Original Study

Colorectal Cancer: Histopathologic Differences in Tumor Characteristics Between Patients With and Without Diabetes

Anurag Sharma,[1] Hanyann Ng,[2] Abhishek Kumar,[1] Kunal Teli,[1] Jeewanjot Randhawa,[1] James Record,[1,3] Michael Maroules[4,5]

Abstract

Diabetes is associated with a greater risk and poorer clinical outcome in colorectal cancer. A review of 534 patients with colorectal carcinoma found worse histopathologic features at diagnosis in patients with diabetes in comparison with patients without diabetes. These histopathologic features are associated with poor prognosis in colorectal cancer and support the fact that diabetes is associated with a poorer prognosis in colorectal cancer.

Background: Current literature suggests that diabetes is a possible predictor of risk and worse outcome in colorectal cancer (CRC). The objective of this study was to explore if there are histopathologic differences in CRC between populations with and without diabetes. **Patients and Methods:** Retrospective analysis was done on 534 patients with CRC. Patients were divided into diabetic and nondiabetic subgroups. Data were collected for lymphovascular invasion, tumor location, depth invasion, staging, level of differentiation, histologic type, and presence of tumor components (mucinous, signet ring, or neuroendocrine). **Results:** Univariately, patients with diabetes had deeper tumor invasion, greater lymphovascular invasion, and higher TNM staging (OR and 95% CI, 2.06 [1.37, 3.10], 2.52 [1.74, 3.63], and 2.45 [1.70, 3.52], respectively; $P < .001$). Covariate adjustment retained the significant effect of diabetes on tumor characteristics ($P < .005$). Multivariable adjustment significantly linked diabetes with signet ring cell carcinoma (log odds, 11.40 ± 5.28; $P = .03$) and tumor components (log odds, 0.58 ± 0.25; $P = .02$). Patients with diabetes with hyperlipidemia had more well-differentiated tumors (log odds, −0.96 ± 0.47; $P = .04$). Transverse tumors were more common in patients with diabetes (log odds, 1.74 ± 0.72; $P = .02$). **Conclusion:** Patients with diabetes had worse histopathologic CRC features. Hyperinsulinemia, insulinlike growth factor receptor activation, and hyperglycemia in diabetes can activate mitogenic pathways stimulating proliferation, invasion, angiogenesis, and metastasis. Future research is needed to identify responsible pathways for targeted therapy and to examine the role of better glycemic control and treatment in patients with CRC and diabetes.

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Introduction

Colorectal cancer (CRC) is the third most diagnosed cancer in men and women in the United States, with incidences of 54.0 per 100,000 and 40.2 per 100,000, respectively.[1] CRC is also the third most common cause of cancer-related death.[2] It is associated with a number of genetic, dietary, and lifestyle-related risk factors. Nonmodifiable risk factors include age, family history of CRC, and hereditary syndromes such as nonpolyposis cancer and adenomatous

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[1]Department of Internal Medicine, Mount Sinai School of Medicine (St Joseph's Regional Medical Center) Program, Paterson, NJ
[2]St George's University School of Medicine, Grenada, West Indies
[3]Department of Internal Medicine, New York Medical College, Valhalla, NY
[4]Department of Hematology and Oncology, Department of Medicine, St Joseph's Regional Medical Center, Paterson, NJ
[5]Department of Hematology and Oncology, Seton Hall University, School of Health and Medical Sciences, South Orange, NJ

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Address for correspondence: Anurag Sharma, MD, Department of Internal Medicine, Mount Sinai School of Medicine (St Joseph's Regional Medical Center) Program, 703 Main St, Paterson, NJ 07503
E-mail contact: sharmaan@sjhmc.org, sharmaanurag.rk@gmail.com

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polyposis.[3] Lifestyle-related factors include diets high in fat but low in fiber, lack of exercise and physical activity, obesity, alcohol consumption, and diabetes mellitus.[4-6]

There are 25.8 million people with diabetes and 79 million people with prediabetic metabolism in the US population.[7] The annual cost of diagnosed diabetes, including direct medical costs and loss of productivity, is 245 billion dollars.[7] Diabetes increases the relative risks of liver, pancreatic, endometrial, colorectal, breast, and bladder cancers.[8] Specifically, patients with diabetes have 1.2- to 1.5-fold greater risk for developing CRC.[8] In addition to having an increased risk for CRC, patients with diabetes also have worse disease-free, overall, and cancer-specific survival.[8-11]

