Behavioral, familial and comorbid illness risk factors of colorectal cancer: a case control study

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Abstract

Introduction Though colorectal cancer is a disease of public health importance, there is little evidence about risk factors of colorectal cancer in South Asians.

Objectives We aimed to determine the behavioral, familial and comorbid illness risk factors for colorectal cancer among Sri Lankan adults.

Methods We conducted this study among 325 participants (65 incident colorectal cancer cases, 130 hospital and 130 community controls) in five major health care institutions and communities in areas with high incidence in Sri Lanka. Behavioral, genetic and comorbid risk factors were assessed through an interviewer administered questionnaire. Risk factors were evaluated using bivariate and multivariate logistic regression.

Results Adjusted logistic regression showed that frequent consumption of red meat (OR 3.06, 95% CI 1.26-7.43) and deep fried food (OR 2.54, 95% CI 1.22-5.39), hypertension ≥ 10 years (OR 3.3, 95% CI 1.3-8.6), colorectal cancer (OR 4.91, 95% CI 1.70-14.18) and other cancers (OR 3.0, 95% CI 1.14-7.81) among first degree relatives and age >50 years (OR 2.6, 95% CI 1.1 to 5.9) were significant risk factors compared to hospital controls. Frequent consumption of deep fried food (OR 4.2, 95% CI 1.7-10.1), being an ever smoker (OR 3.2, 95% CI 1.1-9.3), a current or former drinker (OR 5.4, 95% CI 1.1-27.8) and hypertension ≥ 10 (OR 5.1, 95% CI 1.7-15.6) were risk factors compared to community controls.

Conclusion The behavioral, familial and comorbid illness risk factors identified should be considered in designing preventive strategies and identifying high-risk individuals for screening for colorectal cancer.

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Introduction

Colorectal cancer contributes significantly to global burden of morbidity and mortality due to cancer [1]. Though considered a disease of the West, there is evidence that the incidence is increasing in Asian countries [2]. In Sri Lanka, the incidence of colorectal cancer has increased markedly in recent years. The latest data on cancer in Sri Lanka for the year 2010 indicate that colorectal cancer is ranked the fourth commonest cancer among men (age standardized rate 6.2/100,000) and sixth commonest cancer among women (age standardized rate 5.1/100,000) [3].

Though several cohort and case-control studies have investigated the risk factors for colorectal cancer, evidence shows that there is geographical variation. Consumption of red meat is a risk factor while consumption of fruits and vegetables are protective [4,5]. There is increasing evidence that physical activity is protective though most of these studies have been conducted in males [6,7]. There is some evidence of a positive association between alcohol and cigarette smoking and colorectal cancer. [8,9,10]. There is clear evidence that the risk for colorectal cancer increases with age, especially after the fifth decade of life [11,12]. Though genetic risk factors such as history of colorectal cancer or other cancers such as breast, ovarian and endometrial cancers among first degree relatives are established as risk factors in literature, there is no consensus regarding the magnitude of risk [13,14].

There are only a few studies from Asia and no studies from South Asia regarding risk factors for colorectal cancers. Therefore, we designed a case control study to determine the behavioral, familial and comorbid illness risk factors for colorectal cancer among adults in Sri Lanka.

Methods

An unmatched case control study was conducted

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between October 2014 and November 2015 in two districts, which continuously reported the highest incidence of colorectal cancer in Sri Lanka.

Colorectal cancer cases were defined as histologically confirmed incident cases (diagnosed within six months of the study) aged ≥30 years, with no previous diagnosis of any other cancer and resident in the above two districts.

The study utilized two control groups from the hospital and community. Hospital controls were defined as persons with negative colonoscopy findings which excluded colorectal cancer, aged ≥30 years, with no previous diagnosis of any other cancer and resident in the same districts. Hospital controls were selected from individuals who came for screening and patients diagnosed with other conditions such as hemorrhoids and unexplained abdominal pain of short duration. Community controls were defined as persons with no history and documentary evidence of colorectal or any other cancer, aged ≥30 years and resident in the above districts.

Sample size was calculated using the formula for unmatched case control studies with two controls per case [15]. Since several risk factors were studied, hypothesized odds ratios associated with several exposures were used to calculate sample size and the largest estimated sample size was used (risk factor for colorectal cancer of consuming less fruits and vegetables OR 4.0) [6]. The proportion of adults in the community exposed to this risk factor was taken as 73% [16]. The desired probability of type 1 error and type 2 error was taken as 0.05 and 0.2 respectively. Estimating a 15% non-response rate, 65 cases of colorectal cancer, 130 hospital based controls and 130 community controls were recruited for the study.

