Identification of patients at-risk for Lynch syndrome in a hospital-based colorectal surgery clinic

Patrícia Koehler-Santos, Patricia Izetti, Jamile Abud, Carlos Eduardo Pitroski, Silvia Liliana Cossio, Suzi Alves Camey, Cláudio Tarta, Daniel C Damin, Paulo Carvalho Contu, Mario Antonello Rosito, Patricia Ashton-Prolla, João Carlos Prolla

Patrícia Koehler-Santos, Patricia Izetti, Jamile Abud, Carlos Eduardo Pitroski, Silvia Liliana Cossio, Patricia Ashton-Prolla, Genomic Medicine Laboratory, Experimental Research Center, Hospital de Clínicas de Porto Alegre, Porto Alegre - RS, 90035-903, Brazil

Patrícia Koehler-Santos, Carlos Eduardo Pitroski, Patricia Ashton-Prolla, Post-Graduate Program in Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre - RS, 90035-003, Brazil

Patrícia Koehler-Santos, Silvia Liliana Cossio, Patricia Ashton-Prolla, National Institute for Population Medical Genetics, Porto Alegre - RS, 90035-903, Brazil

Patricia Izetti, Medical School, Federal University of Rio Grande do Sul, Porto Alegre - RS, 90035-003, Brazil

Jamile Abud, João Carlos Prolla, Profa. Post-Graduate Program in Gastroenterological Sciences, Federal University of Rio Grande do Sul, Porto Alegre - RS, 90035-003, Brazil

Suzi Alves Camey, Department of Statistics, Federal University of Rio Grande do Sul, Porto Alegre - RS, 91501-970, Brazil

Suzi Alves Camey, Post-Graduate Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre - RS, 90035-003, Brazil

Suzi Alves Camey, Research and Post-Graduation Group, Hospital de Clínicas de Porto Alegre, Porto Alegre - RS, 90035-003, Brazil

Cláudio Tarta, Daniel C Damin, Paulo Carvalho Contu, Mario Antonello Rosito, Division of Coloproctology, Hospital de Clínicas de Porto Alegre, Porto Alegre - RS, 90035-903, Brazil

Cláudio Tarta, Daniel C Damin, Paulo Carvalho Contu, Mario Antonello Rosito, Department of Surgery, Federal University of Rio Grande do Sul, Porto Alegre - RS, 90035-003, Brazil

Patricia Ashton-Prolla, Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre - RS, 90035-003, Brazil

Patricia Ashton-Prolla, Department of Genetics, Federal University of Rio Grande do Sul, Porto Alegre - RS, 90035-003, Brazil

João Carlos Prolla, Service of Pathology, Hospital de Clínicas de Porto Alegre, Porto Alegre - RS, 90035-903, Brazil

Author contributions: Koehler-Santos P identified and interviewed all consecutive colorectal cancer patients who agreed to participate in the study; Koehler-Santos P and Izetti P designed the database and performed the analysis under the supervision of Camey SA, and were directly involved in writing and editing the manuscript; Abud J, Pitroski CE and Cossio SL helped with acquisition of the data from patient databases; Tarta C, Damin DC, Contu PC and Rosito MA are the primary physicians of all patients and participated in patient identification; Prolla JC and Ashton-Prolla P were directly involved with the concept and design of the study, evaluation of patients at-risk and editing of the manuscript.

Correspondence to: Patricia Ashton-Prolla, MD, PhD, Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Porto Alegre - RS, 90035-903, Brazil. pprolla@hcpa.ufrgs.br

Received: February 8, 2010
Revised: March 23, 2010
Accepted: March 30, 2010
Published online: February 14, 2011

Abstract

AIM: To determine the prevalence of a family history suggestive of Lynch syndrome (LS) among patients with colorectal cancer (CRC) followed in a coloproctology outpatient clinic in Southern Brazil.

METHODS: A consecutive sample of patients with CRC were interviewed regarding personal and family histories of cancer. Clinical data and pathology features of the tumor were obtained from chart review.

RESULTS: Of the 212 CRC patients recruited, 61 (29%) reported a family history of CRC, 45 (21.2%) were diagnosed under age 50 years and 11 (5.2%) had more than one primary CRC. Family histories consistent with Amsterdam and revised Bethesda criteria for LS were identified in 22 (10.4%) and 100 (47.2%) patients, respectively. Twenty percent of the colorectal tumors had features of the high microsatellite instability phenotype, which was associated with younger age at CRC diagnosis and with Bethesda criteria ($P < 0.001$). Only...
5.3% of the patients above age 50 years had been previously submitted for CRC screening and only 4% of patients with suspected LS were referred for genetic risk assessment.