The interaction between diabetes and colorectal carcinogenesis is complex and not completely understood. Diabetes can influence the process of carcinogenesis through various mechanisms. Most tumor cells express insulin and insulinlike growth factor (IGF)-1 receptors.[12] Stimulation of these receptors can occur in diabetes, owing to the presence of hyperinsulinemia secondary to both endogenous production and exogenous administration of insulin.[13-17] Activation of these receptors is capable of stimulating downstream mitogenic signaling pathways resulting in proliferation and progression of cancer.[18,19] Hyperglycemia is another possible mechanism for promotion of tumorigenesis in diabetes.[15] ATP generation in glycolysis predominant tumor cells requires high glucose levels.[20] This, in fact, forms the basis of positron emission tomographs.[8] Thus, having constant high glucose levels in patients with diabetes might help in the progression of cancer cells. Chronic inflammation associated with diabetes and obesity via various mitogenic cytokines may be a third possible mechanism for malignant progression.[8] The authors questioned if this interaction between diabetes and carcinogenesis would result in differences in biologic behavior of the tumor in the present patients with CRC. The authors hypothesized that there are histopathologic differences in CRC between populations with and without diabetes.

Patients and Methods

Settings

This study was conducted at a 750-bed inner city tertiary care teaching hospital in Paterson, NJ. The protocol was approved by the St Joseph's Healthcare System Institutional Review Board.

Participants

The study included 650 patients with primary diagnoses of CRC who were in the tumor registry from January 2001 to December 2012. Medical records were retrospectively reviewed for these patients. Of the 650 patients, 116 were excluded based on the following criteria:

1. Biopsy reports were unavailable in the medical records.
2. Tumor stage was not definite at diagnosis (Tx, Nx, Mx).
3. The patient was less than 18 years old.
4. A cancer of unknown primary origin was present in the colon.

After 116 patients were excluded based on the aforementioned criteria, 534 patients were selected for the study. These patients were divided into diabetic (n = 282) and nondiabetic (n = 252) subgroups. Patients were included in the diabetic subgroup if they had a documented diagnosis of diabetes mellitus or they met the American Diabetic Association (ADA) criteria for diabetes before pathologic diagnosis of CRC. Patients on medications that could increase glucose levels, such as corticosteroids and dextrose infusion, were excluded. The ADA criteria used to determine if patients had diabetes mellitus were as follows:

1. Hemoglobin A_{1c} values $\geq$ 6.5%
2. Fasting blood sugar levels $\geq$ 125 mg/dL, with high fasting values recorded 2 or more times
3. Random blood glucose levels $\geq$ 200 mg/dL, with high random values recorded 2 or more times

Baseline variables for all patients included age, gender, race, hypertension, and hyperlipidemia. The authors reviewed the pathology, operative, imaging, and colonoscopy reports of both subgroups to analyze the following tumor characteristics:

1. Invasion depth or thickness of the tumor (pT): Information on depth of invasion was collected from pathology reports available after surgical resection of the tumor. Depth of invasion or tumor thickness was defined by the American Joint Committee on Cancer (AJCC) criteria (seventh edition)[21] for colon and rectal cancer staging. Depth of invasion was classified as In-situ/Tis (intraepithelial or invasion of lamina propria), T1 (tumor invades submucosa), T2 (tumor invades muscularis propria), T3 (tumor invades through muscularis propria into pericolorectal tissues), and T4 (tumor penetrates to the surface of visceral peritoneum or tumor directly invades or is adherent to other organs or structures).[21] Depth of invasion was further grouped into low (Tis, T1, and T2) and high (T3 and T4) for analysis.
2. Presence of lymphovascular involvement: Vein invasion was identified as being present if tumor cells were observed (on hematoxylin and eosin staining) in an endothelial-lined channel with a smooth muscle wall. Similarly, lymphatic vessel invasion was identified if tumor cells were present in an endothelial-lined channel devoid of smooth muscle. Patients with established lymph node involvement and distant metastases were included as having positive lymphovascular involvement, because absence in such patients is usually a sampling error.[22]
3. Tumor grade: Tumor grades included well differentiated (more than 90% gland formation), moderately differentiated (50% to 90% gland formation), and poorly differentiated (less than 50% gland formation).
4. Histologic type: Four major histologic types were collected including adenocarcinoma, neuroendocrine, mucinous carcinoma (more than 50% of the tumor was composed of extracellular mucin), and signet ring cell carcinoma (more than 50% of the tumor was composed of intracellular mucin).[23]
5. Presence of tumor components: Tumor components were classified as present if the tumor had presence of any percentage of mucinous, signet ring, or neuroendocrine cells.
6. Tumor location: Tumor location was categorized as right (cecum, hepatic flexure, and ascending colon), left (splenic flexure and descending colon), transverse, and rectosigmoid (rectum and sigmoid colon).