

Risk Factors for Colorectal Adenocarcinoma in an Indigenous Population in East Africa

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Introduction: The incidence of colorectal cancer (CRC) is increasing in East Africa. Changes in lifestyle and dietary changes, particularly alcohol consumption, smoking, and consumption of cooked meats with a reduction in fibre in the diet may be responsible. The objective of our study was to determine the risk factors responsible for CRC in Uganda.

Methods: We recruited 129 participants with histologically proven colorectal adenocarcinoma and 258 control participants from four specialized hospitals in central Uganda from 2019 to 2021. Controls were block matched for age (± 5 years) and sex of the case participants. The risk factor variables included; area of residence, tribe, body mass index (BMI), smoking, alcohol consumption and family history of gastrointestinal cancer. We used conditional or ordinal logistic regression to obtain crude and adjusted odds ratios for risk factors associated with CRC.

Results: In bivariate analysis, case participants were more likely to be associated with urban residence (cOR: 62.11; $p < 0.001$); family history of GI cancer (cOR: 14.34; $p = 0.001$); past smokers (cOR: 2.10; $p = 0.080$); past alcohol drinkers (cOR: 2.35; $p = 0.012$); current alcohol drinkers (cOR: 3.55; $p < 0.001$); high BMI 25–29.9 kg/m² (cOR: 2.49; $p < 0.001$); and high BMI ≥ 30 kg/m² (cOR: 2.37; $p = 0.012$). In the multivariate analysis, urban residence (aOR: 82.79; $p < 0.001$), family history of GI cancer (aOR: 61.09; $p < 0.001$) and past smoking (aOR: 4.73; $p = 0.036$) were independently associated with a higher risk of developing CRC.

Conclusion: A family history of gastrointestinal cancer was a risk factor for CRC. While population-based CRC screening may not be feasible in low income-countries, targeted CRC screening for first-degree relatives with CRC should be considered in East Africa. Molecular genetic studies need to be carried out to determine the role of hereditary factors in our population. Prevention strategies should be adopted to avoid smoking in our population which was associated with an increased risk of CRC.

Keywords: colorectal cancer, East Africa, risk factors, urban, family history, CRC screening

Introduction

In East Africa, colorectal cancer (CRC) has high morbidity and mortality as it presents at an advanced stage in the affected population.¹ As the sixth most common cancer in Sub-Saharan Africa, it contributes significantly to the cancer burden in this part of the world.^{2,3}

Over the last two decades, there has been a steady increase in Ugandan patients presenting with CRC.⁴ Between the years 1991 and 2010 there has been a 4.1% per year percentage change in the incidence rate for Ugandan female patients. For all patients, during the period 1991–1995, the age-standardized incidence rate was 6.8 per 100,000 and increased to 11.0 per 100,000 for the period 2011–2015. For this time period, there was a 2.2% annual percentage change in the incidence rate of CRC.^{4,5}

In Uganda, although the burden from CRC remains low compared to high-income developed countries, the increase in CRC may be due to an improvement in the diagnosis of this disease. However, an increase in the prevalence of risk factors may also account for the steady increase in CRC.⁶

In high-incidence countries, five percent of CRC cases are caused by genetic disorders such as familial adenomatous polyposis and hereditary nonpolyposis colorectal carcinoma, and sixty-five per cent are sporadic colorectal cancers caused by lifestyle and dietary factors.⁷ In Uganda, 40% of CRC patients are under 49 years of age,⁸ and therefore hereditary factors may also play an important role. However, only 12.4% of colorectal cancers in Uganda exhibit features of signet ring or mucinous histology, which are histological subtypes associated with Lynch syndrome.⁸ Furthermore, other parts of the world, have also reported an increase in the number of young adults presenting with CRC.⁹

Changes in lifestyle, in particular smoking and alcohol consumption, and dietary changes such as an increase in the consumption of cooked meats and a reduction in fibre in the diet, may be responsible for the steady increase in CRC in this part of the world. In the USA, alcohol consumption and smoking result in a one in five probability of CRC.¹⁰ The risk increases with an increase in BMI with obese individuals having a higher risk. Compared to individuals with a BMI of 23, elderly individuals tend to have a 5–100% higher risk of CRC with a BMI of 30.¹⁰

It has been postulated that individuals living in urban areas in Uganda, have a higher risk of certain health behaviours such as decreased physical activity, smoking, alcohol consumption and adoption of a Western diet.¹¹ Furthermore, compared to rural parts of the country, there is also an increased rate of obesity and diabetes. In East Africa, the interplay between environmental and hereditary factors responsible for the aetiology of CRC remains poorly understood.