Eligible cases were recruited from the National Cancer Institute, Sri Lanka, when patients presented for treatment. Community controls were randomly selected using the voters list, which comprises all individuals aged >18 years, from the same geographical areas as the cases. Hospital controls were selected consecutively from medical wards of four major tertiary care health institutions. Information from selected and eligible community controls were obtained during one or more visits to their residence.

Assessment of risk factors

A pre-tested structured questionnaire was administered by four trained medical officers, to collect information on socio-demographic characteristics, behavioral factors (dietary habits, tobacco smoking, alcohol consumption, physical activity), familial factors (history of colorectal cancer and other cancers such as breast, ovarian and endometrial, among first degree relatives) and comorbid illness (intestinal polyps, diabetes mellitus, ischemic heart disease, hypertension, hemorrhoids, inflammatory bowel disease, chronic gastritis, past surgeries.). Genetic and comorbid illness were verified using medical records of participants.

Dietary risk factors were assessed by inquiring about average weekly frequency of consumption of ten food item groups during three time periods of life (during the last 10 years, period between last 10 to 20 years and period 20 years or more from the time of data collection). Frequency was recorded as ≥ 4 times per week, 3 times per week, 2 times per week and occasionally or never. The food groups used in the dietary risk factor analysis is shown in Table 1.

Tobacco smoking and alcohol consumption was assessed based on the CDC (Center for Chronic Diseases and Control) classification of smoking status (never smoker, current smoker, former smoker) and alcohol consumers (lifetime abstainer, former drinker, current drinker) [17].

Table 1. Food groups used in the dietary risk factor analysis

Food group	*Food items*
Coffee	Coffee
Dairy products	Ice cream, yoghurt, curd, fresh milk, milk powder, butter
Baked food	Pastries, pizza, savory or any type of buns, bread, cake
Deep fried food	Chinese rolls, cutlets, patties, samosa, wade, potato chips, deep fried meat or fish, deep fried snacks (e.g. bites, cashew nuts).
Sugar sweetened beverages	Sweetened drinks and frizzy drinks
Red meat	All fresh, minced and frozen beef, pork and lamb
Processed meat	Ham, bacon, sausages, tinned meat of beef and pork
Chicken	All fresh, frozen or minced chicken
Fish	Fresh, canned, salted or smoked fish
Fibrous food	Green leaves, leafy vegetables and all types of fruits

Levels of physical activity were based on the CDC guidelines on physical activity [18]. Intensity of the physical activity (light, moderate, heavy) were assessed in the three domains of occupational activity, household activity, exercise and sports activity. Occupational activity included the occupations done for at least for eight hours per week for four months of the year. Household activity included activities done for at least seven hours per week for four months of the year. Exercise and sports activity included activities done at least two hours per week for four months of the year.

Reliability of the study instruments were assessed employing test-retest method among cases and the two control groups. Kappa coefficient of the risk factors was 0.88 to 1.00, indicating that the reliability of the study instrument was good. The same data collectors collected information from cases and controls using the same questionnaire.

Data analysis

Data was analysed using SPSS Statistical Package for Social Sciences (Version 20). Two sets of risk factors for colorectal cancer were determined by conducting unmatched analyses between cases and the two groups of controls. All potential risk factors were stratified into two levels by amalgamating categories.

Consumption of a food item ≥ 4 times per week and 3 times per week were amalgamated as 'frequently' while 2 times per week, occasionally and never were amalgamated as 'rarely or never' category.

Level of physical activity was categorized by selecting the highest level of intensity in any of the physical activity categories (occupational, household or exercise and sport activity) during the three time periods. Moderate and heavy activity were amalgamated into one category while no or light activity was categorized into one group. Colorectal cancer or other cancer among first degree relative with supporting medical records diagnosed ≤60 years of age was categorized as one category. Not having colorectal cancer among first degree relatives, colorectal cancer among first degree relative with no supporting medical records and colorectal cancer in first degree relative diagnosed after 60 years of age were amalgamated into the other category as verification with medical records was an integral part of the assessment. The age limit was decided according to expert opinion and evidence from literature [13,14]. Presence of a comorbid factor for > 10 years or diagnosed before 10 years with supporting medical records was categorized as one category, while absence of disease, presence of disease for > 10 years or diagnosed before 10 years but no supporting medical records and presence or diagnosis of disease for < 10 years with or without medical records were amalgamated as another category. The time duration was decided according to expert opinion and evidence from literature [19].

