



RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF COLORECTAL CANCER IN SOKOTO, NIGERIA

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ABSTRACT: Background: Colorectal cancer is a leading cause for patient presentation to surgical clinics worldwide. Risk factors and stage of disease presentation varies widely from different regions of the world. While sporadic cancers account for majority of cases in the general population, hereditary factors have assumed prominence in the etiopathogenesis of the disease in recent times due to advancement in molecular screening and diagnosis. In most developed economies disease presentation is early with better outcome compared to the low income countries of Africa and parts of Asia where it continues to carry poor prognosis as a result of late presentation. **Aim:** To determine the risk factors associated with development of colorectal cancer among adults presenting to the surgical clinic of a tertiary hospital in North-west Nigeria and highlight the predominant clinical stage of the disease. **Method:** A seven-year prospective study between 2012 and 2018 where consecutive patients presenting to our clinic with colorectal cancer were recruited and administered questionnaires to obtain information on demographics, clinical stage and risk factors. **Results:** A total of 109 patients were seen. Of this, 54.1% (59) were males while 45.9% (50) were females giving a male: female ratio of 1.2:1.0. The mean age was 44.7 years while the median age was 45.0 years. Fifty-one percent (56) of patients had no identifiable risk for colorectal cancer, 22.9%(25) admitted to excess intake of roasted beef and cheese, 11.0%(12) had positive family history of colorectal cancer, 5.5%(6) had history of familial adenomatous polyposis (FAP) confirmed by histology, 3.7% (4) were treated for colonic schistosomiasis in the past while ulcerative colitis, angiosarcoma and carcinoid tumor accounted for 1.8%(2) of risks each. Fifty-one percent (56) of patients presented with TNM stage III disease, 35.8% (39) with stage IV and 12.8% (14) with stage II. No patient was seen with stage I disease. **Conclusion:** Diet rich in animal fat and roasted beef together with family history constitutes important risks for colorectal cancer in this study. Majority of the patients were young and presented with late disease.

KEYWORDS: Colorectal, Cancer, Risk Factor, Colorectal Cancer, Nigeria

INTRODUCTION

Colorectal carcinoma is the third most common malignancy worldwide after lung and prostate cancer in males and breast and cervical cancer in females.¹ It constitutes a major cause of morbidity and mortality worldwide. ¹ Colorectal cancer occurs commonly in the developed countries of Canada, USA, Western Europe, Australia and New Zealand accounting for over 60% of all cancers. Incidences in these areas are above 40 per 100,000 population.^{2, 3} The disease is however less common in developing countries of Asia, South



America and sub-Saharan Africa with incidences below 5 per 100,000.² In 2009, the incidence of large bowel cancer in Sokoto (North West Nigeria) was put at 5 cases per annum with almost equal male to female ratio.⁴ Overall, colorectal cancer was the fifth most common cancer in Zaria (North West Nigeria) in 2015 and the seventh commonest cancer in Sokoto in 2017.^{5, 6} Several factors are known to increase the risk of developing colorectal cancer and majority are non- hereditary conditions linked to environmental and lifestyle practices while only about 5 to 10% are due to recognized hereditary factors.⁷ Recent reports showed increasing frequency of colorectal cancer in hitherto low incidence areas of Asia and sub-Saharan Africa due to changing dietary lifestyle to the “Western” type and increased awareness and better reporting of the disease.^{8, 9} However, some parts of North America and Western Europe have witnessed a decline in colorectal cancer incidence due largely to early detection and better management of precancerous conditions.^{9, 10} In Africa, the disease continues to carry poor prognosis due to late presentation and inadequate facilities for proper management.¹¹

METHODOLOGY

This was a seven-year prospective cohort study carried out between 2012 and 2018. Consecutive patients presenting with colorectal cancer to the surgical clinic of Usmanu Danfodiyo university teaching hospital, Sokoto, Nigeria were recruited and administered semi-structured questionnaires to obtain information on patient demographics, clinical stage and risk factors associated with colorectal cancer. Data obtained by interview and staging investigations were entered into the questionnaires at the clinic while case notes of patients with history of precancerous conditions were retrieved for information on histologic confirmation and also entered into the questionnaires.

Risk and stage classification: Identified risk factors for colorectal cancer were grouped in order of frequencies and presented as absolute values and percentages. The disease was staged using the AJCC (*American Joint Committee on Cancer*) staging classification. Continuous variables were assessed for any association with colorectal cancer using the Pearson correlation coefficient (r) and the linear regression model. A P -value of 0.05 was considered significant.