Therefore, to clarify the uncertainties in the East African context, the objective of our study was to determine the risk factors responsible for CRC in Ugandan patients.

Methodology

Study Design

This was a case-control study.

Study Setting

The study sites were four specialized hospitals, which included Masaka Regional Referral Hospital, Mulago National Referral Hospital, Uganda Martyrs' Hospital Lubaga and Mengo Hospital. Together, these four sites receive over 100 incident cases of CRC per year. All the health facilities that participated in the study are located in central Uganda and receive patients from all regions of Uganda.

Recruitment of Participants

Consecutive case participants with a histologically proven diagnosis of colorectal adenocarcinoma were recruited prospectively during the study period from September 2019 to September 2021. Controls were randomly selected male or female participants who were recruited from patients with other conditions in the same surgery wards and non-relatives of case participants accompanying or visiting the case participants in the respective hospitals. The participants were socioeconomically and ethnically diverse, representing the patient population that came to the four specialized hospitals in central Uganda and the diversity of the Ugandan population.

Controls came from the same catchment as the cases, and there were two control participants for every case participant recruited to increase the power of this study. Controls were block matched for age (± 5 years) and sex of the case participants. To minimize misclassification of undiagnosed cases, controls had a negative faecal occult blood test before final enrolment. The choice of non-relative controls, was to minimize the genetic, environmental and dietary exposure correlation between cases and controls which would have inflated the sample size.

Selection Criteria for Participants

Case participants who had incident histologically proven colorectal adenocarcinoma and were able to provide written informed consent were included. Case participants in poor general health were excluded due to interference with the established patterns of clinical care.

The inclusion criteria for controls included participants with a negative faecal occult blood test who were able to provide written informed consent. Controls did not have any type of cancer as determined from their general physical

examination and medical history. Relatives of case participants and participants testing positive for faecal occult blood were excluded as controls. Participants not willing to provide faecal samples for faecal occult blood testing were also excluded as controls.

Those control participants who tested positive for faecal occult blood, were referred for a colonoscopy to the endoscopy units in the respective hospital sites. The two matched controls were delineated as control A and control B. During the matching, the first control to be identified was delineated as “A” and the second as “B”.

Study Variables

The study variables were obtained through the history taken from all the study participants using a pre-coded and pretested interview administered questionnaire. The same interview-administered questionnaire was used for case and control participants. The variables included age, sex, area of residence (urban or rural), tribe, body mass index (BMI), alcohol consumption, smoking, diabetes, use of hormone replacement therapy, family history of colorectal cancer and family history of gastrointestinal cancer.

Age was block matched (± 5 years) for case and control participants, while sex was matched for case and control participants. BMI was determined by measuring weight in kilograms per height in metres squared. Smoking use was determined through history taking with a response of “yes” or “no”, including the type, amount and duration of smoking. Alcohol consumption was determined from the history by responding to “yes” or “no”, including the type, amount and duration of alcohol consumption.

Urban residence included participants residing in gazetted urban centres and ungazetted trading centres having a population exceeding 1000 persons according to the 1991 Population and Housing Census (National Population and Housing Census, 2014). Rural residence included all localities and excluding areas of urban residence.⁸⁸

Quality Assurance and Laboratory Methods

The diagnosis of invasive colorectal adenocarcinoma was confirmed on hematoxylin and eosin staining of the tissue slides. The histopathological type and grade were determined on all the tissue slides. Two experienced consultant pathologists read all the tissue slides for each case participant.

Data Analysis

Data were statistically analyzed using STATA version 14.0. Categorical variables were summarized as percentages, and continuous variables were summarized as the means (standard deviation). In the bivariate analysis, the relationship between CRC status and categorical exposure variables was assessed by using Pearson’s or Fischer’s exact chi-square tests as appropriate. Secondary, crude and adjusted odds ratios of having a given risk factor and their associated 95% confidence intervals were estimated via two forms of logistic regression models depending on model convergence. Thus, we used matched analysis using conditional logistic regression and unmatched analysis using ordinary logistic regression.

