Positive Association Between Diabetes Mellitus and Risk of Colorectal Cancer

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Abstract

Introduction: In recent years, many studies employed and found an association between type 2 diabetes mellitus and colorectal cancer. Although increased risk of colorectal cancer in individuals with Non Insulin Dependent Diabetes Mellitus (NIDDM) has been observed in previous studies, limited information is available on the colorectal cancer associated with NIDDM in Iran. The purpose of this study was to define colorectal cancer risk associated with diabetes mellitus.

Material & Methods: The present study was designed as an unmatched case control study. Cases were 393 patients with histologically confirmed colorectal carcinomas and 393 controls were randomly selected among the healthy participants in a health survey. To control potential confounding factors such as sex, age, smoking habits and Body Mass Index (BMI), multiple logistic regression model was fitted to obtain Odds Ratio of colorectal cancer and the corresponding 95% CIs, according to history of diabetes mellitus.

Results: Overall, 86 (10%) cases versus 15 (1.7%) controls gave a history of diabetes mellitus. The corresponding multivariate OR was 6.77 (CI 95%: 3.84-11.92) indicating that having a positive history of diabetes mellitus increases one's risk of colorectal cancer about six-fold. The risk of colorectal cancer was slightly increased for women ($p<0.05$). Current smokers were at a higher CRC risk (OR=2.83, CI95%:2.13-3.76) than never smokers.

Conclusion: We found a strong positive association between NIDDM and prevalent colorectal cancer. In summary, these findings provide further indirect epidemiological evidence for the hypothesis that hyperinsulinaemia may be important in the development of colorectal cancer.

Keywords: diabetes mellitus, colorectal cancer, case control study

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Introduction

There are nearly one million new cases of colorectal cancer diagnosed worldwide each year and half a million deaths [1]. The incidence of colorectal cancer has increased in Iran in recent years and colorectal cancer is the fourth most common cancer in both genders [2-4].

In recent years, many studies employed and found an association between type 2 diabetes mellitus (DM) and colorectal cancer [5]. Accumulating evidence shows that type 2 diabetes mellitus is associated with a 40-60% increased risk of colorectal cancer [6]. Dietary and lifestyle risk factors for developing insulin resistance and type 2 diabetes, such as western diet, physical inactivity and obesity, have also been linked to an increased risk of colon cancer [7]. Hyperinsulinemia is present during the early stages of type 2 DM [8] and preclinical studies have shown that insulin stimulates proliferation, decreases apoptosis, and promotes intestinal carcinogenesis [9]. In fact, insulin and its structural homologue, insulin-like growth factor-I, are growth factors of intestinal epithelial cells and mutagens that affect colonic tumor cell growth in vitro [10]. Thus, people who have NIDDM may be expected to be at even greater risk of colorectal cancer than those who have either of the risk factors alone [11].

Table1. *Distribution of cases and controls according to Diabetes Mellitus and selected covariates*

	Cases	Controls
	Number (%)	Number (%)
Sex		
Male	521(60.4)	356(41.3)
Female	341(39.6)	506(58.7)
Age		
40-65	247(28.7)	223(25.9)
>65	615(71.3)	639(74.1)
Diabetes Mellitus		
Diabetic	86(10)	15(1.7)
Non diabetic	776(90)	847(98.3)
Smoking		
Current smoker	215(24.9)	81(9.4)
Never smoker	647(24.9)	781(90.6)
BMI		
Underweight	50(5.8)	20(2.3)
Normal	354(41.1)	295(34.2)
Overweight	398(46.2)	403(46.8)
Obese	60(7.0)	144(16.7)

Although increased risk of colorectal cancer in individuals with Non Insulin Dependent Diabetes Mellitus (NIDDM) has been observed in previous studies, limited information is available on the colorectal cancer associated with NIDDM in Iran. The purpose of this study was to define colorectal cancer risk associated with diabetes mellitus.

