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DIABETES AND COLORECTAL CANCER SURVIVAL

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Abstract: Type 2 diabetes mellitus (T2DM) and colorectal cancer are causes of morbidity and mortality worldwide. T2DM and colorectal cancer share common risk factors related to westernized lifestyles, including high body mass index and central adiposity, low physical activity, cigarette smoking, and diets characterized by low intake of fruit and vegetables and high intake of red and processed meats and refined grains and sugars. Epidemiologic studies show that T2DM is quite convincingly associated with higher risk of colorectal cancer incidence and mortality, even after accounting for their shared risk factors. Whether T2DM is related to poorer prognosis after colorectal cancer diagnosis is less understood and controversial, although some larger studies suggest poorer prognosis among patients with T2DM. The impact of diabetes treatments, such as metformin or insulin, on colorectal cancer risk also is characterized poorly. This review describes studies on the association of diabetes and its treatments with colorectal cancer mortality, incidence, and survival. Potential clinical and biological explanations for these associations are explored.

Introduction

Colorectal cancer is the third most common cancer globally with an estimated number of 1.9 million new cases in 2020 . The etiology of colorectal cancer involves a complex interplay between genetic and environmental determinants. Currently, around 140 genetic variants have been identified by genome-wide association studies (GWAS) explaining ~12% of the variability in colorectal cancer risk . However, limited research has been conducted to understand the interaction between genetic and environmental/lifestyle risk factors on the risk of colorectal cancer. Understanding how genetic variation may modify the association of environmental and lifestyle exposures with colorectal cancer risk may potentially uncover novel biological pathways underlying disease etiology and contribute to the development of prevention strategies.

Type 2 diabetes (T2D), the most common form of diabetes, is an established risk factor for colorectal cancer . The biological mechanisms that underlie the association between T2D and colorectal cancer risk are not fully understood but likely entail exposure to hyperinsulinemia and insulin resistance as well as hyperglycemia, which often precede onset of T2D . However, it is possible that other, yet-to-be recognized, molecular pathways mediate the T2D-colorectal cancer relationship.

Gene-environment interaction (GxE) studies have been employed to investigate whether genetic variants modify the association of diet, lifestyle, and drugs with colorectal cancer . A previous GxE analysis of diabetes and risk of colorectal cancer was limited by small sample size and was focused on candidate genes . To provide further insights into the molecular pathways of diabetes with colorectal cancer risk, we undertook a large-scale genome-wide GxE analysis that tested for interactions between common and rare variants and diabetes in 31,318 colorectal cancer cases and 41,499 controls.

Diabetes is a chronic metabolic condition characterized by the failure of the pancreas to create sufficient insulin or by the inability of the body to use the insulin it produces. Type 1 diabetes mellitus (T1DM) usually presents during the period from childhood to young adulthood and comprises approximately 5-10 % of the disease . T1DM is fundamentally the result of pancreatic islet β-cell dysfunction, whereby the pancreas fails to produce sufficient insulin to stimulate the uptake of glucose from circulation to target tissues. T1DM patients require lifelong insulin treatment. The causes of T1DM are poorly understood, but evidence suggests that a complex interplay between genetic predisposition, epigenetics, and environmental factors may underscore the autoimmune reaction related to the disease .

Type 2 diabetes mellitus (T2DM) comprises approximately 90 % of the disease and is usually diagnosed in adults. In the early stages of T2DM, the peripheral depots for glucose no longer react to insulin—a state referred to as insulin resistance—and high levels of glucose remain in circulation (hyperglycemia). The pancreas initially responds to the excess glucose by producing an overabundance of insulin, creating hyperinsulinemia. Often with prolonged T2DM, the β-cells in the pancreas will fail, resulting in decreased endogenous insulin levels and the eventual requirement for insulin treatment. Risk factors for T2DM are relatively well-understood and largely relate to western lifestyles, including overweight and obesity (as indicated by the body mass index (BMI) and central adiposity), lack of sufficient physical activity, high fat/carbohydrate diet, low fruit and vegetable diet, high alcohol intake, and cigarette smoking . T2DM also appears to have an underlying genetic etiology with approximately 60 genetic loci identified so far from genome wide association studies (GWAS) . The other nonmodifiable risk factors for T2DM include race, age, family history of T2DM, and history of gestational diabetes . Concurrent with secular trends for obesity among children and adolescents , T2DM is now diagnosed increasingly in younger age groups .