Variables in the multivariable models were included in a stepwise fashion and were based on biological plausibility, literature review and a bivariate p-value of up to 0.2. Candidate variables for multivariable modelling were first assessed for collinearity and in all instances, two or more variables with a correlation of at least 40% were not included into the same multivariable model. In the final model, only variables with a p-value < 0.05 were considered statistically significant.

Results

A total of 387 participants were included in this study. The study groups were composed of 129 case participants and 258 control participants. The mean age (SD) of the case participants was 54 (16.2) years. The mean age of control A participants was 53.4 (16.1) years and of control B participants was 53.3 (16.3) years. The 129 case participants included 67 (51.9%) colon cases and 61 (46.7%) rectal cases (Table 1).

In Table 2, 61.2% of cases resided in an urban setting compared to 48.5% of controls ($p=0.018$). Approximately 5% of cases compared to no controls had a family history of CRC ($p=0.001$) and 10.1% of cases compared to 0.8% of controls had a family history of GI cancer ($p<0.001$).

Table 1 Distribution of Colorectal Cancer Case Participants

Site	Categories	Number of CRC Case Participants	Percentage (%)
Colon	Caecum	11	8.6
	Ascending colon	14	10.9
	Hepatic flexure	2	1.6
	Transverse colon	3	2.3
	Splenic flexure	1	0.8
	Descending colon	8	6.3
	Sigmoid colon	19	14.8
Colorectal	Rectosigmoid	9	7.0
Rectum	Rectum	61	46.7

Table 2 Descriptive Statistics of Demographics and Family History for Participant Groups

Variable	Categories	Cases (n)	Cases (%)	Controls (n)	Controls (%)	p-value
Sex	Male	66	51.2	130	50.4	0.886
	Female	63	48.8	128	49.6	
Mean (SD) age Age Groups (Years)	<20	54.0 (16.2)		53.3 (16.21)		0.921*
	20–39	3	2.3	5	1.9	
	40–59	20	15.5	44	17.1	
	60+	53	41.1	110	42.6	
		53	41.1	99	38.4	
Residence	Rural	50	38.8	133	51.6	0.018
	Urban	79	61.2	125	48.5	
Family history of CRC	Yes	6	4.7	0	0	0.001*
	No	123	95.4	258	100	
Family history of GI cancer	Yes	13	10.1	2	0.8	<0.001
	No	116	89.9	256	99.2	
Tribe	Baganda	65	50.4	141	54.7	0.428
	Others	64	49.6	117	45.3	

Note: *Fischer-exact chi-square test.

Demographics and Family History of Colorectal Cancer and Gastrointestinal Cancer

In bivariate analysis, the odds of being a CRC case were higher among patients who resided in an urban setting than among those in a rural setting (cOR=62.11, 95% CI, 30.62–125.99) and among patients with a family history of GI cancer (cOR=14.34, 95% CI, 3.19–64.60). Compared to patients who had never smoked, past smokers were twice as likely to have CRC (cOR=2.10, 95% CI, 0.91–4.82). With alcohol intake, compared to patients who were never drinkers, the odds of having CRC were 2.35 (95% CI, 1.20–4.59) and 3.55 times (95% CI, 1.87–6.75) in patients who were past and current drinkers, respectively. Compared to patients with a BMI of <25, the odds of being a CRC case were more than two times (cOR=2.49, 95% CI, 1.50–4.14) and 2.37 times (95% CI, 1.21–4.64) in patients who had a BMI of 25–29.9 and ≥ 30 , respectively.

Body Mass Index

Case participants having a BMI $\geq 30\text{kg/m}^2$ were 14.7%. There were 8.5% of control A participants and 8.5% of control B participants who had a BMI $\geq 30\text{kg/m}^2$. An increased risk of CRC was associated with increasing BMI ($p=0.001$) (Table 3). The risk of developing CRC in obese patients was 2.37 (cOR:2.37; 95% CI: 1.21–4.64), and in the multivariate analysis, it was 1.23 (aOR:1.23; 95% CI: 0.44–3.41) (Table 4).

