

Original Research Article

Type 2 diabetes mellitus: a risk indicator for colorectal cancer

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ABSTRACT

Background: Worldwide, colorectal cancer is the fourth most common cancer and affects both men and women equally. Increasing evidence suggests that abnormal glucose metabolism may be associated with increased risk of colorectal cancer. The aim of this case control study was to determine the association of colorectal cancer with type 2 diabetes mellitus (T2 DM) and other risk factors of colorectal cancer among adult Bangladeshi population.

Methods: We included patients of colorectal cancer as cases and the controls were mostly cancer patients other than colorectal cancer and relatives of the patients attending in National Institute of Cancer Research Hospital (NICRH) in Dhaka. Three hundred samples (100 cases and 200 controls) were selected purposively.

Results: It was found that in cases 19% participants had T2 DM before colorectal cancer whereas 10.5% participants in controls had similar history. Appropriate statistical analysis reported that cases having T2 DM has 2.86 times higher chance to develop colorectal cancer (OR 2.68, 95% CI: 1.21-5.96) compared to controls. We also got significant inverse association with colorectal cancer with obesity (OR 0.43, 95% CI: 0.19-0.97), positive smoking history (OR 0.32, 95% CI: 0.19-0.60) and low fruits and vegetable intake (OR 0.33, 95% CI: 0.19-0.60).

Conclusions: This was a unique study for Bangladesh which showed results consistent with the finding of studies done globally. Therefore, we accept our research hypothesis as T2 DM is a risk indicator for colorectal cancer, however obesity, smoking and less fruits and vegetable intake are also risk factors for colorectal cancer among Bangladeshi population.

Keywords: Colorectal cancer, Type 2 diabetes mellitus, Risk indicator

INTRODUCTION

Globally colorectal cancer is the second leading cause of cancer-related deaths world-wide and diabetes mellitus increases the risks of a wide spectrum of cancers including colorectal cancer.^{1,2} In 2014, globally 422 million adults were living with diabetes compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from

4.7% to 8.5% in the adult population. Over the past decade, diabetes prevalence has risen faster in low and middle-income countries than in high-income countries.³ According to Bangladesh Bureau of Statistics cancer is the sixth leading cause of death (BBS, 2004). Hospital-based cancer registry has been started at National Institute of Cancer Research Hospital (NICRH) and Oncology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) since 2009 in Bangladesh.⁴

However, International Agency for Research on Cancer (IARC) has reported cancer-related death rate in Bangladesh to be 7.5% in 2005 and predictive to increase by 13% in 2030. Cancer of the colon and rectum is the most common among male cancer survivors in most Asian countries.⁵

A study has reported, after a median follow-up of 4.5 years, among diabetic study population 2,759 cases of colorectal cancer were observed. They found, type 2 diabetes was associated with a 1.3 folds increased risk of colorectal cancer (HR 1.26, 95% CI: 1.18-1.33) however, no association was found with treatment stages. The study stated a trend of increased colorectal cancer risk was observed with longer duration of obesity. Risk of colorectal cancer was significantly increased for patients with recorded duration of obesity of 4-8 years (HR 1.19 95% CI: 1.06-1.34) and >8 years (1.28 CI: 1.11-1.49).⁶ Although patients with type 2 diabetes have elevated risks of liver, pancreatic, kidney, and endometrial cancer, little is known about the association of cancer in patients with type 1 diabetes. Therefore, there is risk difference between type 1 and type 2 diabetes mellitus with colorectal cancer which is not adequately documented yet.