Materials and Methods

The present study was designed as an unmatched case control study to assess the impact of Non Insulin Dependent Diabetes Mellitus on the risk of colorectal cancer.

Cases were 862 patients older than 40 years with histologically confirmed colorectal carcinomas who were registered in the cancer registry center of Research Center for Gastroenterology and Liver Diseases (RCGLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Eight hundred sixty two controls were randomly selected among the healthy participants (age >40) in a health survey conducted by the Department of Health System Research (HSR) of RCGLD in which a total of 2790 subjects were invited to participate in an interview about functional gastrointestinal disorders [12, 13]. Information about age, sex, history of diabetes mellitus, weight, height and smoking habits was extracted from cancer registry and HSR forms for cases and controls, respectively.

To control potential confounding factors such as sex, age, smoking habits and Body Mass Index (BMI), multiple logistic regression models were fitted to obtain ORs of colorectal cancer and the corresponding 95% confidence interval, according to history of diabetes mellitus. BMI was calculated as body weight (kg) divided by the square of height (m) and categorized according to the World Health Organization (WHO) classification: Underweight: BMI<18.5, Normal weight: BMI 18.5-25, Overweight: BMI 25-30, Obese: BMI≥30. All tests were two sided, with statistical significance attributes to $p<0.05$. Statistical analysis was performed with SPSS software (version 13.0).

Results

Table 1 shows the distribution of cases and controls according to age, sex, history of NIDDM and selected covariates. Overall, 86 (10%) cases versus 15 (1.7%) controls reported history of diabetes mellitus.

The risk of colorectal cancer was obviously increased for subjects with a positive history of diabetes mellitus. The OR was 6.19 (95% CI: 2.63 to 12.6) in men and 6.52 (95% CI: 3.1 to 13.7) in women.

Table 2. *Odds Ratio (OR) of colorectal cancer and 95% confidence intervals according to family history of colorectal and other cancers*

		Cases Number (%)	Controls Number (%)	OR 95% CI
Sex				
Male	Diabetic	50 (9.6)	6 (1.7)	6.19 (2.63-14.6)
	Non diabetic	471 (90.4)	350 (98.3)	
Female	Diabetic	36 (10.6)	9 (1.8)	6.52 (3.1-13.7)
	Non diabetic	305 (89.4)	497 (98.2)	
Age				
40-65	Diabetic	26 (10.5)	3 (1.3)	8.63 (2.57-28.92)
	Non diabetic	221 (89.5)	220 (98.7)	
>65	Diabetic	60(9.8)	12(1.9)	5.65(3.01-10.61)
	Non diabetic	555(90.2)	627(98.1)	
Smoking				
Smoker	Diabetic	15(7)	1(1.2)	6.00(0.78-6.18)
	Non diabetic	200(93)	80(98.8)	
Non smoke	Diabetic	71(11)	576(89)	6.75(3.77-12.1)
	Non diabetic	14(1.8)	767(98.2)	
Body Mass Index				
Underweight	Diabetic	0 (0)	1 (5)	0.27 (0.19-0.40)
	Non diabetic	50 (100)	19 (95)	
Normal	Diabetic	40 (11.3)	7 (2.4)	5.24 (2.31-11.88)
	Non diabetic	314 (88.7)	288 (97.6)	
Overweight	Diabetic	38 (9.5)	5 (1.2)	8.4 (3.27-16.56)
	Non diabetic	360 (90.5)	398 (98.8)	
Obese	Diabetic	8 (13.3)	2 (1.4)	10.92 (2.25-23.12)
	Non diabetic	52 (86.7)	142 (98.6)	

In our database, patients were recorded as current smokers (have smoked a cigarette within the last month) and never smokers. Analysis according to patients' smoking history revealed that 16 of the 101 subjects under study (15.8%) with diabetes were smokers compared to 280 of the 1623 without diabetes (17.3%). Of the 16 diabetic patients with a history of smoking, 15 (93.8%) had colorectal cancer, compared to 71 of the 85 non-smokers (83.5%). Increase of Body Mass Index in diabetic patients showed a significant association with risk of colorectal cancer ($p<0.05$). Having diabetes mellitus in older patients was associated with a further elevation in colorectal cancer risk.

