Dietary Risk Factors for Colorectal Cancer in an Indigenous East African Population

Chapter · December 2022

DOI: 10.9734/bpi/pramr/v2/4525E

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Print ISBN: 978-81-960551-7-2, eBook ISBN: 978-81-960551-6-5

Dietary Risk Factors for Colorectal Cancer in an Indigenous East African Population

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ABSTRACT

Introduction: Low-income countries in East Africa have a lower incidence of colorectal cancer (CRC) than high-income countries; however, the incidence has steadily increased in the last few decades. In East Africa, the extent to which genetic and environmental factors, particularly dietary factors, contribute to the aetiology of CRC is unclear. Therefore, the objective of our study was to determine the relationship between dietary factors and CRC in an indigenous population in East Africa.

Methods: We conducted a case-control study and recruited 128 cases and 256 controls, block matched for age (±5 years) and sex. Data regarding diet were obtained from all the participants using an interview-based questionnaire. The potential dietary risk factors and protective factors evaluated included the type, frequency of meat consumed and the type and frequency of fibre foods consumed. The frequency was either 4x and above/week or 2-3x/week or 1x/week or never. Ordinal and conditional logistic regression analyses were used to determine the odds ratios associated with the different risk and protective factors.

Results: The mean age (SD) was 53.5(16.2) years and the male:female ratio was 1:1 for all the participants. The most significant risk factors included consumption of boiled beef 2-3x/week (aOR:1.63; p<0.001) and consumption of fried chicken 2-3x/week (aOR: 2.60; p=0.027). Consumption of high fibre foods, including:- cassava for ≥4x/week (aOR: 0.40; p=0.016), millet for 1x/week (aOR: 0.49; p=0.034) and for ≥4x/week (aOR:0.32; p=0.001), spinach for ≥4x/week (aOR:0.30; p=0.003), and potatoes 2-3x/week (aOR: 0.44; p=0.041), were protective against CRC.

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Conclusions: The consumption of cooked meat increases the risk of CRC, while the intake of high-fibre foods may reduce the risk of CRC among Ugandans. We recommend nutritional educational programmes to increase public awareness regarding the protective role of a high fibre diet and to limit the intake of cooked meat in our indigenous East African population.

Keywords: Colorectal cancer; East Africa; protective factors; risk factors; high-income developed countries; low-income developed countries.

1. INTRODUCTION

In 2020, colorectal cancer (CRC) was the third most common malignancy with 1.9 million incidence cases and 935,000 deaths worldwide [1,2]. High-income developed countries have a high incidence of CRC; however, in low-income developing countries, while there is a lower incidence, this has steadily increased in the last few decades.

In Uganda, the age-standardized incidence rate has steadily increased from 6.8 to 11.0 per 100,000 from 1991 to 2015 [3,4]. This increase in the incidence rate of CRC poses a public health challenge even though the burden from CRC is below that found in high-income developed countries. To reduce CRC morbidity and mortality, awareness among the population regarding the prevention of CRC, promotion of a healthy lifestyle and implementation of screening programmes are necessary.

During the last few decades, the increase in the incidence of CRC in East Africa, has resulted from an improved diagnosis; however, other reasons have been postulated [5]. These include the increased prevalence of risk factors in our community, which may be responsible for an increase in noncommunicable diseases such as CRC [5-8].

In East Africa the extent to which genetic and environmental factors particularly dietary factors contribute to the aetiology of CRC is unclear. It has been postulated that hereditary factors are important in Africa, as 25% of the affected individuals are younger than 40 years of age [5,9] and have mucinous histology, which is consistent with Lynch syndrome [10]. A high frequency of early-onset CRC among African-Americans has been found, and this supports genetic hereditary factors being responsible for being a risk factor for CRC [11].

However, the importance of environmental factors is also explained by the high frequency of CRC among African-Americans [12]. In 2014, the age-standardized incidence rate of CRC in white Americans was 43.2 and in black Americans was 55.4 per 100,000 population [12]. It has also been shown that there is an increase in CRC in older individuals in Zimbabwe emphasizing the importance of environmental factors [13].

