SYSTEMATIC REVIEW

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Diabetes mellitus and colorectal cancer – a revealed connection

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Abstract: *The burden of colorectal cancer (CRC) is increasing all over the world. The prevalence of diabetes mellitus is increasing. It is estimated that diabetes affects 387 million people worldwide. It is predicted that 552 million people worldwide will develop diabetes by 2030. A large pool of data indicate that DM increases by 2 fold the risk of CRC. This is the reason to firmly suggest the inclusion of DM in the criteria for CRC screening as an important measure to decrease the mortality of this ailment.*

INTRODUCTION

Type 2 diabetes mellitus and colorectal cancer are major causes of morbidity and mortality in the United States and other Western countries.

The burden of colorectal cancer (CRC) is increasing all over the world. It is recognized as the second cause of cancer death in USA and in Western Europe. Also, it is a third cause of cancer in men and a second cause of cancer in women. Every year there are 1,2 million new cases in the world. The highest incidence is encountered in Australia (75/100000), New Zeeland, North America and Europe[1]. In Romania the incidence has doubled from 1994 (13/100000) to 2005 (23/100000)[2]. The lifetime risk of CRC is 5%. 90% of cases appear after the age of 50; beneath this age threshold is rare encountered but the current trend indicates an increasing prevalence in young[3].

It is estimated that diabetes affects 387 million people worldwide. It is predicted that 552 million people worldwide will develop diabetes by 2030. In the United States, about 23.6 million people or 7.8% of adults have DM and by 2050, the number of people in the United States with diagnosed DM is estimated to grow to 48.3 million[4]. The prevalence of diabetes mellitus in Romania is 11.6% as PREDATTOR Study has concluded in 2014[5]. Even those figures are very high it is appreciated that almost one-third of diabetics is undiagnosed[6].

STUDIES THAT CONFIRM THE RELATION BETWEEN DM AND CRC

In 1910, Maynard[7] provided the earliest reports on the association between DM and cancer of any type. In 1984, Williams et al[8] published a retrospective study that documented a statistically significant, over 2-fold increase in the prevalence of DM in CRC

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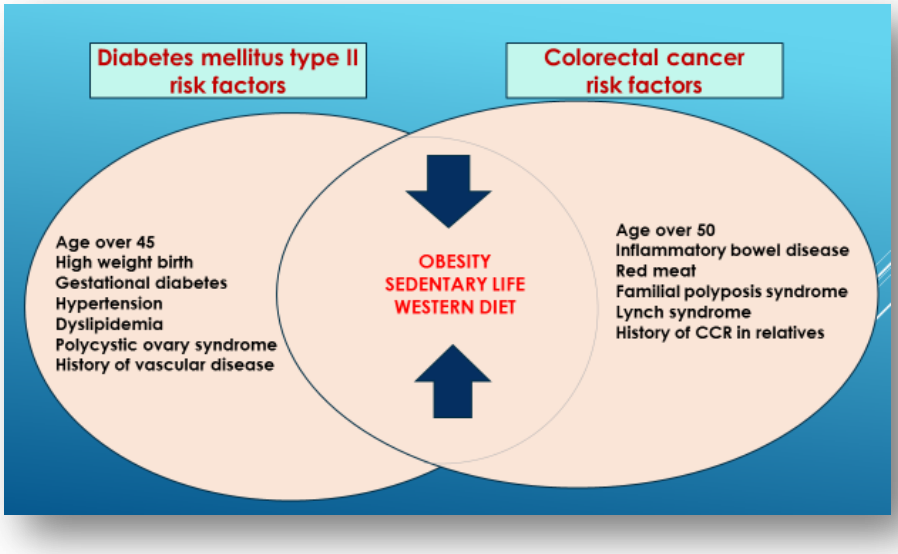
patients compared with age-matched controls. The search for a pathological explanation for this connection has led to the so-called hyperinsulinemia hypothesis. Giovannucci[9] hypothesized that insulin, an important growth factor, may at high serum concentrations increase the risk of CRC by promoting growth of colon tumors, and acting as a cell mitogen. Other proposed explanations for the increased risk include decreased bowel transit time and elevated fecal concentrations of bile acids[10]. Yang et al.[11] showed that insulin treatment may further elevate risk for CRC among patients with type 2 DM.

Figure 1: Risk factors for DM and CRC



Overall, studies indicate that diabetes risk increases twofold for liver, pancreatic, and endometrial cancer and 1.2- to 1.5-fold for colorectal, breast, and bladder cancer, but is associated with decreased risk for prostate cancer[12]. Diabetes is an independent risk factor for liver cancer. Cancer patients with diabetes relapse, and die, sooner than those without the disease.

Although proving a causal connection in observational human studies is uncertain and may take decades, preclinical research is revealing possible biochemical links between cancer and diabetes, which also share many risk factors.

The American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 recommend that clinicians be aware of an increased risk of CRC in cigarette smokers and obese patients[13], but do not highlight the increased risk in patients with DM. Obesity and smoking are associated with the incidence of both type 2 DM and CRC[14]; thus, they also could be important positive confounders of the association between DM and CRC.

