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## THE ASSOCIATION BETWEEN DIABETES, INSULIN USE, AND COLORECTAL CANCER AMONG WHITES AND AFRICAN AMERICANS

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### Abstract

Colorectal cancer and diabetes are common diseases that share many risk factors. It has been hypothesized that diabetes is a risk factor for colorectal cancer. We used two large population-based case-control studies from North Carolina to determine whether diabetes and/or insulin therapy were associated with colon cancer and/or rectal cancer (defined as cancer of the sigmoid colon, rectosigmoid, or rectum) and whether this association differed by race. Cases and matched controls from the North Carolina Colon Cancer Studies I and II were interviewed about demographics, dietary factors, diagnosis of diabetes, and use of medications to treat diabetes. Odds ratios and 95% confidence intervals were estimated using unconditional logistic regression. Colon and rectal cancer cases reported a higher prevalence of diabetes than their respective control groups. Compared to Whites without diabetes, Whites with diabetes had an adjusted odds ratio of 1.40 (95% CI 0.93, 2.12) for colon cancer and 1.38 (95% CI 1.00, 1.90) for rectal cancer. Diabetes was not associated with colon or rectal cancer among African Americans [OR 1.17 (95% CI 0.81, 1.70) and OR 0.75 (95% CI 0.44, 1.28), respectively]. Among Whites with diabetes, insulin use was positively associated with rectal cancer. The same association was not seen for African American diabetics using insulin however the number of African Americans using insulin was small. In sum, diabetes was positively associated with rectal cancer and approached a positive association with colon cancer among Whites. No association was present among African Americans. Insulin use was also positively associated with rectal cancer among Whites.

### Keywords

Colon Cancer; Rectal Cancer; Diabetes; Insulin; Risk Factors

### INTRODUCTION

Colorectal cancer is one of the most common cancers in the United States (1). Diabetes is also highly prevalent in the United States. These diseases share many risk factors (2–4). There is also evidence suggesting that diabetes is an independent risk factor for colorectal cancer; a meta-analysis showed an overall positive association (2). The mechanism underlying the

relationship between type II diabetes, colon, and rectal cancer may be via insulin resistance, a condition that is associated with elevated levels of insulin and insulin-like growth factors (IGFs). Insulin and IGF-1 stimulate cellular proliferation; IGF-1 can inhibit apoptosis (2,4–6). Enhanced proliferation of mutated cells or failure to eliminate aberrant cells may contribute to colorectal carcinogenesis (4,7). We have previously shown that elevated insulin may contribute to the development of adenomas, the precursors to most colorectal cancer (8).

Yang et al (3) demonstrated that chronic insulin therapy increased the risk of colorectal cancer among type II diabetes patients. In their study, colon and rectal cancers were combined. However, colon and rectal cancers may have distinct risk factors. For example, research from the European Prospective Investigation into Cancer and Nutrition Study demonstrated that the risk of colon cancer was associated with increased waist-hip ratio (9) and decreased physical activity (10), but these factors were not associated with rectal cancer (9,10). In addition, race may be a potential effect measure modifier. Previous research has shown heterogeneity between the risk of colorectal cancer and diabetes drugs by race (11,12).

We investigated the potential association between diabetes and colon and rectal cancer by race. We also performed an exploratory analysis to assess insulin therapy as a risk factor for rectal cancer.

## MATERIALS AND METHODS

### Study Population

The North Carolina Colon Cancer Studies I and II (NCCCS I and NCCCS II) were population-based case-control studies conducted in 33 counties of North Carolina. Cases were identified using the rapid case ascertainment system of the North Carolina Central Cancer Registry. Patients with a first diagnosis of histologically confirmed invasive adenocarcinoma of the colon (cecum through sigmoid colon) between October 1996 and September 2000 were classified as potential cases in the NCCCS I. The NCCCS II included patients with a first diagnosis of histologically confirmed invasive adenocarcinoma of the sigmoid colon, rectosigmoid, or rectum (hereafter collectively referred to as rectal cancer) between May 2001 and September 2006. Patients with cancer of the sigmoid colon were included in the NCCCS II in order to increase enrollment and because it may be difficult to distinguish between rectosigmoid and sigmoid cancers. Individuals with sigmoid cancers were therefore included in both studies. Additional eligibility requirements were: aged 40–80 years, residence in one of the 33 counties, able to give informed consent and complete an interview, had a driver's license or identification card issued by the North Carolina Department of Motor Vehicles (if under the age of 65), and had no objections from the primary physician in regards to contacting the individual.

Controls, identified and sampled during the respective study dates, were selected from two sources. Potential controls under the age of 65 were identified using the North Carolina Department of Motor Vehicles records. For those 65 years and older, records from the Center for Medicare and Medicaid Services were used. Controls were matched to cases using randomized recruitment strategies (13,14). Recruitment probabilities were done using strata of 5-year age, sex, and race groups.