Changes in the traditional Ugandan diet and the adoption of a Western diet, especially in urban areas of Uganda may be the environmental factors responsible for this increase in the incidence rate of CRC. Dietary changes such as the increased consumption of cooked meat and processed meat together with a reduction in high fibre foods may be responsible [14]. Lifestyle changes such as smoking and alcohol consumption and an increase in the incidence of noncommunicable diseases such as diabetes are also risk factors that may be responsible for the steady increase in CRC in our environment [14].

To our knowledge in Uganda, no study has investigated the relationship between dietary factors and CRC. Therefore, the objective of our study was to investigate the relationship between dietary factors and CRC in an indigenous population in East Africa.

2. METHODOLOGY

2.1 Study Design

This was a case-control study in which cases and controls were block matched for age (±5 years) and matched for sex.

2.2 Study Setting

The study was conducted in four specialized hospitals in central Uganda. These included Masaka Regional Referral Hospital, Mulago National Referral Hospital, Uganda Martyrs' Hospital Lubaga and Mengo Hospital.

2.3 Study Sample

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

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

2.4 Selection Criteria for Participants

Case participants who had incident histologically proven colorectal adenocarcinoma and were able to provide written informed consent were included. Duplicate cases and case participants in poor health that may interfere with established patterns of care were excluded.

The inclusion criteria for controls included participants with a negative faecal occult blood test who were able to provide written informed consent. Controls had no 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.

2.5 Study Variables

The study variables were obtained through the history taken from all the study participants using a precoded and pretested interview administered questionnaire. The same interview-administered questionnaire was used for case and control participants. The variables include age, sex, type and frequency of meat consumed (either 4x and above/week or 2-3x/week or 1x/week or never) and the type and frequency of fibre consumed (either 4x and above/week or 2-3x/week or 1x/week or never).

Age was block matched (±5 years) for case and control participants, while sex was matched for case and control participants.

2.6 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.

2.7 Data Analysis

We conducted data analysis using STATA version 14.0 where we summarized categorical variables by percentages. During bivariate analysis, we used either conditional or ordinal logistic regression models to establish relationships between high fibre foods or meats (variables) and CRC status. We then included high fibre foods or meats with a p-value of 0.20 at bivariate into a multivariable model by forward selection in a stepped wedge manner. We reported variables with a p-value less than 0.05 in the multivariable analysis as independently associated with CRC status.

3. RESULTS

There were 128 CRC case participants and 256 control participants. The mean age (SD) of the case participants was 53.9 (16.2) years, and that of the control participants was 53.3 (16.2) years. The male:female ratio for all the participants was 1:1.

Table 1. Relationship between the consumption of different types of meats and CRC status

Characteristic(s)	Categories	cOR	95% CI		p-value
Roast Chicken	Never	1.00			
	1x a week	1.88	1.18	3.01	0.008
	2-3x a week	1.95	0.94	4.04	0.073
	4+ x a week	-	-	-	-
Fried Chicken	Never	1.00			
	1x a week	1.42	0.89	2.26	0.142
	2-3x a week	3.10	1.48	6.47	0.003
	4+ x a week	0.51	0.06	4.37	0.538
Boiled Chicken	Never	1.00			
	1x a week	1.68	1.07	2.64	0.025
	2-3x a week	2.31	0.99	5.41	0.054
	4+ x a week	-	-	-	-
Boiled beef	Never	1.00			
	1x a week	0.96	0.51	1.79	0.889
	2-3x a week	2.98	1.58	5.59	0.001
	4+ x a week	2.15	0.92	5.02	0.078
Roast Lamb	Never	1.00			
	1x a week	0.77	0.33	1.78	0.537
	2-3x a week	2.08	0.49	8.85	0.319
	4+ x a week	4.65	0.41	53.26	0.217
Fried Pork	Never	1.00			
	1x a week	1.27	0.79	2.03	0.317
	2-3x a week	1.12	0.51	2.46	0.783
	4+ x a week	0.72	0.14	3.59	0.688
Roast Pork	Never	1.00			
	1x a week	1.06	0.59	1.90	0.846
	2-3x a week	1.33	0.49	3.55	0.576
	4+ x a week	1.55	0.34	6.94	0.570

Table 1 shows the crude odds ratios for the relationship between CRC status and types of meat, while Table 2 shows the crude odds ratios for the relationship between CRC status and high-fibre foods.