In Sweden, a cohort study was conducted to examine cancer incidence among 29187 patients who were hospitalized for type 1 diabetes from 1965 through 1999. Using data for the entire Swedish population as a reference, relative risks of cancer were estimated by age, sex and calendar year of follow up adjusted standardized incidence ratios (SIRs). They observed 355 incident cases of cancer, which corresponded to a 20% increase in overall cancer incidence among type 1 diabetes patients (SIR=1.2, 95% confidence interval CI=1.0 to 1.3). Therefore, type 1 diabetes reported to be associated with a modest excess cancer risk overall and risks of specific cancers that differ from those associated with type 2 diabetes.⁷

One research has found the risk of CRC was significantly associated with insulin use to a random effects model (RR, 1.69; 95% CI, 1.25 -2.27). However, when subgroup analyses were conducted according to the study types, no associations were detected in cohort group (RR, 1.25; 95% CI, 0.95-1.65; I, 75.7%) but significant association was detected in case control group (RR, 2.15; 95% CI, 1.41-3.26; I², 89.1%).^{2,8}

Increasing evidence suggests that abnormal glucose metabolism may be associated with increased risk of colorectal cancer. HbA1c concentration appeared continuously related to incident colorectal cancer risk, with lowest rates observed in those with HbA1c below 5%. Known diabetes was also associated with incident of colorectal cancer, with relative risk (RR) 3.18 adjusting for age and sex and RR 2.78 adjusting for age, sex, body mass index, and smoking compared with those without known diabetes, the results were statistically significant. HbA1c concentrations appeared to explain the increased

colorectal cancer risk associated with diabetes in multivariate models.⁹

In Bangladesh, colorectal cancer (CRC) is one of the ten leading causes of cancer mortality. However, studies on the disease burden and risk factors analysis are lacking. Particularly there is no study on associated factors of colorectal cancers as yet. To our best knowledge this is the first study in Bangladesh to assess correlation between colorectal cancer and diabetes. Studies from developed countries reveals that diabetes is a risk factor for developing colorectal cancer therefore this study is aimed to find out the relationship of colorectal cancer with type 2 diabetes mellitus among Bangladeshi population. We expect the results will help policy planners in setting appropriate strategy to prevent the risk of CRC in Bangladeshi population and thus will help to achieve the NCD goals of the country.

METHODS

The study was a hospital based cross sectional study conducted from January to June 2018. A purposive sampling of total 300 participants (100 cases and 200 controls) from National Institute of Cancer and Research Hospital (NICRH), Dhaka were included in the study after taking voluntary informed consent from each participant. We included participants as cases and controls after checking following selection

Exclusion and inclusion criteria

We included the participants (patients) of both sexes aged between 40 and 70 years and who were well enough to communicate with the interviewer and willing to participate in the study.

Cases

The cases were patients diagnosed as colorectal cancer by gold standard (colonoscopy and histopathology or any other cytological examination) fulfilling the above-mentioned selection criteria.

Controls

Cancer patients other than colorectal cancer attending the National Institute of Cancer and Research Hospital (NICRH), Dhaka mostly (n=160) and a few of them were the relatives of the patients who were healthy (n=40) and represents the general population of the community. Two controls for one case were enrolled (case: control=1:2). Generally, the cancer patients are referred to NICRH from different part of Bangladesh. So, the study subject to some extent are representative population of Bangladesh.

A semi-structured questionnaire was developed and was pretested before using. The questionnaire comprised of socio-demographic factors (age, sex, marital status, religion, place of residence, type of residence, education, occupation, monthly family income and monthly

expenditure), behavioral risk factors (tobacco use, alcohol consumption, insufficient fruit and vegetables intake, inadequate physical activity) and metabolic risk factors (obesity, hypertension, diabetes and family history of chronic diseases).

Data were collected by face-to-face interview by qualified research staffs. Data was collected about the respondent's socio-demographic situations and lifestyle factors including behavioral factors. Fruit and vegetables intake were assessed in serving size (1 standard serving=80 grams of fruit and vegetable) by using standard serving bowls and serving size show-cards. Level of physical activity was assessed by asking how many minutes they usually walk in a week (both moderate and vigorous types). Other physical measurements (height, weight and blood pressure) were taken appropriately by following the standard procedures. Blood pressure was measured two times in sitting position with Omron digital blood pressure machine.