Inclusion/exclusion criteria: All consenting patients with colorectal cancer were recruited for the study while patients with colorectal (precancerous) lesions not confirmed by histology were excluded.

Data analysis: Results were analyzed using the *IBM windows statistical package for social sciences (SPSS)* version 23.0

RESULTS

A total of 109 patients were seen. Out of this, 54.1% (59) were males while 45.9% (50) were females giving a male: female ratio of 1.2:1.0. The mean age (\pm standard deviation) was 44.7 (\pm 15.5) years, while the median age was 45.0 years. The modal age was also 45.0 years. (Table1) In 51.4% (56) of respondents, no identifiable risk for colorectal cancer was found.



However, in 48.6% (53) of patients, the following risk factors were identified: Diet (cheese & roasted beef), 22.9% (25); family history, 11.0% (12); familial adenomatous polyposis (*FAP*), 5.5% (6); schistosomiasis, 3.7% (4) and inflammatory bowel disease (ulcerative colitis), 1.8% (2). Others included left colonic angiosarcoma and carcinoid tumor of the caecum, 1.8% (2) each. Colonic precancerous lesions together constituted 14.6% (16) of identified risks. (Table 2) There was a significant association of identified risk factors with colorectal cancer across age group. (Pearson correlation coefficient [r] =0.307, 95% confidence interval [CI] =1.00, 3.67, P-value=0.001) (Table 3) Majority of the patients presented late with TNM (*Tumor, Node, Metastasis*) stage III, 51.4% (56); while 35.8% (39) presented with stage IV and 12.8% (14), with stage II disease. No patient was seen with stage I disease. (Table 4).

DISCUSSION

Colorectal cancer occurred at a mean age of 44.7 years in this study showing a disease more prevalent in younger population than most quoted Western average of between 63 and 72 years.¹² The figure agreed with the mean age of 45.2 years earlier reported from this center by Mba N in 2009.⁴ Other series from Africa and parts of Asia have reported similar young age with almost equal male: female ratio.^{8, 11, 13, 14}

Roasted beef ('suya') and animal fat (cheese) constituted important risks for colorectal cancer in this study with 22.9% (25) of patients having positive history. It has been postulated that diets high in red meat could promote carcinogenesis via its highly bioavailable iron content and the dietary heterocyclic amines and polycyclic aromatic hydrocarbons formed during the cooking and roasting process.¹⁵⁻¹⁸ Charcoal-roasted meat called "Suya" is commonly consumed in this part of the country where nomadic pastoral practice is predominant. High dairy fat is also known to constitute major risk factor for colorectal cancer because it favors development of intestinal flora which degrades primary bile salts to potentially carcinogenic secondary *N*-nitroso compounds^{2, 3, 19} Excess primary bile acids in the intestine from high dietary fat are also converted to carcinogenic secondary deoxycholic and lithocholic acids by bacteria action.²⁰

Familial cancer was unexpectedly high in this study at 16.5% (18). Of this, 5.5% had familial adenomatous polyposis (*FAP*) leaving 11% with hereditary non-polyposis colon cancer (*HNPCC*). Hereditary non-polyposis colon cancer (Lynch syndrome) is an autosomal dominant condition which predisposes individual and family members to cancer.²¹ It is characterized by early-onset colorectal cancer and occurrence of various other cancers in the individual and close relatives. Identification of carriers of mutated mismatch repair genes, *hMSH2* and *hMLH1* within affected family is the hallmark of diagnosis of this condition.²¹ In Nigeria, diagnosis of *HNPCC* is based solely on patient and family history. However, a recent study by Adebamowo *et al* demonstrated germ-line mutation in *MSH2* gene in two of five Nigerian patients with colorectal cancer.²² *HNPCC* has recently attracted more attention in Nigeria due to the young patient population and increased presence of mucinous and signet ring histologic types.²²⁻²⁴ Familial adenomatous polyposis (*FAP*) on the other hand is an autosomal dominant hereditary condition linked to mutation of the adenomatous polyposis coli (*APC*) gene located on chromosome 5q2.²⁵ *FAP* by definition is a hereditary condition in which the colon contains more than a hundred adenomatous polyps.²⁶ In Nigeria diagnosis of *FAP* is mainly clinical and by confirmation of multiple adenomatous polyps at histology as



most laboratories are still unable to confirm the chromosomal defect of the APC gene. *FAP* is rare in Nigeria but there are increasing reports of the condition in recent time due perhaps to better diagnosis.²⁷⁻²⁹ This may also highlight a condition more prevalent than previously thought especially considering the young patient population of colorectal cancer in Nigeria.