### Data Collection

Interviews were conducted by trained nurse interviewers at participant's residence or another convenient location. Participants were asked questions about demographics, lifestyle, diet, and medical history. In both the NCCCSs I and II, participants were asked, "Has a doctor ever told you that you had diabetes?" The NCCCS II inquired further about type and duration of medications used by those who reported having diabetes. Participants were asked to report

their weight one year prior to diagnosis (cases) and interview (controls), in order to capture weight prior to any changes resulting from the cancer in the cases.

## Data Analysis

We utilized logistic regression modeling and included offset terms to account for the randomized recruitment strategy (13,14) as well as a variable that accounted for the matching factors. Heterogeneity of the association by race was assessed using likelihood ratio tests. Race was found to be an effect measure modifier in the NCCCS II (likelihood ratio test  $p$ -value<0.10). Therefore, we included an interaction term for diabetes and race in all models. The 10% change-in-estimate approach was used to assess the following variables for confounding: highest level of education, smoking status, physical activity, Body Mass Index (BMI) one year prior to diagnosis/interview, nonsteroidal anti-inflammatory drug (NSAID) use, family history of colorectal cancer, health insurance, access to care (regular provider/ distance from home), colorectal cancer screening, alcohol intake, energy intake, calcium intake, fiber intake, vegetable consumption, and meat consumption. BMI, family history, energy intake, calcium intake, and screening were found to confound the association and were retained in the final model. The assumption of linearity was assessed and if it was not met, categorical indicator variables were used.

We conducted additional analyses of the relationship between rectal cancer and insulin therapy among diabetics using the same method described above, except with insulin use as the exposure. These analyses were only performed among participants of the NCCCS II because questions about diabetes treatment were not included in the NCCCS I. We conducted an exploratory analysis, first excluding participants who began their insulin therapy less than a year prior to their diagnosis (cases) or interview (controls) ( $n=5$ ). We also performed the analysis excluding those with short durations of insulin use [less than one year ( $n=19$ ) and less than two years ( $n=25$ )].

## RESULTS

Among those who were eligible, the reasons for not being interviewed were refusal (NCCCS I: 14% cases, 36% controls; NCCCS II: 17% cases, 26% controls), untraceable/not able to be reached (NCCCS I: 7% cases, 2% controls; NCCCS II: 8% cases, 18% controls), and physician denial (NCCCS I: 7% cases). A total of 1691 individuals (643 cases, 1048 controls) completed interviews for the NCCCS I, giving study cooperation rates (interviewed/(interviewed +refused)) of 84% (Whites: 89%, African Americans: 79%) for cases and 63% (Whites: 64%, African Americans: 61%) for controls. Response rates (interview/eligible) for cases and controls were 72% (Whites: 77%, African Americans: 68%) and 61% (Whites: 63%, African Americans: 59%), respectively. For the NCCCS II, 2061 interviews were completed (1045 cases and 1016 controls). Study cooperation rates were 81% (Whites: 81%, African Americans: 82%) for cases and 68% (Whites: 68%, African Americans: 65%) for controls, and the response rates were 74% (Whites: 76%, African Americans: 70%) for cases and 56% (Whites: 58%, African Americans: 46%) for controls. In order to conduct race-specific analyses we excluded individuals who self-reported their race as "other" ( $n=53$ ). We also excluded participants who did not answer the question regarding diabetes ( $n=23$ ).

There was a slightly higher prevalence of diabetes reported among cases compared to controls in both studies (20.88% and 18.17% versus 17.72% and 15.99%, for NCCCSs I and II, respectively) (Table 1). Controls were older than cases (NCCCS I: 66.06 versus 63.69 years; NCCCS II: 63.86 versus 61.88 years). In both studies, cases were more overweight or obese than controls, and cases had higher daily mean caloric intake than controls.

The results of the logistic regression models evaluating the association between diabetes and colon and rectal cancer are shown in Table 2. The adjusted odds ratios [95% confidence interval (CI)] for the Whites with diabetes compared to Whites without diabetes were 1.40 (0.93, 2.12) for colon cancer and 1.38 (1.00, 1.90) for rectal cancer. The respective adjusted odds ratios (95% CIs) examining colon and rectal cancers were 1.17 (0.81, 1.70) and 0.75 (0.44, 1.28) comparing African Americans with diabetes to the referent group.

A previous analysis performed with the NCCCS II study population found a decreased risk of rectal cancer with thiazolidinedione use for African Americans (12). If thiazolidinedione use decreases the risk of rectal cancer among African Americans, possibly including individuals taking this drug in the analysis will bias the results. We assessed whether exclusion of thiazolidinedione drug users affected the NCCCS II's results. The association was unchanged for Whites. For African Americans, the point estimate changed but the 95% CI was wide, continuing to reflect no association (OR 1.01, 95% CI 0.54, 1.88).