Odds ratios (OR), and the corresponding 95% confidence intervals (CI), were derived from multiple logistic regression equations, including terms for sex, age, smoking and BMI was 6.77 (95% CI 3.85 to 11.92).

Discussion

This case-control study provided direct support for the hypothesis that Type 2 diabetes mellitus is associated with an increased risk of colorectal adenocarcinoma. This association could be the result of various biological mechanisms. Inherited susceptibility to colorectal cancer-which is defined by familial aggregation-is a composite of shared environmental factors and polygenic mechanisms that include recognized familial syndromes, mismatch repair gene mutations and genetic polymorphisms involved in nutrient or carcinogenic metabolism. These processes may lead to an increase in the rate of tumor initiation and progression.In turn; this increased risk may be potentiated by NIDDM and its determinants. For example, hyperinsulinaemia, which is a characteristic of early NIDDM, may promote colorectal carcinogenesis either directly or indirectly through changes in the insulin-like growth factor system [11].

To date, associations between type 2 DM and risk of CRC have been evaluated in various studies but the reported risk estimates are inconsistent [14-17]. Deficiencies in the methods used to assess DM status have likely contributed to the discrepant observations. One possible explanation for these discrepancies could be the common risk factors shared by the two diseases and the failure to control these covariates. Exact numbers of risk association vary according to the study design and study population, possibly reflecting the complex risk factors associated with colorectal tumourigenesis.

In this study, we found that type 2 DM was associated with a six fold increase in the risk for incident CRC. Recently, Elwing et al. showed that women with Type 2 diabetes mellitus had higher rates of colorectal adenomas compared to women without diabetes[18].

In addition, the association between diabetes and risk of colorectal cancer was presented among individuals with BMI levels. These estimates are in general agreement with those reported in previous studies[10, 16, 19]. It should be mentioned that in our study, only BMI was used as a measure of obesity which may not be an accurate measure of abdominal or visceral fat.

Compared to patients without DM, we found that patients with DM were likely to develop colon cancer at an older age. The cause of this finding is unclear. Khaw et al, demonstrate that the incidence of colorectal cancer increased with aging (58.9 year vs. 65.8 year, $p < 0.001$) and with increasing HbA1c (5.35% vs. 5.86%, $p < 0.001$) [20]. This, however, contradicts the theory proposed by Hu and Meyerhardt (JCO) that with increasing age, patients with DM experience a transition from a hyperinsulinemic and thus an increased carcinogenic state to a hypoinsulinemic state [21, 22].

Unlike other studies, we could find no suggestion of an interaction between smoking and diabetes with respect to risk of colorectal cancer [7, 17, 19, 20].

Limitation of our study is reliance on self-reported information on diabetes report for physician-diagnosed diabetes. The proportion of subjects under study who reported a history of diabetes was substantially lower than estimates of the prevalence in the general population. The possibility of uncontrolled or residual confounding factors cannot be ignored. Detection bias is another concern, because it may be argued that diabetics are under closer observation and are more likely to have their cancer detected than non-diabetics. On the other hand, we could not obtain information on family history of CRC, physical activity, dietary composition, alcohol consumption or any other environmental factor although they are important for colorectal carcinogenesis. In addition, serum insulin and IGF-1 levels were not measured because of the same reason. Further large-scaled, prospective studies are necessary to overcome these limitations.

In summary, these results provide epidemiological evidence for the hypothesis that hyperinsulinaemia may be important in the development of colorectal cancer. This result indicates the necessity of colorectal cancer screening program in patients with Type 2 diabetes. The possible influence of family history on NIDDM and risk of colorectal cancer merits further investigation.

Conflict of interests

The authors have no conflict of interests in this article.

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