Colorectal Adenocarcinoma in East Africa: A Narrative Literature Review

Richard Wismayer[1,2*]

[1]*School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Uganda.*
[2]*Department of Surgery, Masaka Regional Referral Hospital, Masaka, Uganda.*

Author's contribution

The author read, edited and approved the final manuscript.

Review Article

ABSTRACT

This paper is a review of work done on colorectal adenocarcinoma in East Africa showing geographic spread, age and sex ratios, clinical presentation, management and predominant histopathology. A steady increased incidence of CRC in East African countries is currently being documented however this is associated with a higher CRC-associated morbidity and mortality. Whilst the male: Female ratio varies between 1.2:1 to 1.88:1, up to 38% of CRC diagnosis are in patients younger than 40 years, in contrast to only 1.9% of CRC patients in Western developed countries such as the USA. Generally rectal carcinoma is more common than colon carcinoma and abdomino-perineal resections are commonly performed in up to between 54% - 71% due to the advanced stage of presentation of rectal tumours in East Africa. The late stage presentation and delayed effective treatment in East Africa may result in a higher morbidity in CRC patients. Interestingly there is a significant incidence of mucinous adenocarcinoma sub-groups compared to Western developed countries which carry a poor prognosis. A significant proportion of CRC patients have been found to have histological and demographic features which suggest that MSI-tumours and these tumours are more common in younger patients. However only a few authors have looked at the possibility of mismatch repair mutations in the genetic aetiopathogenesis of colorectal adenocarcinoma in East Africa.

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**Corresponding author: E-mail: richardwismayer@rcsi.ie;*

1. INTRODUCTION

Colorectal cancer is the fourth leading cause of cancer death in the world [1,2]. It is the third most commonly diagnosed malignancy in the world and is responsible for 1.4 million new cases and approximately 700,000 deaths in the year 2012 [2]. CRC is the second most common cancer in women worldwide (614,000 cases; 9.2% of the total) and the third most common cancer in men (746,000 cases; 10% of the total) [3]. In Africa colorectal carcinoma is a rare disease and it currently represents 2-6% of all malignant tumors [4,5].

The crude incidence of CRC in Sub-Saharan Africa is 3.69/100,000 for women and 4.38/100,000 for men (overall 4.04/100,000) with a wide variation in the geographical distribution of CRC reported on the African continent. A high incidence in South Africa of 11.9/100,000 whilst low incidences reported in East Africa (6.5/100,000) and West Africa (3.8/100,000 in women; 4.5/100,000 in men) has been reported [3,4,5].