CONCLUSION: A significant proportion of patients with CRC were at high risk for LS. Education and training of health care professionals are essential to ensure proper management.

© 2011 Baishideng. All rights reserved.

Key words: Colorectal cancer; Family history; Hereditary cancer; Lynch syndrome; Microsatellite instability phenotype

Peer reviewer: Vamsi R Velchuru, MRCs, FRCSEd, FRCS (Gen Surg), James Paget University Hospital, Great Yarmouth, 6 Pickwick Drive, Off Market Lane, Blundeston, NR32 5BX, United Kingdom

Koehler-Santos P, Izetti P, Abud J, Pitroski CE, Cossio SL, Camey SA, Tarita C, Damin DC, Contu PC, Rostito MA, Ashton-Prolla P, Prolla JC. Identification of patients at-risk for Lynch syndrome in a hospital-based colorectal surgery clinic. World J Gastroenterol 2011; 17(6): 766-773 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i6/766.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i6.766

INTRODUCTION

Family history of colorectal cancer (CRC) is a clinically significant risk factor and may be reported by up to 15% of all patients with the disease. Lynch syndrome (LS, OMIM: #120435), also called hereditary non-polyposis colorectal cancer syndrome (HNPPC), is the most common inherited colon cancer predisposition syndrome. It is an autosomal dominant syndrome caused by germline mutations in the mismatch repair (MMR) genes hMLH1, hMSH2, hMSH6 and PMS2. The syndrome accounts for 2%-3% of all CRC diagnoses and for 5%-9% of the diagnoses of endometrial cancer in patients under age 50 years[1-4]. Other extra-colonic tumors including ovarian, upper urologic tract, gastric, small bowel, biliary/pancreatic and brain cancers have been described at an increased frequency in families with LS[5]. The cumulative lifetime risk of cancer varies depending on geographic/environmental factors and the age-related incidence of each tumor type[6-8]. Furthermore, the cancer spectrum in families affected with the syndrome varies significantly based upon the DNA MMR gene mutated and the specific mutation[9,10].

Determining the prevalence of LS among patients with CRC is an important public health issue. Affected patients have an increased risk for second primary cancers and their identification can lead to specific screening and intervention recommendations for patients and their at-risk relatives[11-13].

Cancer family history is an important tool to identify at-risk patients and families. The Amsterdam criteria, initially including only CRC and later all tumors of the LS cancer spectrum, define clinical diagnosis of LS and are in themselves an indication for MMR mutation testing. However, even the revised Amsterdam II criteria have a relatively low sensitivity (< 80%) which has turned out to be a major limitation for LS diagnosis. More recently, the Bethesda guidelines were developed to identify a larger proportion of MMR mutation carriers (Table 1)[6,16].

Multiple other strategies for identifying individuals with LS have been proposed, including predictive mathematical models to define prior probabilities of carrying a germline MMR mutation, family history instruments and routine testing of CRCs from patients with specific risk factors (e.g. age < 50 years), but the effectiveness of these approaches continues to be debated and has limited applicability in clinical practice[9,10].

In this study, we aimed to determine the prevalence of a family history suggestive of LS among patients with CRC followed in a coloproctology outpatient clinic of a University Hospital in Southern Brazil, and to identify all potential LS patients who should be referred for genetic counseling. Also, we investigated the frequency of tumors with histopathologic features suggestive of microsatellite instability (MSI) and whether screening recommendations were correctly modified according to the risk identified.

MATERIALS AND METHODS

Ethics

This study was approved at the Institutional Ethics Committee (GPPG-HCPA) under the number 05-257.

Patients

All consecutive patients with a diagnosis of CRC who had an appointment in the outpatient Coloproctology clinic of Hospital de Clinicas de Porto Alegre (HCPA), in Porto Alegre, Southern Brazil, from December 2005 to December 2006, were considered for participation in this study. From a total of 250 patients seen in this period, 212 unrelated patients with adenocarcinoma of the colon and rectum and without a previous diagnosis of inflammatory bowel disease were invited and agreed to participate in the study. After signature of informed consent forms, data regarding personal and family cancer history, pathology reports and additional relevant clinical and/or surgical information were collected. Information included types of cancer and age at diagnosis, presence of multiple (synchronous or metachronous) tumors, type and periodicity of colorectal screening, tumor histology, clinical and histological stage of tumors (Dukes and TNM Staging System), family history of cancer (first, second and third degree). Tumor diagnoses in family members were confirmed by medical records and/or death certificates whenever possible.