A 10 minutes of rest was maintained in between two measurements and the average readings was taken as the final reading following the NICE guideline.¹⁰ In our study, fruits and vegetables (FAVs) intake were defined as insufficient when it was <3 servings/day. Level of physical activity (PA) was defined as inadequate when it was <150 minutes of moderate to vigorous physical activity per week. Overweight and obesity was defined when body mass index (BMI) was ≥ 25.0 (measured as dividing the weight in kg by height in meter. Hypertension (HTN) was defined as systolic Blood Pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or use of anti-hypertensive medications.

Diabetes was defined when fasting blood glucose (FBG) was equal or more than 7 mmol/dl and 2 hours after glucose equal or more than 11.1 mmol/dl according to American diabetes association. We checked for the blood glucose values in diabetic log books, hospital records and prescription by the physicians.

Statistical analysis

The collected data were checked for competences, coded and cleaned and finally exported to statistical package for social science (SPSS) software version-21 for analysis. Descriptive statistics was done to describe the distribution of socio-demographic factors and risk factors among the respondents.

Unadjusted and adjusted odds ratio were calculated by following appropriate statistical modelling (logistic regression) to see the association between targeted depended (colorectal cancer) and independent (type 2 DM) factors. We checked association with other possible risk factors as well. Determinants of risk factors were considered when there were significant associations ($p < 0.05$ at 95% confidence interval) in multivariable analyses.

Ethical approval

The study was approved by both Ethical Review Board Bangladesh Medical Research Council (BMRC) and Review Board of National Institute of Cancer Research Hospital (NICRH), Bangladesh.

RESULTS

The study included 100 cases with colorectal cancer and 200 controls. The respondents had an average age of 47(SD \pm 12). Mean age of the cases was 41.6 \pm 10.7 years compared to 44.8 \pm 11.38 years among controls. About half of the respondents were males (58.3%). Male female ratio among cases and controls were 1.08 and 1.59 respectively. Majority of cases and controls (73% and 85.0% respectively) lived in rural areas. More than one third (37.7%) of the respondents completed their primary education whereas 35% were illiterate. In terms of employment, it was observed that in combined group 17% of the respondents were farmers and 12.0% were private workers. Majority of the female respondents in cases and controls (43.0% and 35.0% respectively) were housewives. Among the respondents 36.3% earned less than Tk 10,000 while 40.0% of them earned between Tk 10000-20000. The mean monthly income of cases and controls were observed to be around Tk 9300 and Tk 12050 respectively (Table 1).

13.3% of the patients had type 2 diabetes in combined groups (cases and controls). Among cases diabetes was 19% patients whereas 10.5.0% were in controls. When we calculated unadjusted odds ratios, the difference was observed to be significant (OR=2.55, p value=0.027). It is mentionable that all our diabetic respondents were having type2 DM. In terms of family history of DM, 28.0% of cases had positive family history of DM while 10.5% of the controls had similar history Regarding duration of DM 33.3% of the patients with colorectal cancers were suffering from diabetes more than 8 years which is less in controls (Table 2).

We didn't find any association with family history chronic diseases with colorectal cancer. 33% ($n=99$) respondents had positive history of any type of chronic family diseases and majority of the family members were having hypertension (40%), however this difference was not statistically significant to suggest any association with colorectal cancer (Table 3).

We estimated age and sex adjusted odd ratios as well for risk factors that could be associated with colorectal cancer. We found diabetes (T2 DM) cases were having 2.6 times higher chance to have colorectal cancer as well and the difference is statistically significant (95% CI: 1.21-5.96, p value 0.15) when adjusted for age and sex. We also looked for correlation of colorectal cancer with duration of diabetes mellitus in less and above 5 years categories. However, we did not find any significant difference between cases and controls.

Table 1: Demographic and socioeconomic characteristics of the study subjects.