In between the years 1957 and 1964, 105 cases of colorectal carcinoma were reported in Kenya giving an incidence of 2.5/100,000 [6]. Eshelman (1966) and Hiza (1974) reported a low incidence of colorectal carcinoma in Tanzania with only four cases of rectal carcinoma and none of colon carcinoma reported [7,8,9]. However, in a recent study by Siegel from Sub-Saharan Africa has shown that in urban areas the incidence of colorectal carcinoma is indeed increasing [6]. Generally, in many East African countries there has been an increased incidence in the incidence rate of CRC. In Kenya there has been an increased incidence of colorectal carcinoma (4.8%) and it is currently the fourth commonest carcinoma in the country [10]. The population incidence of CRC in Kenya is currently 9.6 per 100,000 populations [10]. In Uganda, the
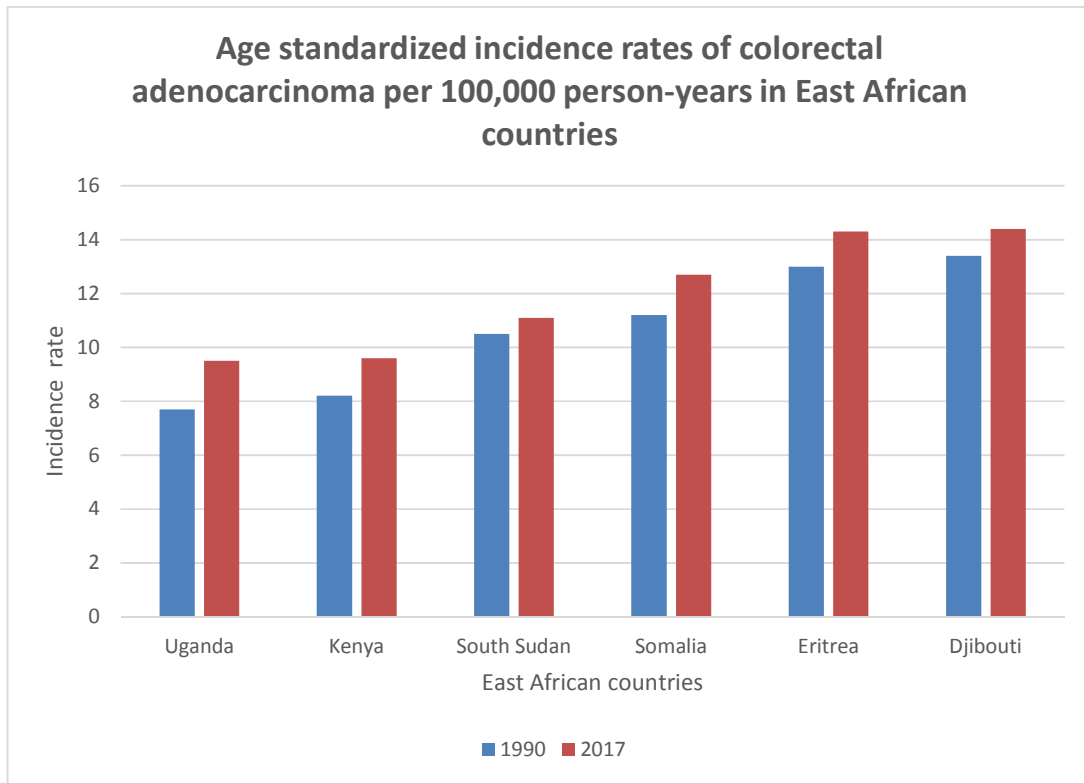
Fig. 1. A bar graph showing the age standardized incidence rates of colorectal adenocarcinoma per 100,000 person-years in East African countries depicting a steady increase in the incidence of CRC between the years 1990 to the year 2017

Kampala Cancer Registry has shown that colorectal carcinoma has a low incidence however there are increases occurring especially among women [11]. In 1977, Ssali et al. [12] reported a low incidence of colon carcinoma at 2.8% and stated that the incidence may be rising. The age standardized incidence rate has since remained oscillating around 7.8 per 100,000 population in males for the years 1991-2010 [11]. The age standardized incidence rate has increased from 5.2 per 100,000 population for the year period 1991-1995 to 9.0 per 100,000 population for the year period 2006-2010 in females [11]. This gives a 4.1% annual percentage change in the incidence of colorectal carcinoma in females in Uganda which is a greater increase than in males [11]. Fig. 1 shows a bar chart depicting the steady increase in incidence of CRC in East African countries over the last few decades. The increase in the percentage change in age-standardized incidence rates between the year 1990 and the year 2017 is 22.1% in Uganda, 17.5% in Kenya, 5.7% in South Sudan, 13.6% in Somalia, 14.3% in Eritrea and 7.2% in Djibouti [11].

Despite the incidence of CRC being low in East Africa, there is a higher CRC-associated morbidity and mortality [1]. The increasing incidence of CRC being reported in East Africa is in turn associated with an increased rise in the burden of non-communicable diseases in East Africa [6]. Improved cancer awareness, an increase in reporting and a shift towards a western diet may be attributing towards the rising incidence of colorectal carcinoma in East Africa [1,6]. The increased incidence may also probably be due to an increase in risk related behaviors such as smoking, alcohol, obesity and dietary changes particularly in urban areas of Sub Saharan Africa [4].

The rarity of colorectal carcinoma in the past and the current steady increase in CRC cases in East Africa makes confirmed cases today worthy of attention. This literature review looks at the work done on colorectal carcinoma by researchers from countries in East Africa to illustrate the results of these authors from the last 20 years.

2. DISCUSSION

Several factors are reported to be linked to the incidence of colorectal adenocarcinoma which include environmental and hereditary factors. Changes in dietary preferences are a result of an important environmental influence which is related to economic development [13]. Economically developed countries such as the UK and USA have a high incidence of CRC however in East Africa a steady increase is being reported [1,6]. Over the past two decades an increase in the incidence of CRC affecting rural populations in East Africa of low socio-economic status has also been reported [14]. This paper looks at as many publications available in East Africa to illustrate the rate and pattern of CRC in this part of the world over the past years.

