Lynch syndrome in a predominantly Afrocentric population: a clinicopathological and genetic study

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Background: We investigated the prevalence of Lynch syndrome as a hereditary cause of colon cancer in the young Jamaican colorectal cancer (CRC) population.

Methods: We identified patients aged 40 years or younger in whom primary CRC was diagnosed at the University Hospital of the West Indies from January 2004 to December 2008. We reviewed the medical records and hematoxylin and eosin (H&E)–stained histopathology slides. Tumour blocks were tested for microsatellite instability (MSI). Patients with MSI–high phenotype (MSI-H) tumours had genetic counselling, after which genomic DNA was extracted from peripheral blood to test for *MLH1* and *MSH2* germline mutations. Patients also had pedigree mapping.

Results: There were 25 patients with CRC aged 40 years or younger with no history of hereditary colon cancer syndrome. The patients' mean age was 33 (range 21–40) years. Histopathologic review confirmed CRC in all patients; 8 of 25 (32%) showed morphologic features suggestive of MSI. We detected MSI-H in 5 of 23 (22%) tumour blocks tested. Review with H&E staining correctly identified 80% of cases positive for MSI-H. The false-positive rate and positive predictive value on H&E review was 50%. The negative predictive value of histomorphologic H&E review was 94%. Three patients were available for and had mutational analysis of DNA mismatch repair genes; 2 were positive for mutations in keeping with Lynch syndrome and 1 had *MLH1* alterations of uncertain significance. All 3 met the Amsterdam criteria for hereditary nonpolyposis CRC.

Conclusion: Thirteen percent of the population had mutations in keeping with Lynch syndrome. This prevalence is similar to that reported for white populations.

Contexte : Nous avons analysé la prévalence du syndrome de Lynch comme cause héréditaire du cancer du côlon dans la population jamaïcaine jeune touchée par le cancer colorectal (CCR).

Méthodes : Nous avons recensé les patients de 40 ans et moins chez qui on avait diagnostiqué un CCR à l'Hôpital universitaire West Indies entre janvier 2004 et décembre 2008. Nous avons passé en revue les dossiers médicaux et les coupes histologiques après coloration à l'hématoxyline-éosine (H-É). Puis nous avons analysé l'instabilité microsatellitaire (IMS) des blocs tumoraux. Les patients présentant des tumeurs à phénotype IMS élevé (IMS-É) ont eu une consultation en génétique, après quoi on a extrait l'ADN de leur génome à partir d'un spécimen de sang périphérique pour un dépistage des mutations affectant les lignées germinales *MLH1* et *MLH2*. On a aussi dressé la cartographie du génome des patients.

Résultats : On a dénombré 25 patients atteints de CCR âgés de 40 ans ou moins sans antécédents de syndrome héréditaire de cancer du côlon. L'âge moyen des patients était de 33 ans (de 21 à 40 ans). L'analyse histologique a confirmé la présence de CCR chez tous les patients; 8 patients sur 25 (32 %) manifestaient des caractéristiques morphologiques d'IMS. Nous avons décelé une IMS-É dans 5 blocs tumoraux sur les 23 (22 %) testés. Un contrôle par coloration H-É a correctement confirmé 80 % des cas d'IMS-É avérés. Le taux de faux-positifs et la valeur prédictive positive de la coloration H-É ont été de 50 %. La valeur prédictive négative du contrôle histologique H-É a été de 94 %. Trois patients étaient disponibles et ont subi une analyse mutationnelle des gènes de réparation du mésappariement de l'ADN; 2 se sont révélés positifs à l'égard de mutations concordant avec le syndrome de Lynch et un présentait des altérations du *MLH1* de portée incertaine. Les 3 patients répondaient aux critères d'Amsterdam de CCR non polyposique héréditaire.

Conclusion : Treize pour cent de la population présentaient des mutations concordant avec un syndrome de Lynch. Cette prévalence ressemble à celle que l'on observe dans les populations de race blanche.

