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EDITORIAL

Is Diabetes a Risk Factor for Colorectal Cancer?

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Throughout the world, adoption of a Western life style has paralleled an increase in the incidence of both type 2 diabetes mellitus and colorectal cancer. This is perhaps not surprising, as the major environmental determinants for type 2 diabetes, including body mass index (BMI), central obesity, physical inactivity, and Western dietary patterns are remarkably consistent with the constellation of risk factors that have been identified for colorectal cancer. Perhaps what has been less clear is whether diabetes, independent of these other risk factors, influences the risk of colorectal cancer. If so, such a finding would have potential implications for more vigorous lifestyle modification or cancer screening of individuals with type 2 diabetes. Moreover, understanding the mechanistic basis for such an association may provide fresh insights into the pathogenesis of both conditions.

A number of early studies reported a higher risk of colon cancer among individuals with diabetes. These studies were limited by small sample size, reliance on death certificates and autopsies for endpoint ascertainment, and inability to control for important confounders including BMI and physical inactivity [1–4]. As such, it was difficult to determine if the association between diabetes and colorectal cancer was merely a reflection of the greater prevalence of known lifestyle risk factors for cancer among those with diabetes. However, more recent high quality prospective studies have shown a significant, albeit more modest association between diabetes and risk of colorectal cancer even after accounting for shared risk factors for both diseases. One of these large, prospective studies, the Cancer Prevention Study, included 866,793 individuals, 15,847 of whom had diabetes [5]. Over 13 years of follow-up, an increased risk of colorectal cancer, even after accounting for BMI and physical inactivity, was noted in men with diabetes (RR = 1.30; 95 % CI 1.03–1.65) and a modest non-significant elevation was seen in women with diabetes (RR = 1.16; 95 % CI 0.87–1.53). In the Nurses' Health Study, diabetes was similarly associated with an increase in the risk of colon cancer after adjustment for BMI and physical activity (multivariate-adjusted RR = 1.49; 95 % CI 1.09–2.06) [6]. By 2005, several case–control and cohort studies had examined this relationship, which was systematically reviewed by Larsson et al. [7]. In their meta-analysis of 6 case–control and 9 cohort studies encompassing more than 2 million participants, a history of diabetes was associated with an increased risk of colorectal cancer (summary RR = 1.30, 95 % CI 1.20–1.40). The results did not vary according to study design, geographic origin (United States vs. Europe), sex, or cancer site.

However, not all subsequent studies have been consistent. In the Cancer Prevention Study II Nutrition Cohort, Campbell et al. [8] found a moderate increase in risk of colorectal cancer among men with diabetes (pooled RR = 1.24; 95 % CI 1.08–1.44), but no such association among women. Inoue et al. [9] using the Japan Public Health Center-Based Prospective Study, observed no increase in risk of colon cancer with diabetes after excluding cancer cases diagnosed within 5 years of diagnosis of diabetes (HR = 1.19, 95 % CI 0.91–1.55 for men and 1.14, 95 % CI 0.70–1.87 for women). Similarly, data from the Japan

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Collaborative Cohort (JACC) showed no statistically significant increased risk of colorectal cancer with diabetes (IRR = 1.37, 95 % CI 0.95–1.96) [10]. The reason for these contrasting results are not entirely clear, but could be related to differences in the populations studied. For example, the risk factors and possibly the underlying pathogenesis of type 2 diabetes may differ in Japan compared to the West.

In light of such inconsistent results, two updated systematic reviews in this issue of *Digestive Diseases and Sciences* by Deng et al. [11] and Sun and Yu [12] are particularly timely. In Deng et al.'s pooled analysis of 6 case–control and 18 cohort studies, which included more than 3 million participants, diabetes was associated with a RR for colorectal cancer of 1.26 (95 % CI 1.20–1.31), with no significant heterogeneity among studies ($Q = 26.11$; $P_{\text{heterogeneity}} = 0.296$; $I^2 = 11.9$ %). These results were consistent according to the study design, sex, or cancer site. Similarly, in the meta-analysis by Sun and Yu, which included 11 case–control and 28 cohort studies, diabetes was associated with a RR for colorectal cancer of 1.29 (95 % CI 1.23–1.35). However, in their analysis, there was significant heterogeneity between the studies ($Q = 62.89$, $p = 0.007$, $I^2 = 39.6$ %). Consistent relative risks were observed in subgroup analyses by sex, study type, and cancer site. Based upon these analyses, there is now more reasonable certainty that type 2 diabetes is independently associated with colorectal cancer.