2.1 Age and Sex Distribution of Colorectal Carcinoma

In East Africa a significant proportion of patients are young with a median age at diagnosis of 41-59 years [15-18]. Between 19% to 38% of patients younger than 40 years of age present with CRC [16,17]. This is in contrast to only 1.9% of patients in the USA who are younger than 40 years and present with CRC [19]. Among African-American patients, early-onset CRC has also been described [20]. In Kyadondo in Uganda, colorectal carcinoma has been found to be more common in women whilst in the Western world men have a higher incidence of CRC [11]. In Uganda, colorectal carcinoma is diagnosed at a median age of 55 years [11]. 30.6% of CRC patients are under 50 years of age, 6.9% of CRC patients were under 30 years of age and 69.4% of CRC patients were either 50 years or above in a study from Uganda [11]. This finding suggests that genetic factors may play a part in the aetiology of this early onset CRC in African patients [20]. The male to female ratio in East African studies currently report a ratio of 1.2:1 to 1.88:1 [14,16,17,21].

2.2 Presentation of Patients with Colorectal Carcinoma

Patients present in a way that is determined by the anatomical location of the CRC in the large bowel. In East Africa several studies have shown that there is a predominance of left sided colorectal tumors in particular rectosigmoid tumors [17,22,23]. In Uganda, Dijxhoorn identified only 2 tumors (5.1%) that were in the right colon whilst 37 tumors (94.9%) were located in the left colon [24]. 32 of these 37 tumors left colonic tumors were located in the rectum (86.5%) [24]. In Kenya, Saidi H, found 50% of the tumors located in the rectum, 17.1% in the sigmoid colon, 12.9% in the ascending colon, 11.4% in caecum and 7.1% in the ascending colon [17]. Table 1 shows studies from East

Africa showing the anatomical site location of CRC and percentages together with the most frequent site of CRC from the data presented.

In developed countries a right-sided preponderance of colorectal carcinoma (proximal shift) is generally seen [25,26]. In a Luisiana population, Minardi et al. [27] found CRC to be evenly distributed throughout the colon and rectum. Whilst only 30% of patients had rectal involvement in a study reported by Kam et al in Singapore [28]. The reason for this anatomical difference between East African countries and developed countries is not clear however the reason could be that the rectum and proximal sigmoid colon could be more accessible to investigate by rigid proctosigmoidoscopy than the right colon [29].

In many East African hospitals proctosigmoidoscopy is the only available method of obtaining biopsies in patients with lower gastrointestinal symptoms. There is poor access to colonoscopy facilities and CT scanning with many patients having a laparotomy for diagnosis of CRC in many East African hospitals [29].

A study from Kenya showed that only 23% of patients with colorectal carcinoma had colonoscopy during the years 1993-1998 which improved to 51% during the years 1999-2005 [17]. Similarly a retrospective study from Tanzania also showed that from a total of 901 cases, rectal cancer (482) was more common compared to colon cancer (344) and (75) rectosigmoid junction cancer [30]. Colon cancer was most often diagnosed in males compared to females (162:182) whilst rectum cancer was most often diagnosed in females compared to males (265:219) [30]. Katalambula et al. [30] noted that the risk of colon cancer was significantly higher in patients below 35 years. The same study found that rectum cancer was more common in older patients 80+ years (78.13%) and in patients 50-54 years old. However, Dijxhoorn et al. [24] noted no significant difference between males and females, and no significant difference in age i.e. younger or older patients (<50 years or >50 years) regarding tumor site.

The world age-standardized incidence rate is higher for colon carcinoma than for rectum carcinoma in both sexes in Uganda. In colon carcinoma it stands at 4.0 per 100,000 in males and 4.1 per 100,000 in females for the period years 2008 to 2012 [4]. In rectum carcinoma the world age-standardized incidence rate is lower at 3.8 per 100,000 population in males and 3.5 per 100,000 population in females for the year period 2008 to 2012 [4]. Between the years 1998 to 2007 the colon to rectum cancer rate ratio has been variable in Uganda between 0.5 - 2.5: 1 which contrasts with that seen in the US and UK where the ratio is steadily constant at 2:1 [4]. Table 2 shows the few studies carried out from countries in East Africa which depict the period of study, number of patients studied, sex ratios, ages and colon: rectum ratios.