Worldwide in 2010, an estimated 285 million adults aged 20-79 years had diabetes . By 2030, the number of adults globally with diabetes mellitus is projected to increase to 439 million, with developing countries facing a larger burden of that increase . On a worldwide perspective, high blood glucose is the third leading risk factor for early mortality and diabetes is the ninth leading cause of death . In the United States, diabetes is estimated to affect almost 26 million adults, including 7 million people who are undiagnosed . Diabetes is the seventh leading cause of death in the United States where the lifetime probability of developing the disease may be as high as 1 in 3 . The rapid worldwide increase in the prevalence of T2DM has largely mirrored the growing prevalence of overweight and obesity . Historically, diabetes has been long appreciated as a major cause of macrovascular and microvascular diseases, such as heart disease, stroke, kidney failure, and blindness . Men and women with diabetes also have been estimated to die 5-14 years sooner than men and women without the disease . Recent studies, particularly in the past 10-15 years, also suggest higher risks of cancer incidence and mortality for certain cancer organ sites among people with diabetes .

Diabetes and Colorectal Cancer Mortality—Recent Studies

In the 2005 meta-analysis mentioned earlier , the summary RR for the association between diabetes and colorectal cancer mortality was 1.26 (95 % CI 1.05-1.5), quite similar to the

estimate for diabetes in relation to colorectal cancer incidence. Several recent studies also have examined this link . For the purpose of this review, mortality studies refer to cohort studies where a group of study participants who are free of colorectal cancer at baseline are followed forward in time for death from colon or rectal cancer and rate ratios are calculated by comparing colorectal cancer death rates among participants with and without diabetes, while adjusting for other factors. In the CLUE II prospective cohort of ~18,000 mostly Caucasian adults, treated diabetes at baseline, compared with not reporting diabetes, was associated with higher risk of colorectal cancer mortality (RR 3.26; 95 % CI 1.56-6.82), after multivariable adjustment that included BMI and smoking . In another largely Caucasian study of more than one million U.S. adults enrolled in the Cancer Prevention Study-II (CPS-II), self-reported diabetes at baseline was associated with modestly higher risks of death from colon cancer (women: RR 1.18; 95 % CI 1.04-1.33; men: RR 1.15; 95 % CI 1.03-1.29) but not associated with risk of death from rectal cancer . The Emerging Risk Factors Collaboration pooled data from 820,900 mostly Caucasian participants representing 97 prospective studies . Diabetes at baseline, defined from a combination of self-reports, medication use, and/or fasting glucose, was associated with higher risk of colorectal cancer death among men and women combined (RR 1.4; 95 % CI 1.2-1.63). In another pooled effort of European studies, the DECODE collaboration combined data from ~44,000 men and women who had results for 2-hour oral glucose tolerance tests. Participants with known diabetes (defined as a previous diagnosis of diabetes or taking antihyperglycemic medications), compared with participants with normoglycemia, had about a twofold higher risk of death from stomach and colorectal cancer mortality combined (RR 2.07; 95 % CI 1.21-3.51).

Diabetes also is associated with colorectal cancer mortality in non-Caucasian populations. Lam and colleagues combined data from 36 prospective studies comprised of ~367,000 participants (74 % from Asia) and identified a modest, although not quite statistically significant, association with colorectal cancer mortality (RR 1.32; 95 % CI 0.98-1.78). One limitation to this analysis was the relatively short average follow-up period of only approximately 4 years. When analyses were restricted to cohorts with 8 or more years of follow-up, a statistically significant association was identified (RR 1.5; 95 % CI 1.03-2.18) . From these recent studies, consistent with the earlier meta-analysis , diabetes is consistently associated with colon cancer mortality among both men and women and among Caucasian and Asian population groups. Whether associations differ by subsite in the colon or rectum is unresolved. More research is needed on the potential impact of diabetes on colorectal cancer mortality in other racial/ethnic groups. Mortality studies reflect the combined influence of diabetes on colorectal cancer incidence and survival. Other studies, based on cancer incidence and survival data, are needed to disentangle the distinct impact of diabetes on these two outcomes. Incidence and survival studies are discussed next.