Variable	Level	Total (n=300)		Case (n=100)		Control (n=200)	
		N	%	N	%	N	%
Age group (in years)	30-40	92	30.7	38	38	54	27
	40-50	67	22.3	21	21	46	23
	50-60	78	26	28	28	50	25
	>60	63	21	13	13	50	25
Age (years)	Mean±SD	47±12		41.6±10.7		44.8±11.38	
Sex	Male	175	58.3	52	52	123	61.5
	Female	125	41.7	48	48	77	38.5
Male female ratio		1.4		1.08		1.59	
Marital status	Married	274	91.3	89	89	185	92.5
	Unmarried	21	7	10	10	11	5.5
	Divorced	5	1.7	1	1	4	2
Religion	Islam	283	94.3	93	93	190	95
	Hinduism	17	5.7	7	7	10	5
Place of residence	Rural	243	81	73	73	170	85
	Urban	57	19	27	27	30	15
Type of residence	Pakka	41	13.7	17	17	24	12
	Semipakka	93	31	30	30	63	31.5
	Kacha	166	55.3	53	53	113	56.5
Educational status	Illiterate	105	35	30	30	75	37.5
	Primary	113	37.7	31	31	82	41
	Secondary	36	12	17	17	19	9.5
	HSC	13	4.3	6	6	7	3.5
	Graduate and above	33	11	16	16	17	8.5
Occupation	Student	8	2.7	3	3	5	2.5
	Gov't service	21	7	8	8	13	6.5
	Private service	36	12	19	19	17	8.5
	Unemployed	28	9.3	5	5	23	11.5
	Business	26	8.7	6	6	20	10
	Farmer	51	17	11	11	40	20
	Laborer	17	5.7	5	5	12	6
	Housewife	113	37.7	43	43	70	35
Family income in taka (monthly)	0-10000	109	36.3	41	41	68	34
	10001-20000	120	40	40	40	80	40
	20001-30000	42	14	13	13	29	14.5
	30001-40001	5	1.7	1	1	4	2
	40001-50000	5	1.7	1	1	4	2
	>50000	19	6.3	4	4	15	7.5
	Mean (BDT)	11133.907		9300.55		12050.58	
Family expense (monthly)	0-10000	56	18.7	9	9	47	23.5
	10001-20000	117	39	49	49	68	34
	20001-30000	51	17	19	19	32	16
	30001-40001	36	12	13	13	23	11.5
	40001-50000	26	8.7	7	7	19	9.5
	>50000	14	4.7	3	3	11	5.5
Mean (BDT)	16,700±13,859		16,900±12034.92		6600±14,714		

**Pakka=concreted house, Semipakka=semi concreted house (border concreted but roof with stainless steel sheets, Kacha=house made with mud/stainless steel sheets/fence; BDT=Bangladesh taka.

Table 2: Test of significance on colorectal cancer and diabetes related information among cases and controls.

Variables	Level	Total (n=300)		Case (n=100)		Control (n=200)		Odds ratio	95% CI		P value
		N	%	N	%	N	%		Lower	Upper	
Diabetic status	Yes (type 2)	40	13.3	19	19.0	21	10.5	Ref.			
	No (non-diabetic)	260	86.7	81	81.0	179	89.5	2.558	1.11	5.87	0.027*
Family history of diabetes	Yes	68	22.7	28	28.0	40	20.0	0.244	0.02	3.84	0.316
	No	226	75.3	71	71.0	155	77.5	0.295	0.02	4.22	0.368
	Don't know	6	2.0	1	1.0	5	2.5	Ref.			
Diabetic family member	None	236	78.7	72	72.0	164	82.0	5.793	0.89	37.43	0.065
	Father	14	4.7	7	7.0	7	3.5	1.694	0.19	15.08	0.637
	Mother	31	10.3	12	12.0	19	9.5	3.024	0.40	22.35	0.278
	Brother	12	4.0	5	5.0	7	3.5	2.492	0.27	22.28	0.414
	Sister	7	2.3	4	4.0	3	1.5	Ref.			

OR=odds ratio was unadjusted.

Table 3: Association with family history of other chronic diseases.