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Colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and women and is the fourth leading cause of cancer deaths in Jamaica.[1,2] These proportions are comparable to those in the United States, where CRC is the third most common cancer diagnosed in men and women and the second leading cause of cancer-related death.[3] Cancer is projected by the World Health Organization to replace chronic cardiovascular noncommunicable diseases as the leading cause of deaths in Western countries in the next 2–3 decades. In Jamaica, this is already the case, with the most recent report of the Ministry of Health recognizing cancer as the leading cause of death.[2]

Recent trends in CRC incidence and mortality in the United States reveal declining rates, which have been attributed to the effect of CRC screening and prevention through polypectomy as well as early detection and improved treatment.[3] This is not the case in Jamaica, as the most recent statistics from the Jamaica Cancer Registry indicated a 25% increase in the incidence of CRC in men for the 2003–2007 period compared with the 1998–2002 period.[4] The Jamaica Cancer Registry records the incidence for all cancers in the metropolis of Kingston and St. Andrew and extrapolates the data for all of Jamaica. There is no CRC registry for hereditary CRC in Jamaica. Whereas there are recommendations for screening for CRC in the Jamaican population,[5] there are no organized national programs, and screening is largely opportunistic with individual variation. Colonoscopy is the screening method of choice and is the required method in patients with a positive alternative screening test. Despite the acknowledged disease burden, given the cost and the limited availability of colonoscopy, it is unlikely that a national screening program for CRC will be implemented in the near future.

The mean age at CRC diagnosis in Jamaican patients is 65.5 years, but about 5.4% are younger than 40 years old.[6] Most patients (60%) present with advanced CRC, with regional or distant metastases.[6] The prognosis for advanced-stage disease is poor, with patients requiring expensive adjuvant therapy to improve survival or therapy with palliative intent. This can account for a significant portion of the health budget as the prevalence of the disease increases.

Most patients with CRC will have sporadic CRC; however, about 15%–30% of patients under age 50 years will have a familial cancer syndrome,[7,8] such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC) or at least a family history of first-degree relatives with the disease. The frequency of HNPCC in our population is unknown, as the necessary confirmatory tests are largely unavailable. Identification of patients with a familial susceptibility to CRC is important, as at-risk family members will benefit from intensive endoscopic surveillance, prophylactic surgery and possibly chemoprevention. There may also be implications for adjuvant chemotherapy, as some studies suggest that patients with defective mismatch repair (MMR) genes may not benefit from flurouracil-based adjuvant chemotherapy.[9,10] Recognizing these syndromes also has an impact on referral for predictive genetic testing where identifying gene carriers improves the efficiency of cancer surveillance and helps to identify family members who require more frequent endoscopy versus those who can receive standard care.[11] There are currently no registries or facilities available in Jamaica that target at-risk groups or provide genetic testing for high-risk patients.

Whereas young patients with CRC in developed countries have been shown to have a relatively high incidence of mutations in their DNA MMR genes, the prevalence of these mutations in the young Jamaican CRC population is unknown. Our patients are predominantly of African descent and appear to have different tumour characteristics than other groups.[12] The possibility of as-yet undiscovered genetic defects exists,[13] and elucidation of these may lead to the identification of new at-risk groups, ultimately allowing earlier diagnosis of and improved outcomes of CRC in young patients in Jamaica.

Methods

We conducted a retrospective review of all patients aged 40 years or younger who received a diagnosis of primary cancer of the colon or rectum at the University Hospital of the West Indies (UHWI) from January 2004 to December 2008. The Department of Pathology, University of the West Indies, maintains a record of all cases of resected colorectal specimens submitted for histopathological evaluation. We manually searched the pathology department's archives and identified all patients who had a histological diagnosis of a primary malignancy of the colon or rectum. We then identified all patients aged 40 years or younger. The age of 40 years was used as a cut-off to define "young-onset" CRC and to increase the possibility of excluding cases of sporadic CRC. Patients with FAP and inflammatory bowel disease were excluded. We reviewed their medical records for clinical details, and patients were contacted for interviews where applicable.