The following observations were made on the type and frequency of meat consumed in the bivariate analysis. Compared to individuals who never consumed roast chicken, those who consumed roast chicken once and 2-3 times a week were 1.88 (cOR: 1.88; p=0.008) and 1.95 (cOR: 1.95; p=0.073) times more likely to have CRC. Individuals who consumed fried chicken 2-3 times a week were 3.10 (cOR: 3.10; p=0.003) times more likely to have CRC compared to those who never consumed fried chicken. Compared to individuals who never consumed boiled chicken, those who consumed boiled chicken once and 2-3 times a week were 1.68 (cOR: 1.68; p=0.025) and 2.31 (cOR: 2.31; p=0.054) times more likely to have CRC.

Consumption of boiled beef at a frequency of 2-3 times a week and 4 times and above every week were 2.98 (cOR: 2.98; p=0.001) and 2.15 (cOR: 2.15; p=0.078) times more likely to develop CRC compared to no consumption of boiled beef. Table 1 shows that consumption of roasted lamb, fried pork, and roasted pork was associated with an increased likelihood of having CRC; however, they did not reach statistical significance.

Table 2. Relationship between the different types of high fibre foods and CRC status

Characteristic(s)	Categories	cOR	95% CI		p-value
Cassava	Never	1.00			
	1x a week	1.11	0.55	2.24	0.767
	2-3x a week	1.10	0.55	2.22	0.779
	4+ x a week	0.53	0.27	1.01	0.052
Millet	Never	1.00			
	1x a week	0.62	0.34	1.12	0.114
	2-3x a week	0.65	0.34	1.24	0.191
	4+ x a week	0.39	0.21	0.70	0.002
Beans	Never	1.00			
	1x a week	0.44	0.14	1.33	0.146
	2-3x a week	0.36	0.12	1.03	0.057
	4+ x a week	0.44	0.16	1.22	0.117
Rice	Never	1.00			
	1x a week	1.03	0.50	2.13	0.930
	2-3x a week	0.79	0.38	1.66	0.534
	4+ x a week	0.46	0.22	0.93	0.032
Maize	Never	1.00			
	1x a week	0.82	0.42	1.61	0.567
	2-3x a week	0.70	0.35	1.39	0.303
	4+ x a week	0.74	0.37	1.47	0.390
Matooke	Never	1.00			
	1x a week	0.82	0.32	2.10	0.676
	2-3x a week	0.71	0.31	1.63	0.419
	4+ x a week	0.90	0.46	1.75	0.758
Sorghum	Never	1.00			
	1x a week	0.76	0.36	1.60	0.470
	2-3x a week	1.46	0.63	3.33	0.375
	4+ x a week	0.46	0.13	1.62	0.228
Cabbage	Never	1.00			
	1x a week	0.72	0.40	1.27	0.255
	2-3x a week	0.61	0.48	1.75	0.799
	4+ x a week	0.59	0.29	1.21	0.151
Potatoes	Never	1.00			
	1x a week	1.03	0.54	1.98	0.919