Four patients had history of chronic Schistosomiasis in this study. Several reports from Africa and the Middle East have shown evidence of possible link between *Schistosoma mansoni* infestation and colorectal carcinoma.³⁰⁻³³ Madbouly et al showed that colorectal cancer associated with *S. mansoni* tend to be multi-centric and mucinous with majority presenting at advanced stage.³⁴ Omer et al also reported a mucinous adenocarcinoma associated with *S. mansoni* infestation with high concentration of ova within the tumour.³⁵ We had earlier reported a case of colorectal cancer co-existing with *Schistosoma mansoni* from this centre.³⁶ Schistosomal cancers occur in younger age group and have a predilection for the rectum.^{37, 38, 35}

Of note is the report of 2 (1.8%) cases of ulcerative colitis (UC) in this study. Both were males in their fifth decade and treated for chronic 'diarrheal disease' before presenting with obstructive features. In our setting UC is still a reportable condition because of its rarity among black Africans.^{39, 40} It is however quite common among Caucasians.^{39, 40} Up to 50% of patients with UC may progress to develop invasive carcinoma after 5 years.⁴¹

Angiosarcoma and carcinoid tumor of the caecum were also identified risks for colorectal cancer in this study. Angiosarcomas are aggressive, malignant tumors of vascular or lymphatic endothelial cells.⁴² They may arise from a pre-existing benign lesion or may be frankly malignant de novo.⁴³ Colorectal angiosarcomas are very rare accounting for less than 1% of all colorectal cancers.⁴⁴ One of the two cases of angiosarcoma from this centre had earlier been reported by Sahabi et al in 2017.⁴⁵ None of our patient was exposed to commonly suggested risk factors like irradiation, chronic lymphedema, long term peritoneal dialysis or intra-abdominal foreign body.^{46- 49} Retroviral screen was also negative in both patients. Confirmation of the angiosarcoma was by positive expression of *CD31* at immunohistochemistry. Carcinoid tumor of the caecum is a rare but slow-growing neuroendocrine tumor arising from the enterochromaffin or Kulchitsky's cells.⁵⁰ They account for less than 1% all colonic tumors.⁵⁰ Majority of colonic carcinoids are located in the caecum.⁵¹ Mohammed et al reported only two cases of colonic carcinoid tumor in 10 years from Zaria, North west Nigeria.⁵² while Obateru et al reported a case of caecal carcinoid in a 56-year-old man from Lokoja, North central Nigeria in 2017.⁵³ Two of our cases with caecal carcinoid tumor were aged 23 and 45 years; female and male respectively and alive after one and two years respectively. They both presented with stage II disease. Unfortunately, however, majority of the patients in this study presented with advanced disease as is the case from most studies in developing economies with poor health indices.^{54- 56}

CONCLUSION

Diet rich in animal fat and roasted beef together with family history constitutes important risks for colorectal cancer in this study. Majority of the patients were young and presented with late disease.



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APPENDIX

Table 1: Age distribution of patients

Age(years)	Frequency	Percentage
15 - 29	20	18.3
30 - 44	30	27.5
45 - 59	38	34.9
60 - 74	17	15.6
75 - 89	4	3.7
Total	109	100.0

Table 2: Identifiable risk factors associated with colo-rectal cancer

Risk factors	Frequency	Percentage
Angiosarcoma	2	1.8
Animal fat/cheese	12	11.0
Roasted beef(Suya)	13	11.9
Carcinoid tumor	2	1.8
Family history	12	11.0
FAP	6	5.5
Schistosomiasis	4	3.7
Ulcerative colitis	2	1.8
Total	53	48.6

Table 3: Pearson correlation and regression coefficients of variables

Variables	r	95% CI	P-value
Age	0.307	(20.56, 39.12)	0.001
Risk factors	0.307	(1.00, 3.67)	0.001
Clinical stage	0.141	(2.53, 3.35)	0.145

Table 4: TNM (Tumor, Node, Metastasis) stage classification of colorectal cancer

TNM Stage	Frequency	Percentage
I	0	0
II	14	12.8
III	56	51.4
IV	39	35.8
Total	109	100.0

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