Smoking

A total of 6.9% of case participants were past smokers, while 5.4% of control A participants and 3.9% of control B participants were past smokers. A total of 6.9% of case participants were current smokers, while 6.2% of control A participants and 5.4% of control B participants were current smokers. A total of 52.6% of case participants smoked more than 5 cigarettes daily, while 33.3% of control A participants and 45.5% of control B participants smoked more than 5 cigarettes daily. Past smokers had a higher risk of developing CRC at 4.73 (aOR:4.73; $p=0.036$) (Table 4).

Alcohol Consumption

A total of 14.7% of the case participants drank alcohol in the past, while 10.1% of control A participants and 6.2% of control B participants drank alcohol in the past. A total of 20.2% of case participants currently drank alcohol, while 8.5% of control A participants and 6.2% of control B participants currently drank alcohol. Case participants had a risk of 3.55 if they were currently drinking (cOR:3.55; 95% CI: 1.87–6.75) and a risk of 2.35 when they were past drinkers (cOR:

Table 3 Descriptive Statistics of Lifestyle Factors for the Participant Groups

Characteristic(s)	Categories	Cases		Control A		Control B		P-value
		N	%	N	%	N	%	
Smoking history	Never	50	86.2	114	88.4	117	90.7	0.874*
	Past	4	6.9	7	5.4	5	3.9	
	Current	4	6.9	8	6.2	7	5.4	
Frequency of smoking per day	<5 cigarettes	9	47.4	10	66.7	6	54.6	0.530
	5+	10	52.6	5	33.3	5	45.5	
Average length of smoking	≤ 5 year	3	16.7	2	18.2	1	8.3	0.970*
	6–10 years	1	5.6	1	9.1	1	8.3	
	11+ years	14	77.8	8	72.7	10	83.3	
Alcohol intake	Never	84	65.1	105	81.4	113	87.6	<0.001
	Past	19	14.7	13	10.1	8	6.2	
	Current	26	20.2	11	8.5	8	6.2	
Frequency of alcohol intake	Daily	9	20.0	8	32.0	3	18.8	0.392*
	Weekly	17	37.8	4	16.0	5	31.3	
	Past Drinkers	19	42.2	13	52.0	8	50.0	
Type of Alcohol	Beer	11	42.3	8	66.7	1	12.5	0.016*
	Spirits	5	19.2	3	25.0	6	75.0	
	Wine	10	38.5	1	8.3	1	12.5	
Quantity of Alcohol	Glasses	10	38.5	3	25.0	4	50.0	0.639*
	Small bottles	11	42.3	6	50.0	4	50.0	
	Large bottles	5	19.2	3	25.0	0	0.0	
BMI	<25	70	54.3	96	74.4	96	74.4	0.001
	25–29.9	40	31.0	22	17.1	22	17.1	
	≥ 30	19	14.7	11	8.5	11	8.5	

Note: *Fischer-exact chi-square test.

Table 4 Multivariate Analysis of Risk Factors Associated with Colorectal Cancer in Ugandan Patients

Characteristic(s)	Categories	cOR	95% CI		P-value	aOR	95% CI		P-value
Sex	Male	1.00							
	Female	1.03	0.68	1.57	0.886				
Age group	<20	1.00							
	20–39	0.76	0.16	3.48	0.721				
	40–59	0.80	0.18	3.49	0.770				
	60+	0.89	0.21	3.88	0.879				
Residence	Rural	1.00				1.00			
	Urban	62.11	30.62	125.99	<0.001	82.79	35.13	195.11	<0.001
Family history of GI Cancer	No	1.00				1.00			
	Yes	14.34	3.19	64.60	0.001	61.09	8.68	430.05	<0.001
Smoking history	Never	1.00				1.00			
	Past	2.10	0.91	4.82	0.080	4.73	1.11	20.10	0.036
	Current	0.98	0.39	2.47	0.966	0.66	0.14	3.07	0.593
Frequency of smoking per day	<5 cigarettes	1.00							
	5+	1.78	0.54	5.89	0.347				
Average length of smoking	≤5	1.00							
	6–10 years	0.50	0.03	8.95	0.638				
	11+ years	0.78	0.14	4.46	0.778				
Alcohol intake	Never	1.00				1.00			
	Past	2.35	1.20	4.59	0.012	0.90	0.32	2.51	0.841
	Current	3.55	1.87	6.75	<0.001	2.57	0.82	8.06	0.105
Frequency of alcohol intake	Daily	1.00							
	Weekly	2.31	0.70	7.63	0.170				
	Past Drinkers	1.11	0.38	3.25	0.855				
Type of Alcohol	Beer	1.00							
	Spirits	0.45	0.11	1.85	0.271				
	Wine	4.09	0.71	23.67	0.116				
Quantity of Alcohol	Glasses	1.00							
	Small bottles	0.77	0.21	2.80	0.691				
	Large bottles	1.17	0.21	6.56	0.861				
BMI	<25	1.00				1.00			
	25–29.9	2.49	1.50	4.14	<0.001	1.24	0.57	2.70	0.590
	≥30	2.37	1.21	4.64	0.012	1.23	0.44	3.41	0.691