Characteristic(s)	**Categories**	**cOR**	**95% CI**		**p-value**
	2-3x a week	0.61	0.32	1.15	0.129
	4+ x a week	0.66	0.34	1.28	0.221
Spinach	Never	1.00			
	1x a week	0.69	0.36	1.31	0.254
	2-3x a week	0.63	0.35	1.13	0.122
	4+ x a week	0.60	0.31	1.19	0.146
Green Peppers	Never	1.00			
	1x a week	1.01	0.55	1.83	0.983
	2-3x a week	0.73	0.40	1.35	0.318
	4+ x a week	0.76	0.43	1.32	0.324
Banana	Never	1.00			
	1x a week	0.40	0.15	1.03	0.058
	2-3x a week	0.42	0.17	1.07	0.069
	4+ x a week	0.38	0.15	0.93	0.034
Watermelon	Never	1.00			
	1x a week	0.61	0.36	1.06	0.077
	2-3x a week	0.76	0.42	1.36	0.348
	4+ x a week	0.84	0.43	1.64	0.613
Oranges	Never	1.00			
	1x a week	0.84	0.52	1.36	0.489
	2-3x a week	0.92	0.46	1.87	0.824
	4+ x a week	0.75	0.38	1.48	0.412
Mangoes	Never	1.00			
	1x a week	0.67	0.36	1.22	0.187
	2-3x a week	0.67	0.35	1.30	0.234
	4+ x a week	0.62	0.31	1.26	0.186

Table 2 shows the observations which were made on the type and frequency of high-fibre foods consumed in the bivariate analysis. Compared to individuals who never consumed cassava, those who consumed 4 times and above/weekly cassava were protected against the development of CRC (cOR: 0.53; p=0.052) (Table 2). Consumption of millet was protective against the development of CRC and at a frequency of 4x and above/weekly reached statistical significance (cOR: 0.39; p=0.002). The same trend was seen with rice and bananas when consumed at 4x and above/weekly. Rice was protective against CRC when consumed at a frequency of 4x and above/weekly (cOR: 0.46; p=0.032). Bananas were also protective against CRC when consumed at a frequency of 4x and above/weekly (cOR: 0.38; p=0.034) (Table 2).

The other high-fibre foods, in particular beans, maize, matooke, sorghum, cabbage, potatoes, spinach, green peppers, watermelon, oranges and mangoes, also had a protective effect against CRC but did not reach statistical significance (Table 2).

In the multivariate analysis the following findings were observed. Consumption of boiled beef 2-3 times/week was associated with a higher likelihood of having CRC (aOR: 4.10; p<0.001) (Table 3).

Table 3. Risk and protective factors against CRC status in the multivariable model

Characteristic(s)	Categories	aOR	95% CI		p-value
Boiled Beef	Never	1.00			
	1x a week	1.10	0.57	2.15	0.773
	2-3x a week	4.10	1.98	8.47	<0.001
	4+ x a week	2.20	0.87	5.56	0.097
Fried Chicken	Never	1.00			
	1x a week	1.53	0.89	2.62	0.126
	2-3x a week	2.60	1.12	6.05	0.027
	4+ x a week	0.44	0.05	4.24	0.478
Rice	Never	1.00			
	1x a week	1.22	0.51	2.89	0.656
	2-3x a week	0.86	0.36	2.05	0.727
	4+ x a week	0.45	0.19	1.02	0.057
Cassava	Never	1.00			
	1x a week	0.96	0.44	2.10	0.916
	2-3x a week	0.78	0.35	1.72	0.534
	4+ x a week	0.40	0.19	0.84	0.016
Millet	Never	1.00			
	1x a week	0.49	0.26	0.95	0.034
	2-3x a week	0.71	0.35	1.45	0.352
	4+ x a week	0.32	0.17	0.63	0.001
Spinach	Never	1.00			
	1x a week	0.82	0.41	1.67	0.592
	2-3x a week	0.64	0.32	1.26	0.199
	4+ x a week	0.30	0.14	0.66	0.003
Potatoes	Never	1.00			
	1x a week	0.80	0.37	1.74	0.572
	2-3x a week	0.44	0.20	0.97	0.041
	4+ x a week	0.55	0.25	1.21	0.136

Fried chicken was also associated with an increased risk of CRC especially when consumed at a frequency of 2-3 times/week (aOR: 2.59; p=0.027) (Table 3). The following high-fibre foods were protective against CRC when eaten at a frequency of 4 times and above/week and reached statistical significance. These high fibre foods included cassava (aOR: 0.40; p=0.016), millet (aOR:0.32; p=0.001) and spinach (aOR:0.30; p=0.003). Consumption of potatoes at a frequency of 2-3x/week had a protective effect against CRC and this reached statistical significance (aOR: 0.44; p=0.041). Rice had an overall protective effect against CRC (aOR: 0.72; p=0.004) (Table 3).