However, the exact mechanism by which type 2 diabetes influences carcinogenesis still remains unclear. There are a number of leading hypotheses, including a growing body of evidence that supports a causal role for insulin and insulin-like growth factors (IGF), which each play important and complementary roles in metabolism and growth and are both known to be elevated in type 2 diabetes. Mechanistically, a number of observations suggest a role for insulin and IGF in colorectal neoplasia. First, both insulin and IGF-1 receptors are expressed on the colonic epithelial cells of normal and cancer tissues; activation of IGF-1 receptors inhibits apoptosis and allows progression through the cell cycle [13–16]. Second, in addition to its direct mitogenic effect, insulin may prime cells to the effects of specific growth factors by influencing farnesylation of *ras* [17], a key step in the localization of *ras* in the plasma membrane that is required for its transforming capabilities. Insulin increases the pool of farnesylated *ras* protein [18, 19], thereby priming the cellular response of growth factors dependent on the *ras* pathway. Mutations that lead to overactivation of *ras* proteins play a role in progression of adenomas to cancer and have been found in over 50 % of colorectal cancers [20]. Third, animal data directly implicate insulin in tumor progression. Insulin has been shown to stimulate the growth of aberrant crypt foci [21] and to increase the number and size of tumors in azoxymethane-treated rats [22].

Human data also support a mechanistic role for insulin and the IGF pathway and risk of colorectal cancer. First, several studies have shown an increased risk of colorectal adenoma and cancer among people with acromegaly, a condition characterized by significantly elevated growth hormone and IGF-1 [23, 24]. Second, in average-risk individuals, a few cohort studies have shown an association between increased levels of circulating pre-diagnosis IGF-1 and risk of adenoma and cancer [25, 26]. In the Physician's Health Study, C-peptide levels, a measure of endogenous insulin secretion, was a better predictor of colon cancer than the metabolic syndrome [27]. Similarly, surrogate markers of hyperinsulinemia, such as post-prandial C-peptide and non-fasting insulin, are more strongly associated with colorectal cancer than fasting insulin concentration, a more specific marker for insulin resistance [28, 29]. Last, the benefit of long-term follow-up in the Nurses' Health Study revealed that the observed increase in risk of colon cancer associated with diabetes was limited to individuals who were recently diagnosed, with colon cancer risk significantly attenuated 15 years after the diagnosis [6]. This pattern also supports a predominant pathophysiologic role for hyperinsulinemia, which is more evident early in the course of diabetes. However, the Sun and Yu meta-analysis, which included 6 studies with information on duration of diabetes, did not observe a significant difference in the association between short duration (<10 years) or long duration (≥10 years) of diabetes in relation to colorectal cancer risk. This would suggest that risk for colorectal cancer persists despite the pancreatic beta cell dysfunction and associated endogenous hypoinsulinemia that characterizes late-stage diabetes. Alternatively, the use of exogenous insulin in late-stage diabetes could offset lower levels of endogenous insulin. Deng et al. examined the effect of exogeneous insulin among 4 of their included studies and did observe an increased risk of colorectal cancer (summary RR = 1.61, 95 % CI 1.18–1.35). However, this data should be viewed with the caveat that there was significant heterogeneity between the studies ($P_{\text{heterogeneity}} = 0.014$).

In contrast with the 2005 meta-analysis by Larsson et al. that did not examine the risk among Asians and African Americans, the two studies by Deng et al. and Sun and Yu were able to assess the risk of colorectal cancer within subgroups of patients with diabetes defined by these specific race/ethnicity. Compared to Europeans, Deng et al. observed a somewhat weaker association between diabetes and colorectal cancer among Asian populations (RR = 1.19; 95 % CI 1.11–1.28), where insulin resistance may play a more predominant role than hyperinsulinemia in the pathophysiology of type 2 diabetes [30]. In contrast, the

Sun and Yu meta-analysis, which included a larger number of studies, did not find a significant difference in risk comparing Asians with Whites. Moreover, there was no association between diabetes and risk of colorectal cancer among African-Americans, although this finding was based on only 2 studies.

In conclusion, the two new meta-analyses by Deng et al. and Sun and Yu further strengthen the evidence base that type 2 diabetes is associated with risk of colorectal cancer. Although the exact mechanism remains unclear, much data support a key role for hyperinsulinemia. Studies focused on racially diverse populations that examine the specific effect of lifestyle modification, screening, and surveillance in patients with diabetes are now needed to assess how to best translate these findings into public health recommendations.

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