“Early-onset” colorectal or endometrial cancer was defined as cancer diagnosed before the age of 50 years. All other extra-colonic tumors described in the LS (ovarian, upper urologic tract, gastric, small bowel, biliary/pancre-
At least one of the following features included the Amsterdam criteria: Three or more relatives with colorectal cancer, one of whom is a first-degree relative of the other two; colorectal cancer involving at least two generations; one or more colorectal cancer cases diagnosed before the age of 50. The sensitivity of the Amsterdam criteria was 61.0% and the specificity was 67.0%.

The Bethesda criteria were used to identify patients with LS or at-risk for the syndrome. The criteria included: colorectal cancer in two or more first- or second-degree relatives with LS-related tumors, regardless of age; colorectal cancer in one or more first-degree relatives with an LS-related tumor, with one of the cancers under the age of 50; colorectal cancer with the MSI-H histology; colorectal cancer in one or more first-degree relatives with an LS-related tumor, with one of the cancers under the age of 50; colorectal cancer in two or more first- or second-degree relatives with LS-related tumors, regardless of age. The sensitivity of the Bethesda criteria was 90.9% and the specificity was 77.1%.

Statistical analysis
SPSS version 16.0 was used for data handling and statistical analyses. Descriptive analysis, categorical variables were described by their absolute and/or relative frequencies and quantitative variables were expressed as mean ± SD. For analytical statistics, the existence of an association between categorical variables was examined using χ². The Student’s t-test was used to determine the significance between different ages at diagnoses among two independent groups. A difference with a P value of less than 0.05 was considered significant.

RESULTS
Clinical information on the 212 patients studied is summarized in Table 2. Mean age of the patients at recruitment was 62.33 years (range: 24-99 years, SD = 12.8 years), and 113 (53.3%) were female. Of the 212 patients, 45 (21.2%) were diagnosed with CRC under the age of 50 years and the mean age at first CRC diagnosis was 59.8 years (range: 20-99 years, SD = 13.1 years). Approximately 5.2% of the patients had a synchronous or metachronous colorectal tumor (n = 11) and the mean age at diagnosis in this group was 51.6 years (range: 36-80 years, SD = 13.1 years), lower than the mean age in patients without metachronous colorectal tumor (59.3 years, range: 20-99 years, SD = 12.8 years), as expected (P = 0.051). Two patients (0.9% of the sample) were diagnosed with familial adenomatous polyposis.

The age at diagnosis of the first cancer varied from 20 to 86 years (mean = 58.9 years; median = 59 years; SD = 12.9 years). A second primary cancer was present in 33 patients: CRC in 11 (33.3%), endometrial in 2 (6.1%), breast in 2 (6.1%), prostate in 6 (18.2%). The age at diagnosis of the second primary varied from 39 to 99 years (mean = 66.5 years, SD = 13.2 years). One patient was diagnosed with four different primary tumors: two colon cancers at ages 36 and 55 years, endometrial can-

Table 1  Clinical criteria for Lynch syndrome

| Name                | Criteria                                                                 | Sensitivity | Specificity |
|---------------------|--------------------------------------------------------------------------|-------------|-------------|
| Amsterdam I         | Three or more relatives with colorectal cancer, one of whom is a first-degree relative of the other two; colorectal cancer involving at least two generations; one or more colorectal cancer cases diagnosed before the age of 50. Amsterdam criteria II. Three or more relatives with histologically verified LS-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of whom is a first-degree relative of the other 2; FAP should be excluded. | 61.0%       | 67.0%       |
| Revised Bethesda    | At least one of the following features: Bethesda 1: Colorectal cancer diagnosed in a patient under the age of 50. Bethesda 2: Presence of synchronous or metachronous colorectal cancer, or other LS-associated tumors, regardless of age. Bethesda 3: Colorectal cancer with the MSI-H histology under the age of 60. Bethesda 4: Colorectal cancer in one or more first-degree relatives with an LS-related tumor, with one of the cancers under the age of 50. Bethesda 5: Colorectal cancer in two or more first- or second-degree relatives with LS-related tumors, regardless of age. | 90.9%       | 77.1%       |

