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RAPID DEVELOPMENT OF COLORECTAL NEOPLASIA IN PATIENTS WITH LYNCH SYNDROME

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Abstract

Background and Aims—Patients with Lynch Syndrome have a high risk for colorectal adenomas and carcinomas. We evaluated the development of colorectal neoplasia in these patients.

Methods—We assessed serial colonoscopy findings from 54 persons from 29 pedigrees with pathogenic mutations in *MSH2* or *MLH1*; we evaluated the development of colorectal neoplasia by age, sex, tumor location, and number (mean follow-up time=9.3 years, colonoscopy interval=1.7±1.2, 112 adenomas and 31 cancers). Differences in colorectal phenotype were analyzed by genotype and dwell time was calculated for advanced neoplasias.

Results—Among mutation carriers, the cumulative risk of colorectal neoplasia was 43% by age 40 years and 72% by 80 years. There were no statistically significant associations between time to development of colorectal neoplasia and sex or mutation type. Most female patients had left-sided neoplasms whereas most male patients developed right-sided lesions. The mean cumulative numbers of neoplastic lesions in patients was 1.3±0.5 by age 30 years and 7.6±6.8 by age 80 years. Polyp dwell time was 33.0±16.2 months and 35.2±22.3 months for advanced adenoma and colorectal cancer, respectively. The 5-year survival rate for patients with colorectal cancer was 96%.

Conclusions—High percentages of individuals with pathogenic mutations in *MSH2* or *MLH1* develop colorectal neoplasia by age 40. Left-sided colorectal neoplasias are more frequent in female patients. The development of 3 or more colorectal neoplasms by age 30 years indicates a possible polyposis syndrome, rather than Lynch Syndrome. Polyp dwell time is short for advanced neoplasias, arguing for annual colonoscopic screening and surveillance.

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Keywords

Mismatch repair (MMR) genes; colon cancer; CRC

INTRODUCTION

Lynch Syndrome (LS), also known as hereditary nonpolyposis colorectal cancer, is an autosomal dominant disorder caused by a germline mutation of one of the DNA mismatch repair genes. The lifetime risk of colorectal cancer in individuals with a deleterious mutation approaches 70 percent, with a mean age of diagnosis in the fifth decade of life (1,2). In addition, these patients have an increased relative risk of transitional cell carcinoma of the ureter and renal pelvis, glioblastoma, sebaceous skin tumors, and adenocarcinomas of the endometrium, stomach, small bowel, ovary, and biliary system (3–6).

Colorectal cancers in Lynch Syndrome are thought to arise from precursor adenomas as occurs in sporadic colorectal cancer. The appellation hereditary nonpolyposis colorectal cancer was given to differentiate this condition from familial adenomatous polyposis (FAP) in which patients develop hundreds of adenomas. However, the multiplicity of adenomas in LS is not well characterized. Therefore, clinically differentiating patients with LS from those with oligo adenomatous polyposis (caused by attenuated FAP or MYH associated polyposis) is often difficult.

In sporadic colorectal cancer, progression through the adenoma-carcinoma sequence is thought to happen over a decade (7). In LS this process is considered accelerated, perhaps occurring in less than 5 years (8). Consequently, most authorities recommend colorectal cancer screening every 1–2 years, starting at ages 20–25 (9). However, polyp dwell-time in LS has never been calculated.

Therefore, the present study analyzes in LS patients, confirmed by mismatch repair gene mutation, the colorectal phenotype including the multiplicity and temporal development of colorectal neoplasia. In addition, the relationship of genotype to colonic phenotype was evaluated.

METHODS

Study population

Patients with Lynch Syndrome in the Johns Hopkins Hereditary Colorectal Cancer Registry were included in this study. All patients had a deleterious germline mutation in either the *MLH1* or *MSH2* mismatch repair genes, and had undergone at least one colonoscopic surveillance procedure. All the patient's enrolled in the study were unaffected with colorectal cancer or Lynch Syndrome-associated cancers prior to their first colonoscopy. This study was approved by the Johns Hopkins Joint Committee on Clinical Investigation (institutional review board).