We examined the association between insulin use and rectal cancer starting with all diabetics in the NCCCS II, except for those who began insulin treatment less than one year prior to diagnosis (cases) or interview (controls) reasoning that the exposure was too recent to lead to colorectal cancer. The 95% CI included the null among both Whites and African Americans although the point estimate for Whites was elevated in a positive direction (Table 3). Also, a short duration may not result in a long enough period of insulin exposure to increase the risk of developing rectal cancer. Therefore, we excluded individuals with less than one year of insulin use. Insulin use was positively associated with rectal cancer among Whites but not African Americans (Table 3). To ensure that we sufficiently excluded a period of use that effectively removed those with too short of a duration of insulin exposure, we performed the analysis again, excluding individuals with less than two years duration of insulin use. The results were relatively unchanged (Table 3).

## DISCUSSION

Using population-based case-control studies, we found diabetes was positively associated with rectal cancer among Whites. The 95% CI for the association between diabetes and colon cancer among Whites included the null but the association was in the same direction as that of rectal cancer. These results are similar to those demonstrated previously. In a meta-analysis examining diabetes and colorectal cancer, the summary risk ratio was 1.30 (95% CI 1.20, 1.40) [1.43 (95% CI 1.28, 1.60) for colon and 1.33 (95% CI 1.14, 1.54) for rectal cancers] (2).

We found no association between diabetes and colon and rectal cancer for African Americans. To our knowledge, previous research has not examined this association by race. It is possible that diabetes is not a risk factor for colorectal cancer among African Americans. Previous research showed that thiazolidinedione drugs may protect against colorectal cancer (12) and when individuals using these drugs were removed from the analysis the point estimate shifted closer to the null from the protective direction. However, the 95% CI was wide and still included the null.

Diabetes may be associated with colorectal neoplasia because of elevated insulin levels. Therefore, we examined the association between insulin therapy and rectal cancer among diabetics. Among Whites, the association was strongest when we excluded participants who had used insulin for less than 2 years. Similarly, Yang et al. (3) demonstrated that the risk for colorectal cancer increased with duration of use. Thus, those with shorter duration may not have had a long enough period of insulin exposure to affect carcinogenesis.

There was no association between insulin use and rectal cancer for African Americans. The number of African Americans who reported insulin use is small leading to imprecise results. Further research among African Americans is needed.

This research has certain strengths. The studies were population-based, and the data were collected in-person by trained interviewers. The data included detailed questions about many potential colorectal cancer risk factors, which was useful in identifying potential confounding variables. One limitation is that the information on diabetes and insulin use was self-reported and has not been validated in our study populations. Also, the number of African Americans available for additional analysis on insulin use was small. Finally, the study may be subject to selection bias. Participation rates for both studies are lower among controls than cases; it is possible that potential controls who refused to participate are different from the controls who did participate.

In conclusion, we demonstrated that the relationships between diabetes and both colon and rectal cancer among Whites were in the positive direction. Among White diabetics, use of insulin was associated with rectal cancer. Neither diabetes nor insulin use were associated with colon or rectal cancer among African Americans.

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**Table 1**  
 Characteristics of the North Carolina Colon Cancer Studies I and II study populations by case status (N=3676)

Characteristics	NCCCS I		NCCCS II	
	Cases (N=637)	Controls (N=1044)	Cases (N=1007)	Controls (N=988)
Diabetes	133 (20.88)	185 (17.72)	183 (18.17)	158 (15.99)
African American Race	290 (45.53)	434 (41.57)	255 (25.32)	168 (17.00)
Mean Age (SD) *	63.69 (10.07)	66.06 (9.49)	61.88 (10.22)	63.86 (9.77)
Female Sex	307 (48.19)	529 (50.67)	436 (43.30)	400 (40.49)
Smoking Status <sup>†</sup>				
Current	105 (16.56)	187 (17.91)	182 (18.09)	141 (14.36)
Former	277 (43.69)	412 (39.46)	447 (44.43)	463 (47.15)
Never	252 (39.75)	445 (42.62)	337 (37.48)	378 (38.49)
Family History <sup>‡</sup>	126 (19.81)	102 (9.83)	119 (12.93)	97 (10.40)
Highest Level of Education <sup>†</sup>				
HS degree or less	409 (64.21)	600 (57.53)	543 (53.92)	426 (43.12)
Some college	122 (19.15)	224 (21.48)	245 (24.33)	254 (25.71)
College degree or more	106 (16.64)	219 (21.00)	219 (21.75)	308 (31.17)
NSAID Use <sup>§</sup>				
Never	73 (11.46)	74 (7.09)	244 (24.23)	167 (16.92)
Occasional	254 (39.87)	316 (30.27)	440 (43.69)	410 (41.54)
Frequent	310 (48.67)	654 (62.64)	323 (32.08)	410 (41.54)
Colorectal Cancer Screening <sup>  </sup>	277 (43.49)	632 (60.54)	388 (39.31)	684 (70.23)
Body Mass Index (BMI) <sup>†</sup>				
Normal (<25 kg/m <sup>2</sup> )	142 (22.87)	278 (27.63)	226 (23.32)	285 (29.69)
Overweight (25–29.9 kg.m <sup>2</sup> )	255 (41.06)	401 (39.86)	350 (36.12)	382 (39.79)
Obese (≥30 kg/m <sup>2</sup> )	224 (36.07)	327 (32.50)	393 (36.12)	293 (30.52)
Mean Energy Intake (kcal/day) (SD) <sup>*†</sup>	2041.69 (862.75)	1795.16 (687.83)	2447.08 (1228.20)	2209.92 (967.80)
Mean Calcium Intake (mg/day) (SD) <sup>*†</sup>	791.22 (469.69)	850.37 (495.49)	844.80 (418.18)	844.93 (406.27)