Diabetes and Colorectal Cancer Incidence—Recent Studies. From early 2011 through October 2012, at least six meta-analyses were published on the topic of diabetes and colorectal cancer risk . the overall summary RRs for the association between diabetes and colorectal cancer incidence is usually around 1.3. Generally, the meta-analyses identified relatively consistent associations across subgroups when stratified by sex and subsite in the colorectum. The relative consistency of associations across subsites in the colon and rectum may be somewhat surprising given that higher associations are usually observed for colon cancer than for rectal cancer with obesity and physical inactivity . Curiously, several meta-analyses also noted that case-control studies generated moderately higher summary estimates than did cohort studies . These somewhat higher estimates could be due to recall bias in case-control studies, whereby case

patients were more likely to accurately report themselves as having diabetes (or not having diabetes) than control participants, perhaps because of better awareness of their health/illness status due to recent contacts with medical providers. Alternatively, the slightly lower estimates derived from cohort studies could be due to nondifferential misclassification of diabetes status during the course of follow-up. Prospective cohort studies with regularly updated diabetes information are particularly important to reduce this form of misclassification.

Whether the association of diabetes with colorectal cancer differs by sex is perhaps a more interesting question than the homogeneity identified by the meta-analyses indicates. First, associations between BMI and colorectal cancer are usually higher among men than among women . Yet, the 2005 meta-analysis by Larsson and colleagues identified nearly identical summary RRs for diabetes and colorectal cancer in men (RR 1.29; 95 % CI 1.15-1.44) and women (RR 1.33; 95 % CI 1.23-1.44) ; importantly, most studies in the meta-analysis included BMI as a covariable. After the publication of that meta-analysis , several studies suggested the RR was higher among men than among women , a trend that is consistent with known associations with BMI . In the most recent of these studies, in the CPS-II Nutrition cohort of ~155,000 U.S. adults with regularly updated self-reported diabetes status over the course of a 15-year follow-up period, T2DM was associated with a 24 % higher risk of colorectal cancer incidence among men (RR 1.24; 95 % CI 1.08-1.44) and there was a null association observed among women (RR 1.01; 95 % CI 0.82-1.23) . The authors speculated that these gender differences might relate to differential use of metformin and degree of glucose control among men compared with women. In the past few years, some studies have shown the opposite trend; that is, the association of diabetes with colorectal cancer incidence is higher among women than among men or similar associations have been shown by strata of gender . These inconsistent findings between studies are difficult to resolve but may be due to chance.

Some studies have assessed the association between categories of T2DM duration and colorectal cancer incidence . Motivation for these analyses is driven, at least in part, by the natural history of T2DM. If hyperinsulinemia or closely related factors are key mediators for this association, risk of colorectal cancer might peak with intermediate duration T2DM, when insulin levels are highest, and then diminish with long term T2DM as the pancreatic β-cells fail to produce sufficient insulin . In both the CPS-II Nutrition study and in the study by Limburg and colleagues , colorectal cancer risk increased linearly with longer duration T2DM in men, in contrast to expectations suggested by the hyperinsulinemia hypothesis. The authors noted that their results emphasized the need for vigilant adherence to recommended guidelines for colorectal cancer early detection among men with longstanding T2DM. Both of these studies also reported consistently null associations with T2DM duration among women . In contrast, other cohort studies among women reported higher RRs for the intermediate duration categories than either of their respective shorter or longer duration categories, providing indirect support that hyperinsulinemia is potentially a marker or mediator of this link. Given population level improvements in glycemic control among men and women with diabetes in the United States , it may be informative to compare earlier studies of T2DM duration and colorectal cancer risk, when glycemic control was generally worse, to future, more modern cohorts, where glycemic control might be reasonably expected to be improved. One might hypothesize, for instance, that in future cohorts with good glycemic control, more frequent null associations for diabetes and colorectal cancer will be observed.