2.35; 95% CI: 1.20–4.59). In the multivariate analysis, current alcohol drinkers had a 2.57 risk of CRC; however, this did not reach statistical significance (aOR: 2.57; 95% CI: 0.82–8.06) (Table 4).

Tribe

There were 50.4% of case participants from the Baganda tribe and 49.6% from other tribes. The risk of CRC with other tribes was 1.26 (cOR: 1.26; 95% CI: 0.83–1.93), and this did not reach statistical significance (Table 3).

After adjusting for potential confounding factors, urban residence (aOR=82.79, 95% CI, 35.13–195), family history of GI cancer (aOR=61.09, 95% CI, 8.68–430.05) and past smoking (aOR=4.73, 95% CI, 1.11–20.10) were associated with the likelihood of developing CRC (Table 4).

Discussion

This study investigated the risk factors related to CRC in an East African population. In our population, the results show that an urban domicile, family history of gastrointestinal cancer and smoking are associated with CRC. The association between age and sex and CRC could not be determined in our study, as these variables were matched.

An association between colorectal cancer and individuals who lived in urban areas within the country was found in our study. In Sub-Saharan Africa, dietary changes have been associated with urbanization, particularly with a reduction in the consumption of plant-based foods and staple starches and an increased intake of meat and fat energy-dense foods.¹² A well-known risk factor for CRC in urban settings is a westernized diet with high consumption of processed meat.¹³

A higher incidence of CRC in urban areas than in rural areas has also been found in studies from the USA and the Middle East.^{13–15} Paquette et al showed that there is a significant difference in the incidence of CRC between urban and rural areas.¹⁶ In Sub-Saharan Africa, an urban residence has also been found to be associated with a higher incidence of colorectal cancer, which is in keeping with the findings in our study.¹⁷ Urbanization is associated with obesity due to a sedentary lifestyle, noncommunicable diseases such as diabetes and behavioural risk factors, in particular smoking and alcohol consumption, which are associated with CRC. However, this difference in the incidence of CRC between rural and urban areas may be due to a difference in access to diagnostic colonoscopy services and health care facilities.¹⁸

Urbanization has been found to be associated with high levels of tobacco smoking, and a study has shown a 1.8 times increased incidence of CRC in the urban area of the Ardabil Province of Iran.¹⁹ Studies have also shown that urbanization is associated with physical inactivity resulting in a high BMI.¹⁵ The prevalence of obesity has been found to be higher in urbanized areas and significantly lower in rural areas.^{20–22} This increased prevalence of obesity due to physical inactivity increases the incidence of colorectal cancer.^{15,20} Industrialization may explain the physical inactivity in individuals from urban communities leading to obesity.¹⁵ Apart from urban individuals having adopted a westernised diet, they also have a higher prevalence of noncommunicable diseases such as diabetes, smoking and alcohol consumption, which results in a more frequent predisposition to the risk factors associated with CRC.

The presentation of many of our CRC study participants was at an age younger than 40 years. The mean age in our study was 54 years for CRC participants; 17.8% of CRC patients were below the age of 40 years, and 58.9% were below 60 years of age. This is in contrast to findings from the USA whereby only 17.4% of CRC patients present under 54 years of age and in the UK only 16% of CRC patients were diagnosed under the age of 60 years.^{23–25} Compared to developed countries, Africa reports a lower median age and a higher proportion of individuals presenting with CRC under 50 years of age.²³ The reason for the younger age may be due to a shorter life expectancy in a younger population or it may be due to a different CRC tumour biology.²³