Table 2  Sample description by criteria for Lynch syndrome (n = 212)

| Lynch syndrome criteria | n (%) |
|-------------------------|-------|
| Amsterdam               | 22 (10.4) |
| Amsterdam I             | 16 (7.6) |
| Amsterdam II            | 6 (2.8) |
| Bethesda (at least 1 of the 5 criteria) | 100 (47.2) |
| Bethesda (2 or more of the criteria) | 41 (19.3) |
| Bethesda by criteria    |      |
| Bethesda 1              | 45 (21.2) |
| Bethesda 2              | 17 (8.0) |
| Bethesda 3              | 27 (12.7) |
| Bethesda 4              | 23 (10.8) |
| Bethesda 5              | 36 (17.0) |
Table 3  Features of the 223 colorectal tumors in the 212 probands

| Feature                        | n (%)         |
|--------------------------------|---------------|
| Tumor site                     |               |
| Ascending colon                | 22 (9.9)      |
| Transverse colon               | 12 (5.4)      |
| Descending colon               | 11 (5.0)      |
| Rectosigmoid                   | 158 (71.1)    |
| Other (cecum, unspecified site)| 19 (8.6)      |
| Total                          | 222 (100.0)   |
| Missing data                   | 1             |
| Differentiation                |               |
| Well differentiated            | 20 (10.0)     |
| Moderately differentiated      | 157 (78.1)    |
| Poorly differentiated          | 24 (11.9)     |
| Total                          | 201 (100.0)   |
| Missing data                   | 1             |
| Mucinous feature               | 15 (6.7)      |
| Total                          | 223 (100.0)   |
| Missing data                   | 2             |
| MSI-high phenotype             | 42 (21.3)     |
| Total                          | 197 (100.0)   |
| Missing data                   | 26            |
| Dukes stage (n = 195)          |               |
| A                              | 6 (3.1)       |
| B                              | 76 (39.0)     |
| C                              | 87 (44.6)     |
| D                              | 26 (13.3)     |
| Total                          | 195 (100.0)   |
| Missing data                   | 28            |

1Cases with missing data were excluded from the analysis; 2Cases included all patients with microsatellite instability-high phenotype, independent of age.

In the overall sample, 22 (9.9%) patients had a tumor in the ascending colon and 21.3% had colorectal tumors with histology suggestive of MSI-high (MSI-H) phenotype (Table 3). The clinical features of patients with and without this phenotype are shown in Table 4. As expected, MSI-H histological features were more commonly seen in patients with CRC diagnosed at a younger age (18 patients from a total of 42, P = 0.001) and in patients who fulfilled the Bethesda criteria (in all 42 patients, P < 0.001). Opposite to what was expected, in a significant number of tumors from individuals fulfilling Amsterdam criteria, histological features suggestive of MSI-H phenotype were not encountered.

Of the 212 charts reviewed, 17% had the family history previously documented. Furthermore, when the previously documented family histories were compared to the pedigrees obtained during patient interview for this study, there was concordance of data in only 56.6% of cases. On the other hand, of the 100 patients with a family history of cancer and fulfilling Bethesda criteria for LS, 57.0% had their family history previously collected and/or reported in the chart by clinicians or surgeons, but a clinical suspicion of LS was not documented in the chart in any of these cases. Only 4% of the patients with clinical criteria for LS were referred for genetic cancer risk evaluation.

Finally, 5.3% of patients with indications for population-based screening by colonoscopy starting at age 50 years had been submitted at least once for colonoscopy before the diagnosis of CRC. Among the 100 patients at risk for LS, only 4.1% had been offered surveillance colonoscopy previously.

DISCUSSION
As in most familial cancer syndromes, early age of onset and multiplicity of cancers have been considered hallmarks of LS. In registry-based series, the mean age at first CRC is about 45 years, compared to 65 years for sporadic CRC, and some LS patients present with CRC in their twenties. Similarly, the mean age of endometrial cancer is about 50 years, which is about 10 years younger than the average age of sporadic endometrial cancer.
As our knowledge of the influences of genetics on cancer risk has increased, so has the need to improve physicians’ awareness of the importance of familial cancer history and its proper recording in the medical chart. Although there is no consensus about the correct method for obtaining information on family cancer history, and using it as a screening tool, general practitioners usually collect the family history data at the time of registration and different groups have reported screening the adult population for increased genetic risk of cancer using postal questionnaires. Unfortunately, however, health professionals in the first line of patient contact are usually unaware of how and when to contact genetic services. Many specialists, especially coloproctologists and gastroenterologists, have a key role in identifying high-risk patients; the ability to suspect a patient to be at risk for a cancer predisposition syndrome is crucial for a rapid diagnosis and to ensure appropriate care.