We reviewed histologic slides for the study patients to confirm the diagnosis of CRC and to look for morphologic features suggestive of microsatellite instability (MSI). The features sought included

- distinct growth patterns (e.g., a medullary pattern with poorly differentiated nests of epithelial tumour cells and a distinct population of interspersed lymphocytes, a cribriform growth pattern and a mixture of distinct growth patterns);
- characteristic cytomorphology, including presence of signet ring cells and poorly differentiated tumours (i.e., > 70% sheet-like growth);

- architectural features, such as a pushing margin, tumours with abundant mucin that appears to suspend small clusters of tumour cells and extensive necrosis; and
- host tumour reactions, including a Crohn-like peritumoral infiltrate or tumour infiltrating lymphocytes.

These features have been described and examined elsewhere as potential morphologic markers of microsatellite instability.[14] Cases with any of the aforementioned features were labelled as suspicious for microsatellite instability. Histopathological data were recorded for these patients, using a standardized data extraction template. Representative blocks of tumour and adjacent normal mucosa with hematoxylin and eosin (H&E) slides from these patients were selected and sent to collaborators at the Zane Cohen Centre for Digestive Disease at Mount Sinai Hospital (Toronto, Ont.) for immunohistochemistry staining of *MLH1*, *MSH2*, *MSH6* and *PMS2* protein expression. Formalin-fixed, paraffin-embedded tissues were sectioned at 4 μm, deparaffinized and rehydrated using xylene and alcohol. The slides underwent microwave antigen retrieval (10 mM citrate buffer, pH 6.0, 3 min at 115°C in microMED T/T Mega; Hacker Instruments and Industries, Inc.). Nonspecific binding was blocked by 20% protein blocker with avidin (Signet Laboratories, Inc.). The slides were washed with Tris-buffered saline. The sections were then incubated with mouse monoclonal antibodies against hMLH1 (1:150, ES05; Novocastra, Vector Laboratories), hMSH2 (1:100, 25D12; Novocastra, Vector Laboratories), hMSH6 (1:300, PU29; Novocastra, Vector Laboratories) and hPMS2 (1:200, A16–4; BD Pharmingen) for 1 hour. The antibodies were detected with the VECTASTAIN Elite ABC Kit (Vector Laboratories).

Patients with MMR immunodeficient tumours were selected for testing for germline mutations of the MMR genes, *MSH2* or *MLH1*. We obtained informed consent and a thorough family history from these patients, and patietns received genetic counselling before we obtaining peripheral blood samples for extraction of genomic DNA.

Briefly, lymphocyte DNA was extracted and screened for mutations by combined methods of multiplex ligation-dependent probe amplification analysis and exon-by-exon sequence analysis of the entire coding regions of *MSH2* and *MLH1* genes. Multiplex ligation-dependent probe amplification reactions were performed according to the manufacturer's instructions (MRC-Holland). Products were analyzed using the 3130xl Genetic Analyzer and the GeneMapper 4.0 software (Applied Biosystems). Sequencing reactions were carried out in forward and reverse orientations using the ABI Prism BigDye Terminator Ready Reaction Mix (Applied Biosystems) and analyzed on an 3130xl Genetic Analyzer, according to the manufacturer's protocol.

Our study protocol was approved by the UHWI/University of the West Indies/Faculty of Medical Sciences Ethics Committee.

Statistical analysis

Data were summarized using frequencies and percentages for all categorical variables as well as means and standard deviations where applicable.

Results

In all, 463 patients received a diagnosis of CRC during the study period. Of these, 29 (6%) were aged 40 years or younger at the time of diagnosis. Four patients were excluded from this study owing to FAP (n = 3) and inflammatory bowel disease (n = 1). The study group therefore consisted of 25 patients, 14 (56%) of whom were women. The mean age was 33 (range 21–40) years.

All patients presented with symptomatic disease, and the most common symptom was bleeding per rectum (70%), followed by abdominal pain (50%) and change in bowel habits (40%). Four patients (16%) had a family history of CRC. The sigmoid colon was the most common site of cancer followed by the rectum. Overall, 72% of lesions were distal to the splenic flexure. Most patients (60%) presented with regional or distant metastases, and no patient had stage 1 CRC. Clinical and pathological features of the patients are shown in Table 1.