4. DISCUSSION

This case-control study assessed the dietary practices and types of food that may promote or protect against CRC in Uganda. Our results showed that intake of red meat, particularly boiled beef and fried chicken, was associated with an increased relative risk for the development of CRC. The intake of cassava, millet, spinach and potatoes was inversely associated with the risk of developing CRC.

4.1 High Fibre Foods

Our study showed that the consumption of food rich in dietary fibre such as rice and spinach, has an inverse relationship to the development of CRC, and these findings have been supported by previous epidemiological studies [15-20]. Other high-fibre foods, such as beans, cabbage, matooke, bananas, oranges and mangoes, were also protective against CRC; however, these effects did not reach statistical significance in our study.

Dietary fibre prevents the conversion of primary to secondary bile acids by binding to bile acids. It also results in the promotion of the excretion of bile acids into the colon and prevention of the reabsorption of bile acids. Short-chain fatty acids are produced from the fermentation of fibre by colon bacteria. These short-chain fatty acids cause apoptosis, which inhibits tumor development. Dietary fibre also increases faecal bulk and reduces insulin resistance, inflammatory markers and nitric oxide hence reducing any interaction between the colonic mucosa and the faecal mutagens [21]. Several epidemiological studies and clinical trials have shown that consumption of dietary fibre is associated with a reduced risk of CRC [22]. However, the protective effect is determined by the type of fibre consumed with vegetable and fruit fibre having a high protective effect, while cereal fibre has a low protective effect [22].

Therefore, the possible mechanisms for dietary fibre protecting against CRC include (1) fermentation of dietary fibre and the formation of short-chain fatty acids in the colon such as proprionate, butyrate and acetate; (ii) a reduced colonic transit time; (iii) indigestible oligosaccharides and resistant starch reducing the ability of bile acids to act as carcinogens; (iv) folic acid from fruits reduces the risk of CRC; (v) selenium from cereals acts as a cofactor for glutathione peroxidase, which protects against oxidative tissue damage; and (vi) anticarcinogenic compounds in fruits and vegetables, including vitamin C, carotenoids, organosulfides, flavonoids, isothiocyanates, resveratrol and protease inhibitors [23].

The type of fibre consumed also determines the level of protection against CRC. Studies have consistently shown a protective role in fruit and vegetable fibre compared to cereal fibre, which offers no protection against CRC [24-28].

4.2 Vegetables

In East Africa, vegetables are consumed daily by rural populations due to their availability, affordability and accessibility, and they form part of the traditional diet. They include dark green leafy vegetables such as spinach and cassava leaves and cruciferous vegetables such as cabbage. Our study showed a reduced risk of CRC with spinach and cassava leaves. These vegetables have a high content of dietary fibre and are a rich source of folate, ascorbic acid, retinol and minerals such as magnesium and iron [29].

Folates suppress tumor cell proliferation and stabilize tumor suppressor genes, while ascorbic acid and retinol are antitumorigenic due to their antioxidant properties [30]. The main phytochemicals found in these vegetables include alkaloids, phenolic compounds, terpenoids and flavonoids, which are cytotoxic through inhibition of reactive oxygen species and prevent alteration of DNA. Induction of metabolism of 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine from the consumption of these cruciferous vegetables also has been shown in experimental studies to reduce CRC [31].

4.3 East African Staple Crops

Bananas (green bananas, matooke), cereals (sorghum, millet and rice) and tubers (cassava, potato) are the main staple foods in East Africa. Polyphenols, minerals and vitamins that have anticarcinogenic properties are present in these staple crops. Roots and tubers have a high content of non-digestable carbohydrates (NDCs), such as resistent starch and fibre [32]. Our study showed a reduction in risk for CRC with these staple crops, particularly with rice, cassava and potatoes.