Variables	Level	Total (n=300)		Case (n=100)		Control (n=200)		OR	95% CI		P value
		N	%	N	%	N	%		Lower	Upper	
Chronic diseases in family	Yes	99	33.0	35	35.0	64	32.0	8.312	0.49	141.140	0.143
	No	189	63.0	62	62.0	127	63.5	1.071	0.207	5.551	0.935
	Don't know	12	4.0	3	3.0	9	4.5	Ref.			
Type of chronic diseases (n=99)	HTN	41	13.7	20	20.0	21	10.5	1.585	0.259	9.696	0.618
	CHD	20	6.7	2	2.0	18	9.0	9.097	0.976	84.798	0.053
	Cancer	8	2.7	5	5.0	3	1.5	Ref.			
	COPD	21	7.0	7	7.0	14	7.0	3.145	0.457	21.629	0.244

**HTN=hypertension; CHD=chronic heart disease; COPD=chronic obstructive pulmonary diseases; Cancer=any type of carcinoma; OR=odds ratios were age and sex adjusted. ** OR=odds ratio were age and sex adjusted.

Table 4: Association of related physical and behavioural factors among cases and controls.

Variable	Level	B	Odds ratio	95% C.I. for odds ratio		P value
				Lower	Upper	
Diabetes status	Yes	0.989	2.689	1.212	5.966	0.015
	No	Reference				
Diabetes duration	<5 years	-2.021	0.133	0.016	1.114	0.063
	>5 years	Reference				
Family history of diabetes	Yes	0.616	1.851	0.976	3.511	0.060
	No	Reference				
Obesity	Yes	-0.827	0.437	0.197	0.971	0.042
	No	Reference				
Hypertension	Yes	0.212	1.236	0.614	2.489	0.552
	No	Reference				
Smoking status	Yes	-1.132	0.322	0.151	0.689	0.003
	No	Reference				
Ever smokeless tobacco consumption	Yes	-0.245	0.783	0.442	1.387	0.401
	No	Reference				
Alcohol consumption	Yes	0.424	1.528	0.156	14.972	0.716
	No	Reference				
Current coffee consumption	Yes	-0.233	0.792	0.283	2.212	0.656
	No	Reference				
WHO recommended physical activity	Yes	-0.424	0.654	0.371	1.155	0.143
	No	Reference				
WHO recommended vegetable consumption	Yes	-1.081	0.339	0.190	0.605	0.000
	No	Reference				

**OR=odds ratio were age and sex adjusted.

We found interestingly inverse association with colorectal cancer and obesity (OR 0.437, 95% CI: 0.19-0.97, p value 0.042), positive smoking history (OR 0.322, 95% CI: 0.15-0.68, p value 0.003). One reason could be the cases are currently non-obese mostly and non-smoker, therefore it showing inverse association with CRC, however we have discussed these in our discussion section.

It is reportable that we found inverse association with WHO recommended vegetable consumption and colorectal cancer (OR 0.339, 95% CI: 0.19-0.60, p value 0.000). We didn't find any other remarkable association with other factors mentioned in (Table 4).

DISCUSSION

The study was a case control epidemiological investigation to test the hypothesis type 2 diabetes mellitus is a risk indicator for colorectal cancer among the Bangladeshi population.

This hypothesis was formulated from the findings of a cross sectional (descriptive study) study titled "colorectal cancer and its risk factors among Bangladeshi adult population" done earlier by the same group of investigators which suggested T2 DM is a predictor for future CRC.

We found a positive association between T2 DM and colorectal cancer as showed in both Table 2 (unadjusted odds) and Table 4 (age and sex adjusted odds). The relationship between diabetes mellitus and the risk of colorectal cancer was investigated in a multicentre case-control study, conducted in Italy between 1992 and 1996 on 1225 cases of incident, histologically confirmed colon cancer, 728 cases of rectal cancer, and 4154 controls, who were in the hospital for acute, non-neoplastic diseases. This uniquely large case-control study of colorectal cancer confirms that subjects with non-insulin-dependent diabetes mellitus have a slightly increased risk of colorectal cancer which shows similar result as our study did.¹¹ Other studies done by earlier investigators found the similar findings. A meta-analysis of 15 studies (six case-control and nine cohort studies), including 25, 93,935 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. These results were consistent between case-control and cohort studies and between studies conducted in the United States and in Europe.¹²