Histopathologic review confirmed the diagnosis of CRC in all patients, and 8 of 25 (32%) showed morphologic features suggestive of MSI–high phenotype (MSI-H) based on criteria from Alexander and colleagues.[14] Five of 8 (62%) patients showed more than 1 morphologic feature

Table 1. Clinical and pathological characteristics of young patients with colorectal cancer, n = 25

Characteristic	No. (%)*
Female sex	14 (56)
Age, mean (median) [range] yr	33 (34) [21–40]
Primary tumour site	
Sigmoid colon	9 (36)
Rectum	7 (28)
Cecum	4 (16)
Other	5 (20)
Presenting signs/symptoms	
Bright red blood per rectum	18 (72)
Abdominal pain/constitutional symptoms	12 (48)
Change in bowel habits	10 (40)
Emergency presentation	3 (12)
TNM stage at presentation	
I	0 (0)
II	10 (40)
III	9 (36)
IV	6 (24)
Status at time of review	
Alive	18 (72)
Dead	7 (28)

TNM = tumour, nodes, metastasis.
*Unless otherwise indicated.

suggestive of MSI-H. The features identified included mucinous carcinomas in 4 (50%), tumour infiltrating lymphocytes in 4 (50%), cribriform growth pattern with dimorphic histological differentiation in 3 (38%) and a Crohn-like peritumoral infiltrate in 2 (25%) patients. A single patient with a pushing margin was also identified.

Immunohistochemistry was performed on the tumours of 23 patients, with immunodeficiency for MMR detected in 5 patients (22%; Table 2). Four of these patients demonstrated morphologic features suggestive of MSI-H on H&E-stained slides. Tumours in 4 of the 8 patients with histological features suggestive of MSI-H were found to be negative on immunohistochemical mutation analysis. Therefore, histomorphological features led to the correct identifcation of 80% of cases with immunohistochemical mutations in keeping with MSI-H tumours, missing only 1 case; however, histomorphological features incorrectly suggested another 4 cases of possible MSI-H (false-positive rate and positive predictive value by morphology was 50%). The negative predictive value of histomorphological features was 94% in this series.

Two of the 5 patients with immunodeficient tumours were unavailable for mutational analysis of DNA MMR genes at the time of this study. After her primary surgery, 1 of these patients presented to our institution with locally recurrent rectosigmoid cancer, and investigations revealed metastatic disease. She had already died from her disease at the time of this study, and we were unable to obtain her family history. The other patient was lost to follow-up during the study period, but he has since been assessed and has no evidence of recurrent disease. This patient does not have a family history of CRC or other Lynch-associated cancers. Thus, 3 of 5 patients were available for mutational analysis of DNA MMR genes. Two tested positive for deleterious MMR mutations in keeping with Lynch syndrome, whereas the third had *MLH1* alterations of uncertain significance. The detailed family history of the 3 patients revealed that they all met the Amsterdam criteria for HNPCC (Fig. 1).

Table 2. Results of immunohistochemistry analysis for mutations in *MLH1, MSH2, MSH6* and *PMS2*

Patient no.	*MLH1*	*MSH2*	*MSH6*	*PMS2*	MMR mutation
1	1	1	1	1	
2	0	1	1	0	Mutation of uncertain significance
3	1	1	1	1	No
4	1	1	1	1	No
5	1	1	1	1	No
6	1	1	1	1	No
7	0	1	1	0	Yes
8	1	1	1	1	No
9	1	1	1	1	No
10	0	1	1	0	Not accessed
11	1	1	1	1	No
12	1	1	1	1	No
13	1	1	1	1	No
14	1	1	1	1	No
15	1	1	1	1	No
16	1	1	1	1	No
17	1	0	0	1	Yes
18	1	1	1	1	No
19	1	1	1	1	No
20	1	1	1	1	No
21	1	1	1	1	No
22	0	1	1	0	Not accessed
23	1	1	1	1	No

0 = deficient; 1 = intact; MMR = mismatch repair.