In July 2010, the American Cancer Society and the American Diabetes Association released a consensus report that reviewed the science behind the link and evidence for whether diabetes treatments influence cancer risk or prognosis. Published in the July August 2010 *CA: A Cancer Journal of Clinicians*, the report recommended regular cancer screening for diabetics. Preliminary evidence that metformin is associated with lower cancer risk, and exogenous insulin with higher risk[12].

Diabetes is characterized by high levels of both insulin and blood sugar, and both promote cancer cell proliferation in preclinical models In a Nov. 29, 2011, *British Journal of Cancer* study, he examined levels of the two in nearly 5,000 women from the Women's Health Initiative over 12 years. Elevated glucose levels were associated with a nearly doubled risk of colorectal cancer[12].

A recent meta-analysis on 41 studies associated DM with an increased incidence of colorectal cancer

[relative risk, 1.27; 95% confidence interval (CI), 1.21–1.34][15]. No associations between DM and colon cancer were evident among African Americans[16]. A large-scale, population-based study in Japan suggested that diabetic men carried a higher risk for colorectal cancer than diabetic women did. The incidence of colorectal cancer was significantly higher in DM patients than in control patients (HR, 2.10; 95% CI, 1.82–2.42. The incidence of colorectal cancer is higher in males than in females (adjusted HR, 1.34; 95% CI, 1.18–1.53)[17].

CRC risk was higher among diabetics with longer duration of disease[18].

Metanalysis [19] of 15 studies (six case – control and nine cohort studies), including 2 593 935 participants, found that diabetes was associated with an increased risk of colorectal cancer, compared with no diabetes (summary RR of colorectal cancer incidence = 1.30, 95% CI = 1.20 to 1.40), without heterogeneity between studies (*P* heterogeneity = 0.21). The association between diabetes and colorectal cancer incidence did not differ statistically significantly by sex (summary RR among women = 1.33, 95% CI = 1.23 to 1.44; summary RR among men = 1.29, 95% CI = 1.15 to 1.44; *P* heterogeneity = .26) or by cancer subsite. Diabetes was positively associated with colorectal cancer mortality (summary RR = 1.26, 95% CI = 1.05 to 1.50), but there was evidence for heterogeneity between studies (*P* heterogeneity = 0.04). Findings from this meta-analysis indicate that individuals with diabetes have an approximately 30% increased relative risk of developing colorectal cancer compared with nondiabetic individuals.

Risk factors such as obesity, physical inactivity, smoking, Western diet and metabolic syndrome are common in both DM and colorectal cancer patients.

THE PROBLEM OF CONFOUNDERS AS RISK FACTORS

The first metaanalysis to quantitatively assess the effect of certain potentially important confounding variables including obesity, smoking, and physical exercise was published in 2008. It showed a statistically significant association between DM and risks of colon cancer and rectal cancer separately after controlling for obesity, smoking, and physical exercise. The association of DM and cancer risk was stronger for colon cancer than for rectal cancer (summary RR 1.38, 95 % CI 1.26 – 1.51 vs. summary RR 1.20, 95 % CI 1.09–1.31, respectively). This difference may be because the proximal colon, distal colon, and rectum have different embryological origins[20].

The positive association of DM with colon cancer and rectal cancer risk did not decrease when the metaanalysis was limited to studies that controlled for smoking and BMI (summary RR for colon 1.34, 95 % CI 1.17–1.52, and summary RR for rectum 1.28, 95% CI 1.06–1.54). This suggests that the confounding effect of obesity and smoking is relatively weak, and that DM appears to be an independent risk factor for colon cancer and rectal cancer.

Furthermore, as a recent study indicated, persons with DM and CRC may be at increased risk for CRC recurrence, non-response to chemo and radiotherapy treatment, and treatment-related complications. CRC deaths may be reduced through CRC screening programs.[21]

PROPOSED MECHANISMS

Several mechanisms have been proposed to explain the potential relationship between DM and colorectal cancer. Hyperinsulinemia, insulin-like growth factor-1, glucagon-like peptide-1 and the relative binding proteins each play an important role in metabolism, cell growth, proliferation and the regulation of the apoptotic process in colon cells[22].

Mechanistically, insulin stimulates cell proliferation through two pathways. One pathway involves direct binding of insulin to insulin or insulin-like growth factor-1 (IGF-1) receptors, and the other pathway is via inhibition of IGF binding proteins and the resultant increase in IGF-1 availability to the IGF receptor. The IGF system is a potent growth regulator closely linked with carcinogenesis[23]. These data support the notion that IGF-1 has a role in the biological pathway of colorectal neoplasia, beginning at the adenoma stage.

CONCLUSION

The increasing prevalence of DM may, significantly, be responsible for the increasing prevalence of CRC and its mortality. A great pool of data may suggest a need for more intensive CRC screening program in patients with type 2 DM, especially those who receive chronic insulin therapy.

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