Study design

Data was collected on each patient from medical records including colonoscopy and histopathology reports. Abstracted information included, sex; age; date of colonoscopy; age at first and last colonoscopy; number of colonoscopies; number, type, and location of colorectal neoplasia; and the patient's specific germline mismatch repair mutation. From this data, the cumulative number, and cumulative frequency of neoplasms per decade were calculated. Also, the anatomical location of adenomas and colorectal cancers in the colorectum classified as right-sided (cecum, ascending, colon transverse colon, or splenic

flexure) or left-sided (descending colon, sigmoid colon, or rectum) was analyzed. In addition, the above variables were evaluated for association with germline mutation and with younger (18–49 years old) or older (50–89 years old) age. The polyp dwell time for colorectal cancer is defined as the duration of time for transformation of normal colorectal mucosa to colorectal cancer. This was calculated from individual instances in patients in which one colonoscopy was clear of neoplasia and the next subsequent colonoscopy identified colorectal cancer. The number of months between these two colonoscopies was calculated and designated as the dwell time for colorectal cancer for that instance. Then dwell times from these instances were summed and a mean average and standard deviation were calculated. A similar calculation was utilized to determine the dwell time for advanced adenoma (adenoma with villous component). Also the mean dwell time and standard deviation was calculated separately for all instances of proximal (right-sided) colorectal cancers and for distal (left-sided) colorectal cancers. Statistical analysis for differences in dwell time between proximal and distal colorectal cancers was conducted using Fisher exact test and student *t*-tests.

Statistical Analysis

Mean, standard deviation, median, and range were reported where appropriate. Statistical analysis was conducted using Fisher exact test and student *t*-tests. Statistical significance was defined as a *P* value < 0.05. The statistical analyses were performed using the statistical software STATA version 11 (STATA Corp, College Station, TX, USA). Generalized linear latent and mixed models (GLLAMMs) were utilized to estimate a random intercept log linear regression of the response variable colorectal neoplasia location (left side of the colon vs right side of the colon) and the following explanatory variables: gene mutation (MSH2 or MLH1 carrier), sex, and age. This type of regression model was conducted to account for the hierarchical (multilevel) nature of the data with *units* (colorectal neoplastic events) nested in *clusters* (subjects). Odds ratios (OR's) and their 95% CI were estimated for each parameter included in the model. Statistical significance was set at less than 0.05. Also, GLLAMMs were utilized to estimate a random intercept log linear regression of the response variable time-to-colorectal neoplasia (months) and the following explanatory variables: gene mutation (MSH2 or MLH1 carrier) and sex. Again, hazard risks and 95% CI were estimated for each parameter included in the model. Statistical significance was set at less than 0.05.

RESULTS

In total 54 mismatch repair mutation positive patients from 29 pedigrees had one or more colonoscopic evaluations (Table 1). These patients underwent a total of 282 colonoscopies (Table 2). The mean age at first colonoscopy was 39.5 ± 10.8 years and at last colonoscopy was 48.8 ± 12.9 years. The mean colonoscopic follow-up was 9.3 years and the mean interval between colonoscopies in this patient group was 1.7 ± 1.2 years. These evaluations detected a total of 112 colorectal adenomas, 31 colorectal cancers, 32 hyperplastic polyps, and 1 sessile serrated polyp.

The cumulative risk of neoplasia was 43% in the 4th decade of life and rose to 72% in the 8th decade of life (Table 3). By the 8th decade of life 80% of males developed neoplasia compared to 68% of females. GLLAMMs were used to evaluate the association of time to neoplasia to mutation type and sex. There was no increased risk of neoplasia according to mutation type (*p*=0.198) or sex (*p*=0.609). However, this analysis was insufficiently powered to eliminate type II error.

The mean age at first adenoma was 46.5 ± 9.7 and for first colorectal cancer 46.8 ± 9.9 with no statistically significant difference between different gene carriers. The mean numbers of

neoplastic lesions in those affected were 1.3 ± 0.5 for ages 20–29 years; 1.8 ± 1.4 for ages 30–39; 2.2 ± 1.8 for ages 40–49; 3.5 ± 2.9 for ages 50–59 years; 5.3 ± 5.1 for ages 60–69 years; and 7.6 ± 6.8 for ages 70–79 years. A colorectal burden of three or more neoplastic lesions in patients under age 30 or six or more in those under the age 50 was more than two standard deviations from the mean.

