥5 times/week), meat intake (≤1 time/week, 2–4 times/week, and ≥5 times/week), use of fiber supplements (yes vs. no), aspirin use (<3 times/week vs. ≥3 times/week), non-steroidal anti-inflammatory drugs (NSAIDs) use (<3 times/week vs. ≥3 times/week), BMI (<30.0 kg/m$^2$ vs. ≥30.0 kg/m$^2$), time spent in physical activity (≤1 hour/week, 2–4 hours/week, and ≥5 hours/week), alcohol consumption (<2 drinks/week, 2–6 drinks/week, and ≥7 drinks/week), and smoking status (<100 cigarettes in their lifetime vs. ≥100 cigarettes in their lifetime). We evaluated age, education, health insurance, family history of CRC, family history of DM, diet, fiber supplements, aspirin, NSAIDs, obesity, alcohol, smoking, and physical activity as potential confounders. Gender was also evaluated as an effect modifier variable and the study center as an adjusting variable.

### 2.3. Statistical analysis

Sociodemographic, clinical, and lifestyle characteristics in cases and controls were described using frequency distributions for categorical variables and summary measures for quantitative variables. Two-sided tests were used to assess comparability of study groups: the chi-square test or Fisher's exact test was used for categorical variables and the Student's t test or Mann–Whitney test to compare quantitative variables. Unconditional logistic regression models were used to estimate the OR with 95% confidence of CRN, colorectal adenomas, and CRC location in relation to type 2 DM while controlling for demographic characteristics, lifestyle factors, and medical history. Comparisons between DM and colorectal subsite included proximal and distal colon locations. Potential confounding variables were selected for assessment a priori on the basis of their hypothesized association with DM and CRN. The presence of a confounder was empirically assessed by entering potential covariates into a logistic regression model one at a time and comparing the adjusted and unadjusted ORs. The final models included covariates