Discussion

It is generally believed that HNPCC or Lynch syndrome accounts for 2%–5% of all cases of CRCs,[15] but it is fair to say that the true prevalence is unknown, and current estimates of the disease may be an underestimate owing in part to the diagnostic criteria.

Lynch syndrome is inherited in an autosomal dominant manner and with an estimated 50% penetrance, with 1 in 300 to 1 in 500 individuals of the general population in the United States having the disease. This makes it one of the most common Mendelian genetic predispositions to cancer.[16] The clinical presentation is heterogeneous, but is often characterized by the development of CRC at a relatively young age (mean age 45 yr). Affected individuals have more synchronous and metachronous cancers than sporadic CRC, and these patients are also more likely to have right-sided tumours.[15,16] In this respect, our finding that 70% of our young patients with CRC and all those with MMR protein deficiency, which is suggestive of Lynch syndrome, had left-sided cancers is surprising. Although this finding may be owing to our small sample size, it may warrant further investigation in this population. The absence of a family history and of predominantly left-sided tumours is more in keeping with the distribution of sporadic CRC in the Jamaican population,[6] and is similar to the findings of Dozois and colleagues[13] in a set of young patients with CRC who lacked identifiable risk factors. This certainly highlights the possibility of other undetermined mutations playing a role in colorectal carcinogenesis.[17] We chose the age group of 40 years and younger to identify individuals with Lynch syndrome, as this has previously been proposed as an initial alternative to family history,[18] but we may have excluded some patients between ages 40 and 50 years. About 5% of patients with CRC met our inclusion criteria; this is comparable to other studies of populations in the United States.[18,19]

Non-CRCs, including cancers of the endometrium, stomach, ovary and pancreas among others, may also develop in individuals with Lynch syndrome. The wide spectrum of cancers in the affected families was confirmed by 1 patient in our series, who, in addition to having several

family members with CRC, also had a family history of endometrial cancer, sebaceous adenoma and spinal meningioma in first-degree relatives (patient # 17, as illustrated in Fig. 1C). The observation of sebaceous adenoma in this family is consistent with the subset of people with Lynch syndrome described as having Muir–Torre syndrome.

We considered obtaining a detailed family history to be the most important step in identifying families at risk for Lynch syndrome; however, in the absence of a registry and even under the best of circumstances, the information initially provided by patients may be inaccurate.[19] Given this limitation, resource-poor countries, such as Jamaica, need to find the most cost-effective method of identifying these patients. This is especially necessary in the absence of a national screening program for CRC and with the high cost and limited access to surveillance colonoscopy and the low level of awareness of CRC perceived among the general population.

It is generally agreed that using the Amsterdam criteria will allow detection of less than 50% of CRCs.[16] Hence other red flags should include all the variables identified in the Bethesda guidelines, including synchronous or metachronous CRC or tumours displaying morphologic features of MSI-H. More recently it has been proposed that all patients younger than 70 years with incident CRC and endometrial cancer should be screened for Lynch syndrome.[16]

Histomorphological review suggested that 8 of 25 patients were possible carriers of the MSI-H phenotype.[14] Only 4 of these patients, however, had MMR immunodeficiencies. The limitations of histological features in the prediction of MSI status have been reported elsewhere.[14]

Lynch syndrome is caused by germline mutations in 4 DNA MMR genes: *MLH1*, *MSH2*, *MSH6* and *PMS2*. Screening the tumour for MSI or loss of one of the MMR proteins can be performed to identify patients with CRC who are most likely to have Lynch syndrome.[20] Although MSI testing is highly sensitive, immunohistochemistry is equally sensitive, relatively inexpensive, more readily available and nearly 100% predictive of MSI-H.[21] It has been proposed as the preferred method to screen for Lynch syndrome among patients with cancer.[20,22] We chose immunohistochemistry as our screening method for these reasons, and 22% of our patients had absence of staining for one of the MMR genes, which is in keeping with results reported in other publications. Once the patient's tumour is found to be immunodeficient, progress can be made by testing of the proband for the specific germline mutations. Identification of supporting MMR mutations in patients who fulfill the original Amsterdam criteria varies among institutions, with rates of 50% and 70% often reported.[23,24] Two of our patients had mutations in keeping with a diagnosis of Lynch syndrome, whereas a third had alterations of uncertain significance. This patient would not be considered to belong to the familial CRC type X (FCC type X), as,