Nearly 30% of patients in our study reported a positive family history of CRC, which is much higher than observed positive CRC family history in the general population: approximately 9.0% (22). Our findings also indicate that the hereditary CRC phenotype can be easily identified in outpatient coloproctology units, using a systematic approach after proper training of the staff, as reported previously.

Surprisingly, a high number of patients fulfilling Amsterdam criteria were found in our sample (22/212, 10.4%), significantly higher than previously reported in the Brazilian population. Viana et al. reviewing 311 medical records of CRC patients from São Paulo, Brazil, found a frequency of 1.3% in families with Amsterdam criteria. The reason for such a high incidence remains to be explained. One potential limitation of this study is the fact that the outpatient coloproctology clinic from which the patients derive is located in a tertiary care university hospital, and reference center for many diseases in the region. Thus, a higher percentage of high-risk patients, including those at risk for hereditary cancer may exist in this setting than in other general hospitals.

An additional point to consider is the fact that this institution has, since 2001, one of the few cancer risk evaluation clinics in Southern Brazil. This fact, however, would ideally be associated with high indices of correct identification and referrals of the hereditary cases, which was not observed in most cases. Most patients evaluated in our study did not have an accurate family history assessment in their charts, (description of family history was present in the charts of only 57.0% of potential LS patients). Moreover, only 4% of patients with LS criteria were referred for genetic counseling, suggesting that even when detailed family cancer history is obtained, it may not be granted the necessary importance. Previous investigations have already reported significant gaps in the documentation of family cancer history in medical charts.

Analyzing data from the Direct Observation of Primary Care study, Medalie et al. found that only 40% of 2333 audited charts documented the presence or absence of a family history of breast or colon cancer. Even when family cancer history is obtained, its interpretation seems to be problematic as referrals often focus on rarer, hereditary cancer syndromes, neglecting cases of average and moderate risk individuals. Tyler and Snyder found a similar deficiency in the referral process among family physicians: from 10 patients considered at moderate or high risk, only 3 had been identified and none had been referred for cancer genetic consultation.

Also, although previous studies have shown a clear benefit for surveillance colonoscopy in patients with suspected or proven LS, in our series it was not common practice. Several factors could be contributing to this observation: patient’s refusal, physician omission of adequate familial risk assessment and or referral and/or limited access to screening examinations. Our results are in agreement with those previous studies, considering that only 5% of the patients evaluated were undergoing proper screening. The identification of high-risk precursor lesions is considered critically important and colonoscopy screening for individuals with LS is recommended to begin at age 25 years, or 10 years younger than the earliest diagnosis of CRC in the family, whichever comes first, every 1-2 years.

Multiplicity of cancers is a hallmark of LS and according to the literature about 10% of identified Lynch patients have more than one cancer by the time of diagnosis. Although CRC is the most common, other frequent findings include cancers of endometrium, ovary, stomach, small bowel, pancreas, hepatobiliary system, renal pelvis, ureter and glioblastoma. Approximately 20%-40% of patients have been reported to develop metachronous CRC after initial resection if a subtotal colectomy is not performed. Similarly, clustering of more than one Lynch-associated cancer (colorectal and uterine) in an individual patient should raise suspicion of LS. In our population, among all CRC cases, approximately 15% of patients had a second primary cancer. The most common second primary was CRC (metachronous or synchronous), endometrium, breast and prostate.

The most common extra-colonic tumor in LS is endometrial carcinoma, which develops in up to 70% of women who are mutation gene carriers. Thus, the presence of endometrial cancer in the family history of an individual with CRC, a feature encountered in 12 (6.7%) of the patients studied here, should always raise a suspicion of LS. When the endometrial cancer is diagnosed under the age of 50 years, the probability of LS is particularly high. This has been confirmed by a high rate of MMR deficiency (up to 40%) in women with early-onset endometrial cancer. Consistent with this, the National Comprehensive Cancer Network (NCCN) has recently revised its guidelines and currently recommends annual surveillance of the endometrium for LS families, as well as MMR deficiency investigation for all women diagnosed with endometrial cancer under age 50 years.