Nonstarch and starch polysaccharides from these staple crops are anaerobically fermented by colonic bacteria to propionate, butyrate and acetate, which are short-chain fatty acids [32]. Butyrate promotes a normal phenotype in colonocytes and is the preferred substrate for these cells [33,34-37]. Fermentation of resistant starch results in the production of butyrate, which is more protective against CRC than the nonstarch polysaccharides of dietary fibre [32,38-43].

The low pH in the colonic lumen favours gut microbiota to produce short-chain fatty acids, which suppress mutations, alter preneoplastic lesions and bind to carcinogens in the colon [33]. The interaction of colonocytes with short-chain fatty acids results in an improvement in host immunity through the regulation of cytotoxic cells, T helper cells and B cells, which result in suppression of inflammation [34]. Studies have shown a 40% reduction in the risk of colon cancer with a high intake of non-digestible carbohydrates from these staple foods [35].

Cassava was protective against CRC in our study. Cassava contains tamarin, which is a chemical responsible for producing hydrocyanide; hence, through this mechanism, it is protective against CRC. The toxicity from hydrocyanide causes the death of CRC cancer cells, and this finding has been found through in vitro experimental studies [36].

Millet was also protective against CRC in our study. Previous studies showed in vitro and in vivo that foxtail millet bran (FMBP) produced a secretory peroxidase against CRC [37]. Foxtail millet bran (FMBP) targets cell surface glucose-regulated protein 78 (csGRP78) which is abnormally located on CRC. FMBP also acts against the nucleotide-binding domain (NBD) of csGRP78 which interferes with the activation of STAT3 (signal transducer and activator of transcription 3) in

CRC cells and results in the accumulation of reactive oxygen species and hence CRC cell growth inhibition [37].

In our study, maize was found to be protective against CRC; however, this did not reach statistical significance in bivariate analysis. Studies have shown that resistant starch from maize, compared to potato starch, produces more butyrate, which is preferable for colonocytes [38]. Our findings showed that the consumption of potatoes 2-3x weekly was protective, as it is a high fibre food which produces antioxidants and also short-chain fatty acids in particularly butyrate, with is preferable for colonocytes [38].

The Ugandan diet tends to consist of a variety of cassava, maize, potatoes and millet-based meals, and hence, these high-fibre foods tend to be protective against CRC.

4.4 Legumes

In East Africa, legumes, in particular beans, tend to be an important protein source in the diet. Beans contain phytoestrogens, which are anti-carcinogenic. Genistein, a phytoestrogen, mediates a cancer promotor EGF protein, which inhibits the proliferation of HT-29 colon cancer cells [44]. Flavanoids in legumes cause apoptosis of colon cancer cells, and the high folate content tends to be anti-carcinogenic.

Our study showed that beans are protective against CRC; however, the results did not reach statistical significance in the bivariate analysis. In Asians, high consumption of legumes has been found to reduce the development of CRC [45]. Hence, since meat which is high in protein is associated with CRC, substituting this food with legumes will potentially reduce the development of CRC, particularly in urban parts of Uganda.

4.5 Fruits

Although our study showed a reduced risk of CRC with fruits, it did not reach statistical significance in bivariate analysis, and this finding is consistent with findings from other studies that have not found significant associations [46-48]. A study from Switzerland showed an inverse relationship between citrus fruit intake and the risk of CRC [49].

The traditional African diet includes vegetable fruits such as green peppers and regular fruits including mango, watermelon and banana. These fruits contain phytochemicals such as phenols and flavonoids, minerals and vitamins A, B, C, D and E. Ascorbic acid has chemosensitizing properties against CRC cells and prevents tumour progression [50]. Tocopherol and retinol reduce epithelial cell proliferation and decrease the toxic effects of reactive oxygen species in the causation of colon cancer. The minerals selenium, zinc, phosphorous and magnesium increase the expression of antioxidant enzymes and have a protective role against CRC.