The location of colorectal neoplasia found on colonoscopy was right-sided for both younger males (R/L=1.60) and older males (R/L =2.67) and left-sided for younger females (R/L =0.52) and older females (R/L = 0.75) (Table 4). The location of colorectal neoplasia between males and females was statistically significantly different overall ($p=0.0012$), and also at both younger ($p=0.042$) and older ages ($p=0.012$) by chi-square analysis. Further analysis of cancer neoplasia location was done by generalized linear, latent and mixed model statistics. In this model which adjusted for mutation type, age, and sex, mutation type was not statistically associated with colorectal neoplasia location ($p=0.125$) and the differences by sex were marginally significant ($p=0.09$). The sample sizes for these analyses provided sufficient statistical power ($>80\%$).

The polyp dwell time was calculated from 15 separate instances of colorectal cancer development in 13 patients and 8 instances of advanced adenoma development in 7 patients. The mean surveillance frequency in those developing colorectal cancer was 1.9 years and for advanced adenoma 2.1 years. The polyp dwell time was 33.0 ± 16.2 months and 35.2 ± 22.3 months for advanced adenoma and colorectal cancer, respectively (Table 5). The dwell time for proximal colorectal cancers (right-sided) was 28.7 ± 16.6 months and for distal cancers (left-sided) was 43.6 ± 28.5 , $p=ns$. The small sample size precluded analysis of the association of dwell time with genotype.

Among 24 patients 31 colorectal cancers were discovered. This included two patients with metachronous carcinomas, one patient with a synchronous cancer, and two patients had 3 colorectal cancers apiece found simultaneously during their colonoscopies. Overall, 22 cancers were right-sided and 9 were left-sided. In the men 11 cancers were right-sided and 1 left-sided; in women 11 were right-sided and 8 were left-sided, $p=ns$. Among these 24 patients, one patient with a solitary lesion diagnosed at 65 died of metastatic colorectal cancer. The 5 year survival rate for those diagnosed with colorectal cancer was 96% (23/24).

DISCUSSION

Little data exist on the colorectal phenotype of patients with Lynch Syndrome. The present study evaluated colonoscopic findings in patients with LS confirmed by germline testing. These individuals were followed by serial colonoscopy with an average interval between procedures of 1.7 years and an average of more than 9 years of follow-up representing the longest follow-up study, to our knowledge, to date.

The overall cumulative risk of colorectal neoplasm in LS patients in the present study group was 43% by age 40. Mecklin et al (10) calculated a similar risk with over 40% of males and over 30% of females with colorectal neoplasms. These rates are strikingly different from the general population in which 1–2% of patients have colorectal adenomas by age 40 (11).

In young adulthood, clinical differentiation between patients with Lynch Syndrome and oligopolyposis syndromes (such as attenuated familial adenomatous polyposis and MYH associated polyposis) is difficult to make. Although colorectal neoplasms are thought to be limited in LS, the present study revealed that the cumulative average number approaches 7.0 ± 6.8 by age 80. However, the mean cumulative number of colorectal neoplasms was 1.3 ± 0.5 and 2.2 ± 1.8 in those affected before age 30 and 50, respectively. Consequently, patients under 30 years old with 3 or more (>2 SD from mean) or under 50 with 6 or more

colorectal neoplasms likely have a polyposis syndrome rather than LS. This information can help guide appropriate management and genetic testing. Cumulative number of colorectal neoplasms by age has not otherwise been studied in LS patients with germline mutations except for the report of Liljegren et al (12). This investigator noted a mean of 1.9 colorectal polyps among a cohort of 108 patients with assumed HNPCC and at risk family members with a mean age of 44.3 yrs at last surveillance colonoscopy.

Polyp dwell time is defined as the duration of the adenoma carcinoma sequence from normal colorectal mucosa to colorectal cancer. In sporadic colorectal cancer, this period is considered, from a variety of sources but more from expert opinion, to be about 10 years (13). In LS, the polyp dwell time is estimated to be much shorter (8,14,15) but has never been calculated. Nevertheless, screening and surveillance guidelines recommend colonoscopy every 1 to 2 years starting at age 20–25 and then annually after 40 years old (9). In the present investigation, the polyp dwell time for development of an advanced adenoma was 33 months and for colorectal cancer 36 months. In addition, the mean age of adenoma and colorectal cancer diagnosis was similar in our study, further arguing for a very short colorectal cancer dwell time. This rapid progression to malignancy in LS supports the previous frequent screening/surveillance recommendations and argues for annual colonoscopy in germline affected individuals even at young age. Of note, the dwell time analysis is limited since missed small or flat adenomas on one colonoscopy could proceed to advanced adenomas or colorectal cancer on the next endoscopy. Although not statistically significant, there was a shorter dwell time for proximal compared to distal colorectal cancer. This finding could support the hypothesis that right-sided tumors were missed by colonoscopy.