Globally, the majority of CRC cases occur in individuals with no predisposing disease or familial history. Given the high frequency of CRC presenting at a younger age in Uganda, the role of hereditary factors as a risk factor needs to be explored.²⁶ Compared to Western developed countries, it has been postulated that there is a higher frequency of Lynch syndrome in Uganda. This may be consistent with studies from Sub-Saharan Africa, which have shown a high frequency of mismatch repair protein deficiency in colorectal cancers.²⁷

In our study, the risk was higher for having a history of colon or rectal cancer in the family. Individuals having relatives with CRC have been shown to have a higher predominance of adenomas with two or more adenomas in the colon.^{28–31} A difference in the location of these adenomas has not been reported in these individuals.^{28–32} Molecular genetic studies are currently being performed on the colorectal cancer tissues of our patient cohort to determine the frequency of hereditary nonpolyposis colorectal carcinoma in our population and to determine whether adenomas are actually predisposing to CRC in our familial CRC patients. Since the cost of population screening for CRC is high, targeting these individuals with a positive family history of CRC for screening may be feasible in the East African context.

Lack of exercise and obesity have been shown in studies to be important lifestyle factors that are associated with CRC.^{33,34} A sedentary lifestyle has been found to be an independent risk factor for CRC.³³ A sedentary lifestyle leads to obesity, and unequivocally, our study showed a positive correlation of a risk of CRC with increasing BMI. However, our

study did not independently examine the effect of a lack of exercise. A recent study showed a fifty percent increased risk of CRC with a sedentary lifestyle.^{33,34}

In obese men, it has been shown that the risk of rectal and colon cancer is twenty percent and fifty percent, respectively.³⁵ A meta-analysis has shown that for every five kilograms increase in body weight, there is a three percent increase in the tendency to develop CRC.¹⁰ A high BMI is associated with a fifteen percent risk of developing rectal cancer and a forty-seven percent risk of developing colon cancer.^{36,37} An increased tendency to develop colon cancer has been found in individuals up to middle age with an increase in weight. However, a lower tendency of developing colon cancer with an increase in weight in middle- and older-aged individuals was reported in the same study.^{38,39}

Due to the small number of diabetic patients recruited in our study we could not report on the relationship between diabetes and CRC. However, independent of a lack of physical exercise and obesity, diabetes has been found in other studies to be a risk factor for CRC.^{40,41} Diabetic patients tend to have high levels of insulin and insulin-like growth factors. Insulin-like growth factors inhibit the apoptosis of colonic epithelial cells, while hyperinsulinaemia causes activation of the Ras pathway, which stimulates carcinogenesis.^{42,43}

Studies in diabetic individuals have shown that colonic tumours may develop when insulin activates aberrant foci in the crypts of the colonic epithelium.^{44–47} Obesity is an independent risk factor for CRC, which has been increasing in the affluent population of Sub-Saharan Africa. Obesity may also be responsible for the steady increase in noncommunicable diseases such as diabetes which in turn may also increase the risk of CRC.

Several studies support the association between alcohol consumption and rectal cancer,^{48–51} while other studies found no association between rectal cancer and alcohol intake.^{52–54} Studies have also reported a significant relationship between alcohol consumption and colon cancer.^{50,51,55–57} From seven studies that confirmed an association between rectal cancer and alcohol, six studies showed that beer intake increased the risk, three studies showed spirits increasing the risk, two studies showed that wine intake increased the risk and one study showed no association between rectal cancer and the intake of wine.^{48–51,58,59} A meta-analysis has shown a forty percent risk of CRC developing in individuals who drink three alcoholic drinks a day, while there is a twenty percent risk of CRC if they drink two to three alcoholic drinks daily.⁷²

In our study, the type of beverage consumed in the form of beer, spirits or wine and the frequency and quantity of alcohol consumed had no association with the development of CRC. An association with CRC was seen even with a small amount of alcohol intake with past and current alcohol drinkers, although this did not reach statistical significance in the multivariable model, possibly because other confounding variables, such as smoking, BMI and area of residence, were also considered in our study. A study observed that biopsies taken from chronic alcoholics showed rectal mucosal hyperproliferation, which is associated with an increased risk of cancer compared to rectal biopsies from controls.⁵⁸

There is sparse evidence regarding the type of beverage effects on CRC, with studies generally showing a strong association with the intake of beer,^{49,58,59} however, there is also an increased risk with wine and spirits.⁵⁹ Some studies have shown no risk of CRC with wine, which suggests that this beverage has anticarcinogenic effects compared to other beverages.⁶⁰