The stew base in East African countries includes green peppers which are rich in antioxidants [30]. The phytochemical, capsaicin in green peppers has been found to have proapoptotic, antiproliferative and cytotoxic effects against colo205 in experimental studies [51].

Migration studies have shown that the incidence of CRC in American blacks is comparable to that in Caucasians. Therefore, environmental dependence through the type of diet consumed plays an important role in the development of CRC. High-income income developed countries have high rates of CRC due to the high consumption of fat and processed meat with a low consumption of dietary fibre [52-54].

In rural Uganda, the typical diet is a carbohydrate-based type of meal that is consumed with vegetable-based soup. In this rural population, high fibre foods and vegetables are the lunch and supper of many, and meat is seldomly eaten routinely.

4.6 Meats

In many parts of rural East Africa, the consumption of meat is low due to the high cost. This is in contrast to the urban population of East Africa which tends to more frequently eat cooked meat.

When meat is exposed to high temperatures there is an increased risk of CRC. Carcinogens known as heterocyclic amines are released when meat is cooked to high temperatures above 180^0C for a long period of time [52-54]. In Uganda, proper refrigeration is not possible due to poor electricity supply. Therefore, for consumption and preservation many Ugandans deep fry meat in used oil. The highest amounts of polycyclic aromatic hydrocarbons originate from meat that is barbecued or grilled [54-56]. This is due to pyrolysis of fat that falls on the heat source forming smoke [57]. The major pyrolysis mutagens include pyridoindole, quino xalines and pyridoimidazole which are found in high heat over cooked beef [26].

Studies from North America have shown that well-done meat contains high amounts of heterocyclic amines (HCAs), which have been found to be carcinogenic and cause CRC [54]. In West Africa, some authors have alluded that charcoal roasted meat also has carcinogenic properties [58,59]. However, meat intake constitutes a small part of the rural Ugandan diet, resulting in minimal exposure to HCAs and PAHs. Therefore, the exposure to these carcinogenic substances is not to the magnitude at which Caucasians tend to be exposed. This difference in diet may explain the generally lower incidence of colorectal carcinoma in Uganda and East Africa compared to the western developed world.

In our study, we observed a positive relation between meat consumption and the development of CRC, particularly for boiled beef. The consumption of this type of red meat was higher among the cases than among the controls. These findings are consistent with Santorelli et al., who carried out a systematic review and determined the association between the consumption of meat and CRC. This systematic review reported that increased consumption of meat increases the risk of CRC [57]. In another study conducted by Abdulbari et al., 20.9% of cases had a higher daily consumption of meat compared to only 17.1% of controls [60]. The World Cancer Research Fund International (WCRF) also reported an increased association with CRC from the consumption of 250g/day of meat [61,62].

We did not find an association between roast pork, fried pork and roast lamb with the risk of CRC. Possible reasons may be due to information bias, which may have resulted from recall or misclassification bias which are limitations of case-control studies. Nondifferential misclassification may result from a cultural context whereby some cases might have stated that they do not eat pork or lamb when they actually do eat these types of meat. Alternatively, participants might have been likely to indicate eating meat in general terms without distinctively classifying the different types. As such, all the meats would have been clamped together as beef, further amplifying the misclassification of the exposure to different meats. These findings may also be in keeping with a study conducted by Ahmed FE, which found that red meat is not a risk factor for CRC [63].

Humans are exposed through their diet to environmental anti-carcinogens and carcinogens, resulting in the mitigation or progression of different cancers [64]. Ugandan patients currently living in rural parts of the country eat a predominantly African diet, which is a high fibre carbohydrate-based diet and has been found to protect against the development of CRC [65]. This is in contrast to a Western diet, which consists predominantly of cooked meat, and fatty refined foods and is low in vegetables and fruits, which are high-fibre foods [65]. A study on African American patients showed that switching their western diet to a traditional African diet had an influence on colonic bacteria and consequently prevented the development of CRC [66].