There is some debate with regard to whether prostate or breast cancers might be part of the LS, since some studies have found a high frequency of such tumors among HNPC families. Oliveira Ferreira et al. found a 26.5% frequency of breast cancer in families fulfilling Amsterdam criteria from São Paulo, Southeastern...
Brazil, a higher rate than found in general population-based studies, which could suggest existence of a subset of mutations in this region that are also associated with a higher breast cancer risk. In our study, we found breast cancer at a frequency of approximately 9% in families fulfilling Amsterdam criteria. Although it is common to see LS pedigrees with breast cancer, most genetic and immunohistochemical studies on familial breast cancers have not found any strong relationship with the MMR system deficiency[35,36]. Recently, a case report of a Lebanese family with LS found a MSH2 gene defect in a breast cancer tumor of early-onset, suggesting that it could be involved in accelerated breast carcinogenesis[37]. However, more studies are needed to define such association.

Different studies have shown that CRC in LS differs from typical sporadic CRCs in location, histology, and natural history. Also, it usually displays findings that are suggestive of MSI, such as intense lymphocytic infiltrates, extensive areas with poorly differentiated tissue and mucinous histology[38]. Overall, 20.3% of the tumors evaluated in this series demonstrated one or more histological features suggestive of MSI-H, similar to previous studies[39]. In the last few years, it has been suggested that histology could be useful in selecting CRC patients for molecular testing for LS[40-43], since limiting testing to patients with MSI-H histology could reduce the burden of molecular testing by 60% compared with testing all patients who meet the Revised Bethesda Criteria. More importantly, it could help identify LS among patients with late onset and no cancer family history[44].

Interestingly, among patients who fulfilled the Amsterdam criteria, only 28.6% presented tumors with features of MSI-H phenotype. This is somewhat surprising and could indicate that in this group of patients, the strong family history of CRC may not be related to abnormalities in the MMR system, and that there could be an increased prevalence of what has been called in the literature the Familial Colorectal Cancer Type X[45]. Recently, Abdel-Rahman et al[46] analyzed the molecular features of the tumors in CRC patients with MMR germline mutations and in sporadic CRC. They concluded that tumors from the MMR gene-negative group exhibited a novel molecular pattern characterized by a paucity of changes in the common pathways to CRC, which could be associated with non MSI-H histology. Molecular studies with this population are now being carried out in order to test such hypothesis.

Large population-based studies have shown that a family history of CRC in first-degree relatives is associated with an increased risk of CRC. In this study we have shown that a significant proportion of patients diagnosed with CRC and followed in an outpatient clinic of a university hospital in Southern Brazil have either a significant family history of cancer or pathology features suggestive of LS. Our findings underscore the importance of adequate familial risk assessment and, also, of considering MSI-H pathology features in the identification of at-risk patients. Education and training of physicians is essential to ensure that hereditary cancer patients and families are identified and properly referred for genetic counseling and long-term cancer screening programs. The reason for the high prevalence of patients at risk for LS in our population requires further investigation.

ACKNOWLEDGMENTS

We are indebted to the patients and their family members who agreed to participate in this study and to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERS), Programa de Pós-Graduação em Ciências Gastroenterológicas (UFRGS) and Fundação de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre (FIHC-P) who provided funding for this study. PKS was supported by a postdoctoral fellowship from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

REFERENCES

1 Wijnen JT, Vasen HF, Khan PM, Zwinderman AH, van der Klift H, Mulder A, Tops C, Møller P, Fodde R. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. N Engl J Med 1998; 339: 511-518
2 Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Nakagawa H, Sotamaa K, Prior TW, Westman J, Panescu J, Fix D, Lockman J, Comeras I, de la Chapelle A. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005; 352: 1851-1860
3 Kauff ND. How should women with early-onset endometrial cancer be evaluated for Lynch syndrome? J Clin Oncol 2007; 25: 5143-5146
4 Lu KH, Schorge JO, Rodabaugh KJ, Daniels MS, Sun CC, Soliman PT, White KG, Luthra R, Gershenson DM, Broadus RR. Prospective determination of prevalence of Lynch syndrome in young women with endometrial cancer. J Clin
Identification of Lynch syndrome patients

Oncof 2007; 25: 5158-5164

5 Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology 1999; 116: 1453-1456

6 Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell 1996; 87: 159-170

7 Potter JD. Colorectal cancer: molecules and populations. J Natl Cancer Inst 1991; 91: 916-932

8 Pande M, Lynch PM, Hopper JL, Jenkins MA, Gallinger S, Haile RW, LeMarchand L, Lindor NM, Campbell PT, Newcomb PA, Potter JD, Baron JA, Frazier ML, Amos CI. Smoking and colorectal cancer in Lynch syndrome: results from the Colon Cancer Family Registry and the University of Texas M.D. Anderson Cancer Center. Clin Cancer Res 2010; 16: 1331-1339