Table 1. Studies in East Africa depicting period of study, anatomical site of tumors, most frequent anatomical site and percentages. The symbol – denotes data was not available for these anatomical sites in these studies

Authors	Saidi H, et al. 2007	Chalya PL, et al. 2013	Dijxhoorn DN, et al. 2014	Medhin LB, et al. 2019	Deressa, et al. 2019
Caecum (%)	11.4	12			
Ascending colon (%)	7.1	7.5	5.1	-	7
Transverse colon (%)	-	3.9	-	-	-
Descending colon (%)	12.9	6	13.5 (including sigmoid colon)	-	2
Sigmoid colon (%)	17.1	-	-	-	3
Rectosigmoid junction (%)	-	54.8	-	-	10
Rectum (%)	50	15.7	86.5	50	69
Most frequent site of CRC	Rectum	Rectosigmoid	Rectum	Rectum	Rectum

Table 2. Studies in East Africa depicting period of study, number of patients studied, sex ratios, ages and colon:rectum ratio

Authors	Period (Year)	Number of patients	Mean age	Male:Female	Colon:Rectum
Saidi H, et al. 2011 (Kenya)	2005-2010	233	53	1.43:1	1:1.02
Chalya PL, et al. 2013 (Tanzania)	2006-2011	332	46	1.6:1	5.38:1
Dijxhoorn DN, et al. 2014 (Uganda)	2006-2010	81	55	1:1.15	1:4.57
Medhin LB et al., 2019 (Eritrea)	2011-2017	241	57.62	1:1.61	1:1
Deressa BT et al., 2019 (Ethiopia)	2016-2017	147	46	1.88:1	1:4.21

Some studies have reported rectal bleeding as the commonest symptom reported from colorectal cancer patients in East Africa [16,17]. Distinguishing a benign from a malignant lesion such as CRC may pose a diagnostic challenge in our environment. A study from the UK showed that the prevalence of rectal bleeding was 14% [31,32]. Several studies has shown that in elderly patients rectal bleeding can predict colorectal cancer especially when in combination with abdominal pain or a change in bowel habit [33,34]. It is therefore reasonable to investigate rectal bleeding by colonoscopy in all cases. Colonoscopy should be carried out for patients presenting with rectal bleeding, change in bowel habit and anaemia and may consequently improve survival in these patients. Patients presenting with right sided CRC tend to have significantly lower haemoglobin levels and these tumors tend to bleed easily in contrast with left sided tumors which present with large bowel obstruction [17]. Therefore colonoscopy should be carried out for adult patients presenting with anaemia with suspected CRC [35-37]. In another study by Saidi HS et al. [17] the most common presenting symptom was abdominal pain (76.9%). The same study reported a change in bowel habit (71.4%), rectal bleeding (54.3%), swelling (34.8%), tenesmus (17.1%), weight loss (14.3%) and bowel obstruction (14.3%). Abdominal pain has been found to be the presenting symptom in other studies, in fact in one account 54% of patients presented with this symptom [34].

Due to patient variability, a change in bowel habit may be difficult to document. A study in Kenya reported a change in bowel habit in 71.4% of CRC patients [17]. In the UK, studies have shown that diarrhea and increased stool frequency are more predictive of CRC than constipation [38]. In East Africa, since left sided colonic and rectal lesions are more common and they commonly present with large bowel obstruction then this symptoms should dictate early referral to hospital and this will inevitably have a positive effect on survival.

A study from Tanzania found that only 3.3% of patients present with early stage CRC (Stage I) compared to 90% presenting with advanced stage CRC (Stage II, III and IV) [16]. In Eritrea, late presentation of CRC is also a common feature and a high proportion of patients (61.7%) present with advanced stages (stage 2 and above) [21]. These findings are consistent with findings from other studies in Africa [17,39,40,41,42]. This is mainly due to the absence of screening facilities for colorectal carcinoma in the East African population. There is considerable evidence that screening with faecal occult blood test and colonoscopy of asymptomatic individuals at an average risk can detect CRC at an early and curable stage which results in a reduction in mortality [43]. Colonoscopy may detect cancer-precursor lesions, such as polyps which when removed reduce the incidence of CRC [44,45]. The late presentation reported in all East African countries may be due to lack of screening programs, lack of accessibility to health-care facilities and lack of patient awareness with the disease.