It is unclear if associations between diabetes and colorectal cancer incidence differ by strata of race/ethnicity . As summarized in the meta-analysis by Sun and Yu, diabetes was quite convincingly associated with colorectal cancer risk among Caucasian (based on 18 studies; RR 1.31; 95 % CI 1.26-1.36) and Asian (based on 9 studies; RR 1.27; 95 % CI 1.17-1.39) population samples, but no associations were observed in the very limited data drawn from black (based on 2 studies; RR 1.07; 95 % CI 0.85-1.33) and Native Hawaiian (based on 1 study; RR 0.89; 95 % CI 0.62-1.27) population samples. Clearly, more work is needed from non-Caucasian and non-Asian study populations, especially because of the marked differences in the prevalence of diabetes in the United States that are noted when comparing non-Hispanic whites (7.1 %) to other racial/ethnic groups, such as African Americans (12.6 %) and Hispanics (11.8 %) . As highlighted in detail elsewhere , Asia is at the epicenter of the diabetes epidemic with approximately 60 % of all diabetes patients worldwide. Asian populations tend to develop T2DM at lower levels of obesity and at younger ages . Although speculative, it seems plausible that T2DM may explain some of the recent trends for higher colorectal cancer incidence and mortality rates in Asia in the past few decades .

These general observations for diabetes and colorectal cancer incidence/mortality are supported by more direct measures of diabetes-related biomarkers. Blood glucose and insulin levels are quite consistent risk factors for colorectal cancer incidence, regardless of T2DM status. A 2008 meta-analysis of epidemiologic studies suggested that biomarkers of glucose control, as measured by hemoglobin A1c or other combinations of fasting/nonfasting blood glucose levels, are associated with higher risk of colorectal cancer (highest vs. lowest categories, RR 1.18; 95 % CI 1.07-1.31) . Many of the studies included in the meta-analysis excluded participants who reported T2DM. A relatively small study , nested within a large European cohort, suggested that hemoglobin A1c, but not self-reported T2DM, was associated with higher risk of colorectal cancer. More recent studies on hemoglobin A1c and colorectal cancer incidence have generally suggested modest associations , and not all studies have been statistically significant . C-peptide, a marker of endogenous insulin secretion, also was associated with risk of colorectal cancer incidence in the meta-analysis (highest vs. lowest categories of C-peptide, RR 1.35; 95 % CI 1.13-1.61) . Recent studies of C-peptide and insulin levels with colorectal cancer risk from prospective cohort studies largely support this summary RR with the exception one recent null study . Similarly, serum levels of insulin-like growth factor-1 (IGF-1), part of the insulin/IGF axis, are associated with colorectal cancer incidence . Collectively, these results suggest that impaired glucose control and hyperinsulinemia are associated with increased colorectal cancer risk. The specific molecular perturbations that occur in a high glucose/insulin/IGF environment are explained in detail elsewhere , but briefly, they relate to enhanced capacity for cancer cells to proliferate, avoid apoptosis, promote inflammation, and invade surrounding tissues and metastasize .

Diabetes and Colorectal Cancer Survival—Recent Studies

In contrast to the rather compelling evidence from mortality and incidence studies, data concerning the impact of diabetes on colorectal cancer survival are less convincing. For this review, survival studies refer to cohorts of colorectal cancer patients who are followed from the time of their cancer diagnosis to death (or other clinically meaningful endpoints) and rates of the outcome are compared among patients with and without diabetes to calculate a RR. As summarized in , several epidemiologic studies have examined this association. For background, the 5-year relative survival among colorectal cancer patients from 1999-2006 in the United

States was 67 %, although there is wide variability according to stage of disease (e.g., 90 % for localized disease compared with only 12 % for patients with distant metastatic disease) . Similar to the situation described above for early studies on incidence and mortality, some earlier survival studies were probably underpowered to detect small RRs and follow-up time was often brief. Additionally, many earlier studies—and even some recent studies—lack data on important confounders, including BMI and physical activity.

A recent meta-analysis addressed the question of whether diabetes was associated with short-term survival among patients with colorectal cancer . The meta-analysis identified four studies on short-term survival, defined as death within 30-days of colorectal cancer surgery. Summary analyses were not conducted in the meta-analysis due to between-study heterogeneity. Of the four studies, the largest was conducted using Veteran's Affairs data among ~32,000 mostly Caucasian men and women wherein a RR of 1.19 (95 % CI 1.04-1.36) was noted for 30-day mortality among patients with diabetes relative to patients without diabetes . Little and colleagues reported 8 % and 2 % (p value: 0.02) 30-day mortality among patients with and without diabetes, respectively, among 727 patients undergoing hepatic resection for metastatic colorectal cancer . Underlying comorbidities and susceptibility to postoperative infections among patients with diabetes may have led to these higher 30-day mortality rates.