The traditional African diet tends to modify colonic fermentation by bacteria, alters motility of the colon and has a protective effect against fibroblast growth factor 18, urokinase-type plasminogen activator receptor gene, telomere/ telomerase-TERT, A33-transmembrane glycoprotein immunoglobulin, cyclooxygenase-2 and carcinoma embryonic antigen receptors in CRC. Hence, this type of diet has a protective role against CRC [67]. Dennis Burkitt reported a low incidence of CRC in rural Africans and conceptualized the idea that the type of diet is linked to colon cancer. He suggested this because Africans eat a lot of fibre in the form of vegetables, fruits and grains with little consumption of meat in their diet [68]. Colorectal adenocarcinoma has been found to be prevalent in communities that have adopted a Western-type diet lacking in fruits, vegetables and fibre and rich in fat and red meat [68-75].

The findings from our study suggest that the intake of traditional high-fibre foods such as cassava and millet and the intake of green vegetables and spinach reduce the development of CRC, while consumption of red meat and fried chicken increased the development of CRC. The Ugandan plant-based diet is a rich source of fibre, phytochemicals and vitamins, which results in a reduction in obesity and hence a reduction in the development of CRC. A reduction in the consumption of red meat, particularly beef, which contains high levels of cholesterol and saturated fats, will also reduce the development of CRC in the Ugandan population.

In view of our findings, we recommend a nutritional educational programme to increase public awareness to limit the intake of red meat and encourage the intake of high fibre fruit and vegetable diets due to their protective role. Educational programmes in primary health care facilities to promote adequate healthy nutrition should also be given importance in Uganda and generally in East Africa.

5. CONCLUSIONS

This study suggests that consumption of cooked meat increases the risk of CRC, whilst intake of high-fibre foods such as cassava, millet, spinach and potatoes may reduce the risk of CRC among Ugandans. In view of these findings, we recommend a nutrition education programme to increase public awareness regarding the protective role of a high fibre diet and limit the intake of cooked meat. Educational programmes at primary health centres on nutrition health promotion should therefore be considered in Uganda, and consumption of foods low in fibre such as meat should be reduced and replaced with vegetables and fruits. This dietary modification will have a significant impact on reducing the development of CRC in Uganda. Targeted CRC screening of patients with average risk factors for the disease should also be considered in our East African population.

6. STUDY LIMITATIONS

Case-control studies tend to be prone to selection bias. To minimize this bias, controls were recruited from the surgery departments of four different specialized hospitals with diseases that had no association with dietary factors. The cases and controls recruited from the private hospitals may have a higher socioeconomic status compared to those recruited from government hospitals; however, studies have shown an inverse association between the risk of CRC and the consumption of vegetables and fruits among individuals of different socioeconomic status [71]. Similar results from controls recruited from different hospital sources suggest that their selection did not affect the results.

The probability of selection bias was reduced in our study due to the high participation rate for both cases (98%) and hospital-derived controls (95%). Participants may recall dietary practices differently and recall bias tends to be a concern in case-control studies. The controls may have recalled their dietary consumption differently from cases as controls did not have malignant disease. If colorectal cancer patients were aware of their diagnosis, this may have led them to consciously change their well-being and health. Therefore, cases were interviewed very soon following diagnosis to reduce bias. To improve the comparability of recall between controls and cases, a standardized questionnaire interview method was used. An adjustment for many potential confounders was made; however, residual confounding bias may have occurred due to poorly measured or unmeasured variables.

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.

AUTHORS' CONTRIBUTIONS

Author RW conceived the concept and proposal, collected data, performed data analysis and wrote the first draft. Author JK performed data analysis and provided statistical support. Authors MO and HW performed critical reviews of the manuscript for intellectual content. All authors approved the final manuscript for publication.

CONSENT

Consent was obtained from all the participants enrolled in this study.

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.

ACKNOWLEDGEMENTS

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 Atuhaire 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-Review History: During review of this manuscript, double blind peer-review policy has been followed. Author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the peer-reviewers. As per the comments of the peer-reviewers and depending on the quality of the revised manuscript, the Book editor approved the revised manuscript for final publication.