Chi-square (χ^2) test was used to assess the associations between variables. A p-value of <0.05 that is based on a two-sided statistical test was considered as significant. Bivariate analysis was carried out to determine the unadjusted odds ratio (OR) with 95% confidence intervals (CI). Backward logistic regression was performed to identify adjusted odds ratio (OR) with 95% confidence intervals (CI). The independent variables used in the backward logistic regression analysis were based on the variables that showed significant association with colorectal cancer in the bivariate analyses (p <0.2) [20].

Written informed consent was obtained from all study participants. Study was approved by the Ethics Review Committee of Faculty of Medicine, University of Colombo, Sri Lanka (EC-15-078).

Results

Response rate was 100%. Among the cases, a majority (n=44, 67.7%) had moderately differentiated adenocarcinomas 22 (33.8%) had rectal carcinoma and 25 (38.5%) had Duke C cancers at the time of diagnosis. Among the hospital controls, a high proportion had colonoscopy performed due to rectal bleeding (n=47, 36.2%). Majority of hospital controls (n=103, 79.2%) showed no abnormality on colonoscopy while several (n=25, 19.2%) were diagnosed with haemorrhoids.

Table 2 shows socio-demographic characteristics of the study population. There were no significant differences between the two control groups except the significantly higher proportion of males among community controls. Mean age was cases 58.9 years (SD ± 9.9), hospital controls 54.8 years (SD ± 12.3) and community controls 53.2 years (SD ± 12.7).

Risk factors identified by adjusted logistic regression are shown in Table 3. Unadjusted analysis showed that frequent consumption of deep fried food ≥ 20 years and hypertension > 10 years were significantly associated with colorectal cancer compared to both control groups (supplementary tables).

Discussion

In this case control study of Sri Lankan adults, several behavioral and familial risk factors and comorbid illnesses were associated with colorectal cancer. This is the first analytical study to evaluate risk factors of colorectal cancer in Sri Lanka and in South Asia. The study included two groups of hospital and community controls. Ideally, only community controls identified using the same criteria for identifying cases, (colonoscopy examination) would have been sufficient. However, in the absence of a routine colonoscopy screening program in Sri Lanka, it was not possible to exclude the presence of colorectal cancer, through colonoscopy screening, in the community controls. This was because of the high cost, invasiveness of the procedure and ethical issues about carrying out colonoscopy in controls for the purpose of a research.

Table 2. Socio-demographic characteristics of the cases and controls

Socio demographic characteristics	*Cases (n=65) Number (%)*	*Hospital Controls (n=130) Number (%)*	*Community Controls (n=130) Number (%)*	P value*
Age in years				
≥ 50 years	52 (80.0)	85 (65.4)	80 (61.5)	0.520
< 50 years	13 (20.0)	45 (34.6)	50 (38.5)	
Sex				
Female	37 (56.9)	64 (49.2)	38 (29.2)	0.001
Male	28 (43.1)	66 (50.8)	92 (70.8)	
Ethnicity				
Sinhalese	62 (85.4)	114 (87.7)	114 (87.7)	1.000
Non-Sinhalese	3 (4.6)	16 (12.3)	16 (12.3)	
Religion				
Buddhist	48 (73.8)	84 (64.6)	78 (60.0)	0.443
Non-Buddhist	17 (26.2)	46 (35.4)	52 (40.0)	
Highest level of education				
≥ GCE Ordinary Level	49 (75.4)	83 (63.8)	69 (53.1)	0.078
< GCE Ordinary Level	16 (24.6)	47 (36.2)	61 (46.9)	
Marital Status				
Married	61 (93.8)	114 (87.7)	123 (94.6)	0.054
Unmarried	4 (6.2)	16 (12.3)	7 (5.4)	

Table 3. Adjusted risk factors for developing colorectal cancer

Predictor Variable	*Adjusted Odds Ratio (95% CI)*	*P value*
Hospital Controls		
Age ≥ 50 years	2.6 (1.1-5.9)	0.028
Frequent consumption of deep fried food for 20 years and beyond †	2.4 (1.2-5.4)	0.013
Frequent consumption of red meat for 20 years and beyond †	3.1 (1.3-7.4)	0.014
Presence of Hypertension diagnosed for 10 or more years	3.3 (1.3-8.6)	0.014
History of colorectal cancer among first degree relatives ≤ age of 60 years	4.9 (1.7-14.2)	0.003
History of breast/ovarian/endometrial cancer among first degree relatives diagnosed ≤ age of 60 years	3.0 (1.1-7.8)	0.026
Community Controls		
Frequent consumption of deep fried food for 20 years and beyond †	4.2 (1.7-10.1)	0.001
Being an ever smoker	3.2 (1.1-9.3)	0.029
Being a current/former drinker	5.4 (1.1-27.8)	0.043
Presence of Hypertension diagnosed for 10 or more years	5.1 (1.7-15.6)	0.004
Education ≥ G.C.E. Ordinary Level	3.5 (1.5-8.3)	0.004