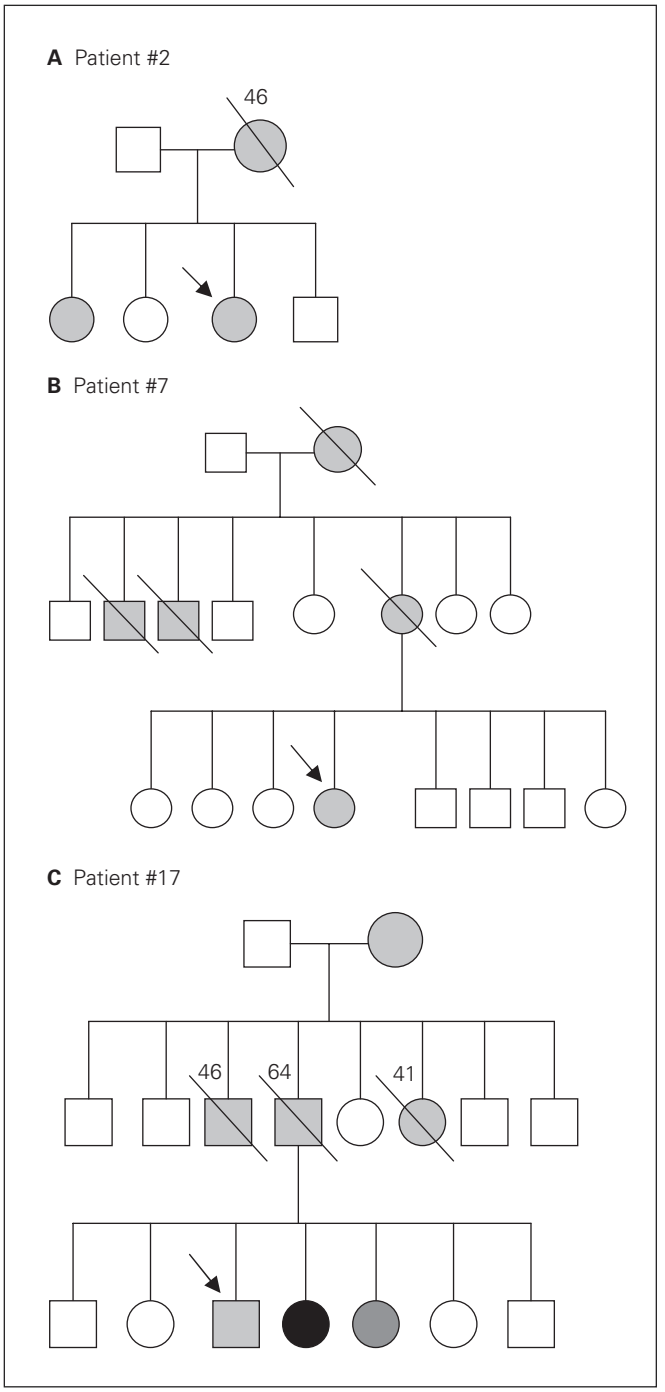

Fig. 1. Pedigrees of patients who were available for mutational analysis of DNA mismatch repair genes. (**A**) Patient #2 carries *MLH1* alterations (p.Pro640Ser; p.His718Cys) of unknown functional significance. (**B**) Patient #7 carries a germline *MLH1* mutation: c. 1923del (Exon 17); consequence: p.Lue642X, which is consistent with a diagnosis of Lynch syndrome. (**C**) Patient #17 carries a germline *MSH2* mutation: c. 1723del (Exon 11); consequence: p.Asp575MetfsX15 "TAG" [STOP] at n.1766_1768, which is consistent with a diagnosis of Lynch syndrome. Squares indicate men; circles indicate women; light grey indicates colorectal cancer; black indicates sebaceous adenoma; dark grey indicates endometrial carcinoma; strikethroughs indicate death and age at death in years (when this data were available); arrows indicate the probands.

although the family met the Amsterdam criteria, there was MMR immunodeficiency. It is likely that this patient also had Lynch syndrome, but given the limitations of the tests available, the classic mutations were not detected. Pedigree analysis showed that all 3 of these patients satisfied the Amsterdam criteria, suggesting that 3 of 23 (13%) patients in our cohort had Lynch syndrome. This again is similar to results reported in other studies that used the age 40 years to screen for Lynch syndrome.[18] Our study did not identify any patient who could be considered to be FCC type X.