9 Balaguer F, Balmáñ J, Castellvi-Bel S, Steyerberg EW, Andreu M, Llor X, Jover R, Syngal S, Castells A. Validation and extension of the PREMM1.2 model in a population-based cohort of colorectal cancer patients. Gastroenterology 2008; 134; 39-46

10 Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Clendenning M, Sotamaa K, Prior T, Westman JA, Panescu J, Fix D, Lockman J, Lajunenese J, Comeras I, de la Chapelle A. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008; 26: 5783-5788

11 Burke W, Petersen G, Lynch P, Botkin J, Daly M, Garber J, Ko M-J, McTiernan A, Offit K, Thomson E, Varricchio C. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. JAMA 1997; 277: 915-919

12 Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH, Lynch P, Burke W, Press N. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006; 296: 1507-1517

13 Vasen HF, de Vos Tot Nederveen Cappel WH. An evidence-based review on surveillance for Lynch syndrome. Dis Colon Rectum 2006; 49: 1797-1798; author reply 1799

14 Syngal S, Fox EA, Eng C, Kolodner RD, Garber JE. Sensitivity and specificity of clinical criteria for hereditary nonpolyposis colorectal cancer associated mutations in MSH2 and MLH1. J Med Genet 2000; 37: 641-645

15 Vasen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991; 34: 424-425

16 Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fishel R, Lindor NM, Burgert LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltonaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004; 96: 261-268

17 Friebel TM, Beutler RA, Lee SM, Bernhardt BA, Felzszoori KJ, Griffin CA. Active recruitment increased enrollment in a hereditary cancer registry. J Clin Epidemiol 2004; 57: 1172-1176

18 Emery J, Rose P. Expanding the role of the family history in primary care. Br J Gen Pract 1999; 49: 260-261

19 Summerton N, Garwood PV. The family history in family medicine: a questionnaire study. Fam Pract 1997; 14: 285-288

20 House W, Sharp D, Sheridan E. Identifying and screening patients at high risk of colorectal cancer in general practice. J Med Screen 1999; 6: 205-208

21 Leggatt V, Mackay J, Yates JR. Evaluation of questionnaire on cancer family history in identifying patients at increased genetic risk in general practice. BMJ 1999; 319: 757-758

22 Oliveira Ferreira F, Napoli Ferreira CC, Rossi BM, Toshihiko Nakagawa W, Aguilar S Jr, Monteiro Santos EM, Vieira Costa ML, Lopes A. Frequency of extra-colonic tumors in hereditary nonpolyposis colorectal cancer (HNPCC) and familial colorectal cancer (FCC) Brazilian families: An analysis by a Brazilian Hereditary Colorectal Cancer Institutional Registry. Fam Cancer 2004; 3: 41-47

23 Viana DV, Góes JR, Coy CS, de Lourdes Setsuko Ayrizono M, Lima CS, Lopes-Cendes I. Family history of cancer in Brazil: is it being used? Fam Cancer 2008; 7: 229-232

24 Medalie JH, Zyzanski SJ, Langa D, Stange KC. The family in family practice: is it a reality? J Fam Pract 1998; 46: 390-396

25 Tyler CV Jr, Snyder CW. Cancer risk assessment: examining the family physician’s role. J Am Board Fam Med 2006; 19: 468-477

26 Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, PeltoMäki P, De La Chapelle A, Mecklin JP. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000; 118: 829-834

27 de Jong AE, Hendriks YM, Kleibeuker JH, de Boer SY, Cats A, Griffioen G, Nagengast FM, Nelis FG, Rookus MA, Vasen HF. Decrease in mortality in Lynch syndrome families because of surveillance. Gastroenterology 2006; 130: 665-671

28 National Comprehensive Cancer Network Guidelines: Genetic/familial high-risk assessment. Available from: URL: http://www.nccn.org

29 Lin KM, Shashidharan M, Ternent CA, Thorson AG, Blatchford GJ, Christensen MA, Lanspa SJ, Lemon SJ, Watson P, Lynch HT. Colorectal and extracolonic cancer variations in MLH1/MSH2 hereditary nonpolyposis colorectal cancer kindreds and the general population. Dis Colon Rectum 1998; 41: 428-433

30 Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 1995; 64: 430-433

31 Cossio SL, Koehler-Santos P, Pessini SA, Mônego H, Edelweiss MI, Meurer L, Errami A, Coffa J, Bock H, Saraiva-Pereira ML, Ashton-Prolla P, Prolla JC. Clinical and histomolecular endometrial tumor characterization of patients at-risk for Lynch syndrome in South of Brazil. Fam Cancer 2010; 9: 131-139