Several biological mechanisms have been postulated regarding the role of alcohol in colorectal carcinogenesis. The contamination of beer with nitrosamine carcinogens from breweries may explain the consistent finding of an association between beer and colorectal cancer in several studies.⁵⁶ Another mechanism is that alcohol consumption damages the liver, resulting in the inhibition of the detoxification of nitrosamines and other carcinogens.⁶¹ Low aldehyde dehydrogenase activity in the colonic mucosa results in the accumulation of acetaldehyde in the colon and rectum, which is carcinogenic.^{60,62} A Japanese study showed an increased risk of colon cancer in individuals who drink alcohol and have a mutant aldehyde dehydrogenase-2-allele.⁶³ The intake of methionine and folate micronutrients is required for the methylation of DNA, which is responsible for gene regulation. A low level of folate and methionine in the diet has been found in men who drink alcohol to increase the risk of colon cancer.⁶⁴

In our study wine was not significantly associated with an increased risk of CRC. This is in keeping with other studies from Italy that showed no increased risk of wine with CRC.^{65,66} Other studies have observed an anticarcinogenic effect in wine.⁶⁰ The cellular events of CRC initiation, promotion and progression are inhibited by phytoalexin called resveratrol found in wine and grapes.⁶⁷ In rats, resveratrol has been found to suppress the growth of human colon cancer cells by

suppressing the growth of aberrant colorectal crypt foci.⁶⁸ The growth of human cancer cells has also been shown to be suppressed by methanol extracts in white and red wine, which contain flavonoids, particularly anthocyanin.⁶⁹

We found that current cigarette smokers had a negative correlation with CRC; however, with past smoking had a positive correlation. This is consistent with results from previous studies.^{70,71} Possible pathophysiological mechanisms behind the decreased risk in current smokers is that peristalsis of the colon may be stimulated by the nicotine in cigarette smoke. Nicotine increases the motor activity and tone of the colon, resulting in a decreased faecal transit time and hence decreasing the tendency to develop colon cancer.⁷²

However, cigarette smoking has also been shown to increase the risk of adenomatous polyps in the colon and rectum, which eventually lead to colorectal cancer. A recent meta-analysis conducted in Europe, the USA and Asia showed that past smokers and ever smokers were strongly associated with CRC; however, for current smokers, the association with CRC was weak.⁷³ Proximal colon cancers were associated with past smokers and ever smokers, while rectal cancers were associated with past, current and ever smokers.^{73,74} In another meta-analysis, it was found that compared to nonsmokers, the risk of rectal and colon cancer was greater for current and past cigarette smokers. Passive smokers are exposed to higher levels of carcinogenic compounds than active smokers.⁷⁵ These high levels of carcinogenic compounds in passive smokers include nitrosamines, carbon monoxide and ammonia.⁷⁶ Carcinogenic compounds generally found in tobacco smoke mainly include arylamines, N-nitosonornicotine, polycyclic and aromatic hydrocarbons.⁷⁶ Our study did not examine the effect of passive smoking on the risk of CRC.

In rectal and colon cancer patients, epigenetic and mutational changes in the BRAF and KRAS genes have been identified. However, heavier smokers tend to have CRC molecular subtypes that are a combination of MSI high and CIMP positive. Therefore, the serrated pathway is commonly involved in the development of CRC in smokers.⁷⁷ In rats, heterocyclic amines in cigarette smoke have been found to mutate the APC (adenomatous polyposis coli) gene causing colon cancer. This mutation in the APC gene has also been found in human colon cancer.^{76–79}

Earlier studies in Sub-Saharan Africa have examined the relative frequency of cancers and outlined possible differences in the risk between different tribes.⁸⁰ In Uganda, the different traditional ethnic groups have been residing in different parts of the country. Although the case participants in our study were recruited from hospitals in central Uganda whose catchment is representative of all of the country, the majority were currently living in different residential areas in Uganda and not in their native home tribal district. Furthermore, there are socioeconomic differences between individuals in the same tribe that were not assessed in this study. This may possibly explain the findings in our study and those of another study in Uganda where the difference in the tribe was not found to be a risk factor for CRC.⁸¹

Limitations

Early undiagnosed colorectal cancers possibly could have been left out due to the lack of population screening, resulting in a selection error. Given the low prevalence of CRC at 9.3% from patients reported to our National Referral Hospital in Central Uganda,⁸¹ the general population at risk of CRC is low; therefore, the effect of this selection error is likely to be small. The relation between age and sex on CRC could not be determined in our case-control study, as they were matched variables.