Limitations

There are some limitations to our report. It was a small study and, whereas our stringent exclusion criterion of patients older than age 40 years increased the pretest probability of detecting mutations in MMR, it possibly underestimated the prevalence of Lynch syndrome in our population. In addition, genetic testing was only possible in 80% of patients who met the inclusion criteria. Despite these limitations, to our knowledge, our study provides the first evidence for the prevalence of Lynch syndrome (13%) in a population of patients with CRC diagnosed at 40 years of age or younger, and also the first report of a family with Muir–Torre syndrome in the Caribbean. In addition, the at-risk family members of those with diagnosed Lynch syndrome were all offered colonoscopic surveillance. Our study confirms that the suspicion of Lynch syndrome in our population should not be limited to patients with typical right-sided location and/or typical histomorphological features of colon cancer, but rather be guided by clinical history and MMR immunodeficiency.

Conclusion

To our knowledge, our study is the first to identify Lynch syndrome in Jamaica and raises the possibility of a subset with Muir–Torre syndrome in the Caribbean population. It represents the first series of clinical, pathologic and genetic features of HNPCC in a predominantly Afrocentric population in this region. Our findings suggest that in this population, the disease has a similar prevalence as in white populations in western countries. In addition, our study highlights the importance of a detailed family history and an early age of onset in identifying patients with Lynch syndrome. It also serves to raise awareness about the genetics of CRC generally in the medical community. The uncharacteristic phenotypic expression with respect to cancer distribution and histomorphology provides supportive evidence for the importance of developing a high-risk CRC registry in Jamaica.

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We hope to hear from you!

Comment *vous* pouvez vous impliquer dans l'AMC!

L'AMC est vouée à jouer un rôle de chef de file auprès des médecins et à promouvoir les normes les plus élevées de santé et de soins de santé pour les Canadiens. Afin de renforcer l'Association et pour qu'elle représente véritablement tous les médecins du Canada, l'AMC a besoin de membres intéressés à occuper des charges élues et à siéger à des comités et des groupes consultatifs. La structure de l'AMC se compose d'organes de régie et d'entités consultatives élus par le Conseil général ou nommés par le Conseil d'administration. Le Conseil d'administration, dont les membres sont élus par le Conseil général et représentent les associations médicales provinciales et territoriales, les résidents et les étudiants en médecine, est chargé de l'administration générale de l'AMC. Il rend compte des questions de régie au Conseil général.

Les comités de l'AMC jouent le rôle de conseillers auprès du Conseil d'administration et présentent des recommandations au sujet de questions particulières intéressant les médecins et la population. Cinq comités principaux sont constitués principalement de représentants des régions, des résidents et des étudiants, tandis que les autres comités statutaires et spéciaux et les groupes de travail réunissent des personnes qui s'intéressent à des sujets précis et possèdent des compétences spécialisées. Des postes pourront devenir vacants dans un ou plusieurs de ces comités en cours d'année.

Pour en savoir davantage sur les modalités de participation, veuillez communiquer avec:

Jacqueline Ethier, Services généraux et de gouvernance, Association médicale canadienne
1867, promenade Alta Vista, Ottawa (Ontario) K1G 5W8
Télécopieur : 613 526-7570, Téléphone : 800 663-7336, poste 2249, involved@cma.ca

Votre participation peut faire la différence.

Nous espérons avoir de vos nouvelles!

ASSOCIATION MÉDICALE CANADIENNE — CANADIAN MEDICAL ASSOCIATION