\* SD: standard deviation

<sup>†</sup> In the NCCCS I data were missing for: smoking (n=3), family history (n=7), education (n=1), BMI (n=54), energy intake (n=9), calcium intake (n=53); In the NCCCS II data were missing for: smoking (n=7), family history (n=142), NSAID use (n=1), screening (n=34), BMI (n=66); energy intake (n=16), calcium intake (n=16)

<sup>‡</sup> Family history of colorectal cancer was defined as a first degree relative having been diagnosed with colorectal cancer.

<sup>§</sup> Nonsteroidal anti-inflammatory drug (NSAID) use was defined as “frequent” for use of NSAIDs at least 15 times/month, “occasional” for use less than 15 times/month, and “never” for no use.

<sup>||</sup> Colorectal cancer screening was defined as having undergone one of the following tests for screening purposes: colonoscopy, sigmoidoscopy, barium enema, or fecal occult blood test.



**Table 2**  
Adjusted odds ratios (ORs) for colon cancer (NCCCS I) and rectal cancer (NCCCS II) by presence of diabetes and race

	NCCCS I (N=1577)				NCCCS II (N=1765)			
	N Cases	N Controls	OR	95% CI	N Cases	N Controls	OR	95% CI
White, No Diabetes	276	505	1.00		555	653	1.00	
African American, No Diabetes	204	297	1.11	0.86, 1.43	162	100	1.27	0.94, 1.71
White, Diabetes	54	69	1.40	0.93, 2.12	111	100	1.38	1.00, 1.90
African American, Diabetes	72	100	1.17	0.81, 1.70	42	42	0.75	0.44, 1.28

\* Adjusted for age (5 year age groups), sex (man, woman, -), colorectal cancer screening (yes, no), energy intake (quartiles), calcium intake (quartiles), BMI (normal, overweight, obese), family history of colorectal cancer (yes, no), and offset



Adjusted odds ratios\* (ORs) and 95% Confidence Intervals for rectal cancer (NCCCS II) by insulin use and race

Table 3

	Began insulin use ≥ 1 year ago <sup>†</sup> (N=307)				Duration of insulin use ≥ 1 years <sup>‡</sup> (N=293)				Duration of insulin use ≥ 2 years <sup>§</sup> (N=287)			
	N Cases	N Controls	OR	95% CI	N Cases	N Controls	OR	95% CI	N Cases	N Controls	OR	95% CI
White, No Insulin Use	76	75	1.00		76	75	1.00		76	75	1.00	
African American, No Insulin Use	36	30	0.76	0.40, 1.46	36	30	0.73	0.37, 1.42	36	30	0.74	0.38, 1.44
White, Insulin Use	40	26	1.74	0.92, 3.31	35	20	2.11	1.05, 4.23	34	16	2.53	1.21, 5.28
African American, Insulin Use	13	11	0.94	0.33, 2.71	13	8	1.46	0.46, 4.61	13	7	1.81	0.55, 6.00

\* Adjusted for age (5 year age groups), sex (man, woman), NSAID use (never, occasional, frequent), calcium intake (quartiles), family history of colorectal cancer (yes, no), education (HS degree or less, some college, college degree or more), and offset

<sup>†</sup> Analysis includes all subjects except those that began insulin treatment less than one year prior to diagnosis (for cases) or interview (for controls)

<sup>‡</sup> Analysis includes all subjects except for those that used insulin therapy for less than one year

<sup>§</sup> Analysis includes all subjects except for those that used insulin therapy for less than two years