2.3 Treatment of Colorectal Adenocarcinoma Patients

The main aim of surgeons managing colorectal adenocarcinoma is curative resection. In East Africa many patients present at an advance

stage and so a number of surgical interventions have been reported. The majority of surgical operations for rectal carcinoma are abdomino-perineal resections which are performed in up to between 54%-71% of patients [46-49] due to the advanced stage of presentation of rectal tumors. Anterior resections for rectal tumors have been reported in only up to between 22% - 26% of patients [46,49] possibly because of the lack of facilities to provide chemotherapy and radiotherapy pre-operatively in rectal carcinoma in East Africa due to the advanced stage of presentation of rectal carcinoma.

The frequency of other operations documented in East African studies include right hemicolectomy in 22.1-43% of patients [16,46], left hemicolectomy in 33% - 58.6% of patients [10,40], transverse colectomy in 3% - 12% of patients and sigmoid colectomy in 3% of patients [16,46]. Table 3 shows the frequency of operations documented in East African studies. A colostomy itself may lead to psychological distress and social stigma and has been reported to lead to suicide and this is actually not related to the location of the CRC tumor [50]. Older patients (>70 years) and a marital status of single have been found to be associated with a

higher risk of suicide [50-52]. Erectile impotence in male patients may result from disruption of the pelvic nerves intra-operatively or psychologically due to the presence of a stoma [53,54]. Since many rectal cancer operations occur in young Africans that are sexually active, the impact operations such as abdomino-perineal resection has on psychological wellbeing needs to be factored in when treatment options are being considered.

Complete resection with adjacent involved lymph nodes in CRC in the early stage is the only chance for cure [23,54]. However many patients with CRC present at a late stage in East Africa and therefore only palliative surgery in the form of a colostomy is possible. Only approximately 3.3% of CRC in East Africa is curable by complete resection in keeping with many studies from developing countries [17,39,40] due to many patients presenting at an advanced stage.

Chemotherapy and radiotherapy play an important role in locally advanced colorectal cancer [55]. Unfortunately in resource poor countries in East Africa, limited access to chemotherapy poses a major challenge in the

Table 3. Studies in East Africa depicting period of study, frequency of the different types of operations and percentages together with the authors of the studies. The symbol – denotes data was not available for these operations in these studies

Surgical procedure	Saidi H, et al. 2011 Frequency	Saidi H, et al. 2011 Percentage (%)	Chalya PL et al. 2013 Frequency	Chalya PL, et al. 2013 Percentage (%)	Deressa BT, et al. 2019 Frequency	Deressa, BT, et al. 2019 Percentage (%)
Rt.Hemi-colectomy	43	22.9	72	22.1	-	-
Transverse colectomy	3	1.6	12	3.7	-	-
Lt. Hemi-colectomy	33	17.6	191	58.6	-	-
Hemi-Colectomy (not specified)	-	-	-	-	18	31
Sigmoid colectomy	3	1.6	-	-	-	-
Anterior resection	22	11.7	8	2.5	8	26
Abdomino-perineal resection	54	28.7	28	8.6	22	71
Colostomy/ Biopsy only No surgery	30	15.9	15	4.6	-	-

treatment of CRC. In most countries, drug side effects and financial difficulties are the main reasons for no adherence to this form of treatment [23]. In locally advanced CRC, radiotherapy when applied preoperatively or postoperatively has been shown to improve local control rates. Studies in resource limited countries have shown that only a few CRC patients have access to this form of treatment and one study reported that only 7.2% of patients had access to radiotherapy [16,23,56].

2.4 Outcome of Management of Colorectal Adenocarcinoma

The higher post-operative complication rate seen in patients with CRC at ~26% may be due to the late stage presentation and delayed effective treatment in East Africa [16]. One study reported a high rate of wound sepsis at 41.9% possible due to the late presentation of CRC with large bowel obstruction [16]. Perineal wounds especially perineal wound breakdown may result in the need for another operation which results in increased hospital stay and costs.