32 Garg K, Soslow RA. Lynch syndrome (hereditary nonpolyposis colorectal cancer) and endometrial carcinoma. J Clin Pathol 2009; 62: 679-684

33 Mecklin JP, Järvinen HJ. Tumor spectrum in cancer family syndrome (hereditary nonpolyposis colorectal cancer). Cancer 2000; 68: 1109-1112

34 Soravia C, van der Klift H, Bründler MA, Blouin JL, Wijnen J, Hutter P, Fodde R, Delozier-Blanchet C. Prostate cancer is part of the hereditary non-polyposis colorectal cancer (HNPPC) tumor spectrum. Am J Med Genet A 2003; 121A: 159-162

35 Müller A, Edmonston TB, Corao DA, Rose DG, Palazzo JP, Becker H, Fry RD, Rueschoff J, Fishel R. Exclusion of breast cancer as an integral tumor of hereditary nonpolyposis colorectal cancer. Cancer Res 2002; 62: 1014-1019

36 Wong EM, Tesoriero AA, Pupo GM, McCredie MR, Giles GG, Hopper JL, Mann GJ, Goldgar DE, Southey MC. Is MSH2 a breast cancer susceptibility gene? Fam Cancer 2008; 7: 151-155

37 Akoum R, Ghaoui A, Brihi E, Ghabash M, Hajjar N. Early-onset breast cancer in a Lebanese family with Lynch syndrome due to MSH2 gene mutation. Hered Cancer Clin Pract 2009; 7: 10

38 Jenkins MA, Hayashi S, O’Shea AM, Burgert LJ, Smyrk TC, Shimizu D, Waring PM, Ruszkiewicz AR, Pollett AF, Redston M, Barker MA, Baron JA, Casey GR, Dowty JC.
Giles GG, Limburg P, Newcomb P, Young JP, Walsh MD, Thibodeau SN, Lindor NM, Lemarchand L, Gallinger S, Haile RW, Potter JD, Hopper JL, Jass JR. Pathology features in Bethesda guidelines predict colorectal cancer microsatellite instability: a population-based study. Gastroenterology 2007; 133: 48-56

Truta B, Chen YY, Blanco AM, Deng G, Conrad PG, Kim YH, Park ET, Kakar S, Kim YS, Velayos F, Sleisenger MH, Terdiman JP. Tumor histology helps to identify Lynch syndrome among colorectal cancer patients. Fam Cancer 2008; 7: 267-274

Wright CL, Stewart ID. Histopathology and mismatch repair status of 458 consecutive colorectal carcinomas. Am J Surg Pathol 2003; 27: 1393-1406

Jass JR. HNPCC and sporadic MSI-H colorectal cancer: a review of the morphological similarities and differences. Fam Cancer 2004; 3: 93-100

Burgart LJ. Testing for defective DNA mismatch repair in colorectal carcinoma: a practical guide. Arch Pathol Lab Med 2005; 129: 1385-1389

Kakar S, Aksoy S, Burgart LJ, Smyrk TC. Mucinous carcinoma of the colon: correlation of loss of mismatch repair enzymes with clinicopathologic features and survival. Mod Pathol 2004; 17: 696-700

Lindor NM, Rabe K, Petersen GM, Haile R, Casey G, Baron J, Gallinger S, Bapat B, Aronson M, Hopper J, Jass J, LeMarchand L, Grove J, Potter J, Newcomb P, Terdiman JP, Conrad P, Moslein G, Goldberg R, Ziegas A, Anton-Culver H, de Andrade M, Siegmund K, Thibodeau SN, Boardman LA, Seminara D. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA 2005; 293: 1979-1985

Abdel-Rahman WM, Ollikainen M, Kariola R, Jarvinen HJ, Mecklin JP, Nyström-Lahti M, Knuutila S, Peitomäki P. Comprehensive characterization of HNPCC-related colorectal cancers reveals striking molecular features in families with no germline mismatch repair gene mutations. Oncogene 2005; 24: 1542-1551

Piñol V, Castells A, Andreu M, Castellvi-Bel S, Alenda C, Llor X, Nicola RM, Rodriguez-Moranta F, Payá A, Jover R, Bessa X. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 2005; 293: 1986-1994

S- Editor Wang JL  L- Editor Logan S  E- Editor Ma WH