In our study, it was found that 28.0% cases had family history of DM compared to 10.5% controls. However, 28.0% cases had family history of DM compared to controls (10.5%) though the difference was not statistically significant. A study conducted earlier reported association of colorectal cancer with family history of DM which may be due to the fact that it was a

population based cross sectional study in a country of East Asia with a different population characteristics and the investigators opined that their study confirmed previous data indicating that insulin and its structural homologue insulin-like growth factor I (IGF-I) may promote colorectal carcinogenesis which was not investigated in our research.¹³

In this study, among the cases, about 33.3% of the patients with colorectal cancers were suffering from T2 DM for more than 8 years and it was quite less in control group in comparison to cases, 67.9% controls were suffering from diabetes for less than three years. However, the difference was not statistically significant (table not shown).

We found hypertension among cases and controls as 23.0% and 20.5% respectively (odds ratio 1.23) although the difference was not statistically significant (p 0.552). We didn't found any association between physical activity while an inverse association between physical activity and the risk of colorectal cancer for the general population was found in meta-analyses of some studies.¹⁴⁻¹⁸ The reason could be our study design is hospital based and small sample compared to those studies.

We also did not found association of colorectal cancer with alcohol intake, coffee consumption, and family history of chronic diseases including diabetes. However, we found statistically significant inverse association with smoking habit between cases and controls (OR, 95% CI: 0.322, 0.15-0.68), Similar result was reported in one article where ever smoking is inversely associated with colorectal cancer (OR, 95% CI: 0.74 (0.55-0.98)).¹⁹ Same study reported previous body mass index (>25 kg/m²) were associated with an increased risk of colorectal cancer, but in our study we consider present BMI which shows inverse association with colorectal cancer, possible reason could be as the cases were getting chemo therapy and radiotherapy and suffering from possible nutritional deficiencies, they have lost weights and it may shows opposite result in this study. However, our study could not reveal much about this. We did not observe any association with smokeless tobacco which is almost consistent with the study done by Vecchia et al.¹¹ We estimated strong inverse association with fruit and vegetable intake (at least 3 serving per day) and colorectal cancer, which is obvious as fibres in vegetables are protective for colorectal cancer which also revealed in our study (OR, 95% CI: 0.33, 0.19-0.60). Similar finding has been reported by one cohort study where colorectal patients with lynch syndrome were less likely to take 4 servings per day fruits and vegetables (8.6% vs 21.7%).²⁰

Strength and limitation

However, we have several study limitations as well. Firstly, most of our controls were cancer patients other than colorectal cancer and a few of them were the relatives of the patients who were healthy and represents

the healthy community. However, we could not take sex matched controls due to time limitation to complete the study within a defined period which was a requirement by the donor. We consider this as our remarkable limitation however we still believe this study will generate evidence as there is a huge research gap on this research topic in Bangladesh. Again, regarding age, we tried to match the controls to our best to maximum ± 5 years of age gap with the age of cases. However, due to non-availability of appropriate age group participants, we had to select a small proportion of controls those were of beyond the stipulated age limit.

Secondly, family expenses were remarkably high for cases compared to controls as all the cases were patients of colorectal cancer and the expenditure included the cost of the treatment. However all the controls were not patients of cancer as some were healthy relatives of the cancer patients, and there is variability in treatment cost depending on the type of the cancer and other associated diseases, we assume that colorectal cancer treatment is comparatively costly than some other type of cancers among the controls, therefore the data shows this disparity in the expenditure among the cases and controls.

Finally, our study sample was small and selected from only one hospital so may not be generalized for the population of Bangladesh. As information was collected from the study subject about their past history of the study variables so, that might include recall bias. Finally, our strength is the case control study design and to our best knowledge there is no other study in Bangladesh has been conducted till to assess correlation between colorectal cancer and diabetes.

CONCLUSION

This was a unique study for Bangladesh which showed results consistent with the finding of the related global studies. It revealed that patient having T2 DM has 2.86 times higher chance to develop colorectal cancer which supported our research hypothesis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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