The mortality rates of CRC in East Africa have ranged from 10.5% to 29.4% which is higher than that reported in West Africa (6.1%) [16,46,57]. This high mortality may be due to the fact that many CRC patients in East Africa present at a late stage. In Uganda the 5-year relative survival of CRC has been found to be as low as 8.3% which is in contrast with the 5-year relative survival of 54.2% for Black American patients [58]. In Kenya the 3-year survival of CRC was 40% which contrasts with a better rate at a longer follow up of 65% for whites at five years. Lack of patients' awareness to present to hospital early with symptoms, lack of screening facilities, lack of adequate treatment facilities, patients presenting at a late stage and differing tumor biology may explain this discrepancy in survival in East Africa. However the determinants of survival of CRC in East Africa have not been carefully examined hence further studies are needed to address this issue.

2.5 Histopathology

Moderately differentiated adenocarcinoma is the predominant histopathological type of CRC reported in a few studies from Uganda and Tanzania as 88.9% and 98.9% respectively [16,24]. The same study of 81 cases from Uganda showed that mucinous adenocarcinoma was more common in younger compared to older patients however the presence of signet ring cells was similar [24]. Poorly differentiated adenocarcinoma is more common in younger patients than those diagnosed at an older age [24]. Whilst the study from Tanzania showed that mucinous and signet ring carcinoma are significantly more common under 40 years [16]. The proportions reported from this study were mucinous adenocarcinoma (11.6%), signet ring adenocarcinoma (4.6%) and anaplastic (undifferentiated) carcinoma (5.2%) [16]. These two studies from Uganda and Tanzania showed that mucinous adenocarcinomas were more frequent in the right colon than the left colon. A poor prognosis was seen with mucinous and signet ring adenocarcinomas compared to non-mucinous adenocarcinomas [16,24,47]. These findings in East Africa concur with other findings from West Africa [51]. These same findings also suggest that there is a higher incidence of mucinous and anaplastic tumors in Africa compared to the Western world.

2.6 Hereditary Non-polyposis Colon Cancer - Lynch Syndrome

There has been an increase in the incidence of a unique early-onset, non-polypoid type of CRC affecting the rural population of Uganda, whose diet consisting of high-fibre, vegetables and fruits and low in fat significantly differs from the high fat diet in high income countries [14]. Interestingly a study in Uganda showed that 27.3% of patients identified with CRC had histological and demographic features suggestive of MSI tumors based on the Revised Bethesda Guidelines [24]. Mucinous and poorly differentiated adenocarcinoma was more likely to be diagnosed on histology in patients under the age of 50 and this suggests that MSI tumors are more common in younger patients [24]. The age distribution and morphological pattern of CRC in Uganda hence differs from published data reported in the UK and US [24].

In East Africa, the connection between family history and the occurrence of CRC is under investigated [21]. Only a few authors have looked at the possibility of mismatch repair mutations in the aetiopathogenesis of colorectal adenocarcinoma in East Africa [24]. Therefore recognizing that a contribution of the aetiology of CRC in East Africa may be due to hereditary genetic factors makes immunohistochemistry testing and MSI testing imperative to be carried out by researchers in the region in order to truly

establish the molecular subtypes of colorectal adenocarcinoma and hence the prevalence of Lynch syndrome in our community.

3. CONCLUSIONS

In East Africa there is a steady increase in the number of CRC patients being treated. This may be due to an increase in the number of cancer registries in the region reporting this cancer. The male: female ratio varies, whilst the median age is around 41-59 years with more left sided CRC than right sided CRC. Mucinous adenocarcinoma which carry a worse prognosis have a higher incidence than the Western world. The majority of authors have stated that familial polyposis syndromes are a rarity in East Africa however some authors have found similarities in the demographics, histopathological type and non-polypoid MSI-H CRC found principally in black Americans.

Colorectal cancer in East Africa requires more unravelling especially in the aetiopathogenesis and therefore immunohisto-chemical staining and MSI testing is being recommended to establish the molecular subtypes and hence the prevalence of Hereditary Non-Polyposis colorectal carcinoma (HNPCC). This will clarify the genetic aetiopathogenesis of colorectal adenocarcinoma in the East African region.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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