Several studies have examined the impact of diabetes on all-cause mortality among colorectal cancer survivors . As summarized in , these studies generally suggest higher risks of death from all causes among colorectal cancer patients with diabetes compared with colorectal cancer patients without diabetes , although a few studies suggest null associations . Because BMI is a strong prognostic indictor for colorectal cancer worsened survival , and because BMI is clearly associated with diabetes status, studies that were able to include BMI in their statistical models offer the only mechanism to assess the adiposity-independent impact of diabetes on colorectal cancer survival. Among studies with available BMI data, Meyerhardt and colleagues reported higher risks of all-cause mortality among 3,549 patients with TNM stage II or III colorectal cancer (hazard ratio (HR) 1.42; 95 % CI 1.22-1.67). Similarly, recent results from the CPS-II Nutrition cohort conducted among 2,278 colorectal cancer patients with invasive, nonmetastatic disease identified a HR of 1.53 (95 % CI 1.28-1.83) for all-cause mortality among patients with diabetes compared to patients without diabetes, after adjusting for BMI, stage, physical activity, red meat intake, and other factors . Two relatively small studies suggested no influence of diabetes on colorectal cancer survival , but their null results may have been simply due to inadequate statistical power.

Less understood are the specific causes of death that contribute to the higher risks of long-term mortality among colorectal cancer patients with diabetes. To date, only a few studies have examined colorectal cancer specific mortality among colorectal cancer patients with and without diabetes. In a hospital-based study of ~2,700 colorectal cancer patients, diabetes compared with not having diabetes was associated with higher risk of colorectal cancer-specific death (RR 1.21; 95 % CI 1.02-1.43) . In the CPS-II Nutrition cohort, including 2,278 colorectal cancer patients, a RR of 1.29 (95 % CI 0.98-1.7) was identified for colorectal cancer specific mortality . Two registry-based studies of 9,395 colorectal cancer patients and 1,194 colorectal cancer patients , however, reported null associations between diabetes and colorectal cancer-specific death. In several of these studies , the risk estimates for colorectal cancer-specific mortality were lower

than risk estimates for all-cause mortality, suggesting that other causes of death may be relevant. Indeed, in the CPS-II Nutrition cohort a greater than twofold increased risk of cardiovascular disease mortality was observed (RR 2.16; 95 % CI 1.44-3.24) . Although associations with cardiovascular disease mortality have not been presented elsewhere, the magnitude of the association is consistent with known associations between diabetes and cardiovascular disease mortality in noncancer patient populations .

There are several potential explanations for the observed associations between T2DM and higher risk of all-cause mortality among patients with colorectal cancer; many of the same mechanisms that may impact on incidence may also impact on prognosis, as described earlier. Patients with poorly controlled or advanced T2DM are at increased risk of macrovascular and microvascular complications . Therefore, the excess mortality risk observed in colorectal cancer patients with diabetes might relate to concurrent illnesses and comorbidities other than cancer. This idea is supported by observations of the greater than twofold increased risk of cardiovascular mortality among colorectal cancer survivors who have diabetes . Other explanations for poorer prognosis among patients with T2DM and colorectal cancer include differences in cancer treatment, response to treatment, and treatment-related toxicity. Studies have shown that patients with colorectal cancer and T2DM were treated less aggressively , experienced more severe chemotherapy-related adverse effects , and had poorer response to treatment than did those without diabetes .

Results

In our primary analysis we found that the association between diabetes and colorectal cancer risk was modified by variants on chromosome 8q24.11 within the SLC30A8 gene based on the 3-d.f. joint test, with rs3802177 being the genetic variant showing the most significant effect.

Discussion

In summary, our results suggest that variation in genes related to immune function and regulation of the insulin receptor and PI3K activity may modify the association between diabetes and colorectal cancer risk. These results provide novel insights into the biology underlying diabetes and colorectal cancer relationship. Further experimental studies are warranted to understand the mechanisms by which these genes play a role in linking diabetes and colorectal cancer development.