† Usual consumption for three or more times per week

Therefore, we used a second group of hospital controls who had undergone colonoscopy. Selection bias in using hospital controls were minimized by recruiting individuals presenting for screening and for other gastrointestinal disorders of short duration.

We used a carefully designed questions inquiring into specific types of food and beverages consumed in Sri Lanka. Consumption of deep fried food was a risk factor when compared with both control groups. This is similar to findings from other studies [6,21]. This must be addressed in prevention programs as deep fried foods are frequently consumed by Sri Lankans. The risk was higher compared to community controls (OR-4.2) than when

compared to hospital controls (OR-2.4). This indicates that hospital controls have unhealthier dietary patterns such as consumption of deep fried food compared to healthy community controls. Studies conducted in the West have shown that consumption of red meat is a risk factor [14]. This study too identified it as a risk factor when compared to hospital controls but was not significant when compared to community controls [14]. Frequent consumption of processed meat and low consumption of vegetables and fruits were identified as risk factors for colorectal cancer in the bivariate analysis when compared with both control groups. These have been identified as risk factors in studies from Europe [5, 22].

Similar to other studies we also found significant association between history of other cancers (breast, ovary and endometrial) among first degree relatives and colorectal cancer when compared with hospital controls. Studies have reported low strength of associations with OR between 1.3 to 1.6 [13, 23]. We verified this information through medical records. Absence of medical records may account for the lack of significance when compared with community controls. Similarly, a significant association in individuals with first degree relatives with colorectal cancer was found when compared to hospital controls. There was no significant association with these familial risk factors when compared with community controls. This may be due to accuracy of information. Higher incidence of colorectal cancer among individuals with a stronger family history of colorectal cancer among first-degree relative < 60 years of age has been well established in cohort and case control studies [13, 24].

In contrast to existing evidence, the present study found that hypertension was significantly associated with colorectal cancer compared to both control groups. One previous study found no association, while another showed a marginal association [25, 26]. A case control study in Australia reported a protective effect of hypertension [27]. Though hypertension is prevalent in Sri Lanka, the present study only included individuals with a history of 10 years verified by medical records. The verification via medical records could have attributed to the higher risk associated with community controls than hospital controls since availability of records was more among hospital controls than community controls.

Age ≥ 50 years was associated with colorectal cancer when compared with hospital controls. This is similar to findings from other countries [11,12]. However, there was no association when compared to community controls. Though higher education level was significantly associated in bivariate analysis with the community controls many studies have not assessed this risk factor. A case control study in China indicated that lower education level was a risk factor [26]. However, it should be noted that this association was not significant when comparing with hospital controls even in the bivariate analysis.

This study had limitations in assessing some of the risk factors. Identification of smoking as a risk factor only among community controls may be due to higher rates of smoking among hospital controls [28]. Similar to smoking, alcohol consumption also may be more prevalent among hospital controls as it is a risk factor for many other gastrointestinal diseases that could have been present among the hospital controls. More importantly, obesity which is a significant risk factor identified in prospective studies, could not be evaluated due to the retrospective nature of this study. Association of established risk factors such as intestinal polyps and inflammatory bowel disease could not be evaluated due to the small number of positives in the absence of medical records among the participants.

Recall bias would have been present as information regarding risk factors such as diet and physical activity over a period of 20 years was recorded. However, it is necessary to identify exposure over a sufficiently long period. As a strategy to facilitate recall, the period of recall was categorized into 'during last 10 years', 'period between last 10 to 20 years' and 'the last 20 years and beyond'. Categorizing as periods of time instead of inquiring into lifetime exposures aids recall. Present study further minimized recall bias by having simple comprehensible closed ended questions. Adequate time was given to both cases and control to recall past exposure.

We recommend addressing behavioral risk factors of colorectal cancers as a primary preventive measure. Knowledge about familial factors, comorbid illness and other non-modifiable risk factors can be used to identify high risk individuals.

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Conflicts of Interest

Authors declare that there are no conflicts of interests.

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