Recall bias was another limitation in our study as the CRC disease history was self-reported however reliable histories were obtained for smoking and alcohol consumption. The lack of data on socioeconomic factors, such as the individuals' level of education, and neighbourhood residential factors, which have been found to be risk factors for CRC in other studies⁸² is a limitation. Data were also lacking on the duration, quantity of alcohol intake and physical activity, which is a potential limitation of our study. However, further follow-up studies will address these risk factors in our East African environment.

While inflammatory bowel disease is a risk factor for CRC, none of our histologically proven adenocarcinomas from our patient cohort in Uganda had features of ulcerative colitis or Crohn's disease on histological examination. This is in keeping with the generally very low incidence of ulcerative colitis in Africa which is currently 5.12/per 100,000 population.^{83–88}

Hospital-based studies may result in selection bias, as they may not be representative of the entire population. The patients who tend to come to these centres are the ones who can afford to come very long distances, so generalization needs to be done with caution. However, our patients were recruited from four major specialized hospitals in central

Uganda that receive patients from all four major regions of the country, giving a high level of confidence about the generalizability of the study findings.

Conclusions

Our study determined the risk factors associated with CRC in an indigenous population in East Africa. A positive family history of gastrointestinal cancer is a risk factor; therefore, it is imperative that molecular genetic studies be carried out to determine the role of genetic susceptibility in our population. Although in low-income developing countries it may not be feasible to carry out population-based CRC screening, our findings show that the feasibility of targeted CRC screening, particularly for first-degree family members, should be considered in our East African population. Lifestyle factors, particularly smoking, were associated with an increased risk of CRC. Urbanization in East Africa has resulted in this urban population changing to a sedentary lifestyle, which leads to obesity, adoption of health-risk behaviours and a westernized type of diet that tends to be associated with CRC. Hence, these findings highlight the importance of adopting prevention strategies to help the population avoid these health-risk behaviours.

Data Sharing Statement

The dataset generated and/or analyzed during this PhD study is available as an Excel supplementary file titled: “Risk factors for CRC in an indigenous East African population”.

Ethical Considerations

This work was part of the PhD study, which was approved by the Higher Degrees Research and Ethics Committee, School of Biomedical Sciences, College of Health Sciences, Makerere University (reference number: SBS-HDREC -630) and Uganda National Council for Science and Technology (reference number: HS-2574). Written informed consent was obtained from all participants included in the study before completing the questionnaire form. Written informed consent was obtained before obtaining a biopsy confirming colorectal adenocarcinoma on the case participants and before obtaining a faecal occult blood sample in control participants. Those control participants who tested positive for faecal occult blood were referred for screening investigations, particularly a colonoscopy, to rule out or confirm colorectal malignancy. All data pertaining to the research were kept as confidential as possible and did not identify any particular individual. The conduct of this study was in accordance with the principles outlined in the Declaration of Helsinki.

Consent for Publication

Written informed consent was obtained from all participants included in the study before completing the questionnaire form. Written informed consent was obtained before obtaining a biopsy confirming colorectal adenocarcinoma in the case participants. For control participants, written informed consent was obtained before obtaining a faecal occult blood sample.

Acknowledgments

This study was part of the PhD work, which was approved by the Doctoral Committee and Higher Degrees Research and Ethics Committee of the School of Biomedical Sciences, College of Health Sciences, Makerere University for the corresponding author. Final approval of this research study was obtained from the Uganda National Council for Science and Technology. The authors wish to thank the clinical staff and research assistants, particularly Dr. Sulaiman Ishaq Mahmud and Dr. Justus Atuhairu who recruited the participants from the Department of Surgery of Masaka Regional Referral Hospital, Mulago National Referral Hospital, Uganda Martyrs' Hospital Lubaga and Mengo Hospital for their support in this research project.

Funding

The authors declare that they received no specific funding for this work. However, the corresponding author personally funded this part of his PhD research study. No payment was received by the authors to write and publish this part of the study.

Disclosure

The authors declare that they have no competing interests.

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