Investigators have determined that patients with LS develop primarily right-sided colorectal cancer. The present study had a similar overall distribution of colorectal cancer with 22 of 31 cancers found in the right colon. However, evaluation of the location of all colorectal neoplasms in this study revealed that women have predominantly left-sided compared to men with right-sided neoplasms, and this difference was marginally statistically significant when adjusted for age and mutation type. There was no association between germline mutation type and location of neoplasia.

Thirty-one cancers were detected among 24 patients. In this retrospective study, 23 of 24 colorectal cancer patients were still alive at 5 years with a survival rate of 96%. Similarly, Jarvenin et al found a 100% survival rate at 5 years in patients with colorectal cancer in the screened group vs 57% in the nonscreened group (11). This strikingly positive survival rate likely reflects both the effect of screening/surveillance and a less aggressive biology of this malignancy.

The findings in this retrospective investigation are limited by several considerations. A small number of patients were evaluated in this study. This factor might account for failure to find statistical significance in analysis of colorectal neoplasia distribution by mutation type or the chance occurrence of a high risk of colorectal cancer in women. As in other retrospective studies, selection bias can influence the data. Although complete information was obtained and verified on all participants, the accuracy of the data was dependent on the medical record. In our investigation, the patients came to a specialized center for management, and, consequently, the element of referral bias cannot be discounted; although none of the patients were enrolled in the study because of colorectal neoplasia. The above factors could have influenced results such as the cumulative risk of colorectal neoplasia and mean cumulative number of neoplasia per patient by age at colonoscopy. Nevertheless, this study attempted to mitigate these factors by extensively investigating a genetically confirmed group of Lynch Syndrome patients with prolonged colonoscopy follow-up.

In summary, by age 50 the majority of Lynch Syndrome patients have been affected by colorectal neoplasia. Left-sided colorectal neoplasia is common especially in females and should not dissuade the clinician from the diagnosis of LS. A burden of 3 or more colorectal neoplasms by age 30 or 6 or more by age 50 probably indicates a polyposis syndrome rather than LS. These guidelines can help determine the appropriate genetic testing to conduct. Polyp dwell time for advanced neoplasia is very rapid in patients with LS. This argues for annual and not biennial colonoscopic screening/surveillance in these patients and pedigrees. Finally, the excellent colorectal cancer 5 year survival in the present study supports literature data that colonoscopy screening/surveillance is a life saving tool.

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Table 1

Characteristics of Study Subjects

No. of patients	54
Sex – no. (%)	
Female	33 (61)
Male	21 (39)
Caucasian race: no. (%)	52 (96)
No. of pedigrees	29
Genotype – no. (%)	
MLH1	30 (56)
MSH2	24 (44)

Table 2

Characteristics of Colonoscopy Surveillance

Total No. of Colonoscopies	282
Mean No. of Colonoscopies per patient	5.2
Age at first colonoscopy – yr. Mean ± SD (range)	39.5±10.75 (19–62)
Age at last colonoscopy – yr. Mean ± SD (range)	48.8±12.9 (26–75)
Mean follow-up – yr.	9.3
Colonoscopy surveillance interval – yr. Mean ± SD (range)	1.7±1.2 (0.5–7.5)
No. of adenomas detected	112
No. of cancers detected	31

Table 3

Cumulative Risk of Colorectal Neoplasia Development by Age and Sex

	Age (years)				
	30–39 n=25	40–49 n=30	50–59 n=21	60–69 n=10	70–79 n=5
Males	33%	64%	72%	80%	80%
Females	50%	59%	65%	68%	68%
Combined	43%	61%	67%	72%	72%

Table 4

Location of Colorectal Neoplasia According to Sex and Age.

Male		Age (yrs) 20–49	R/L Ratio	p-value ^a	Male		Age (yrs) 50–79	R/L Ratio	p-value ^b
	R	16	1.6	0.042		R	24	2.67	0.012
	L	10				L	9		
Female		Age (yrs) 20–49	R/L Ratio		Female		Age (yrs) 50–79	R/L Ratio	
	R	12	0.52			R	21	0.75	
	L	23				L	28		
Males and Females		Age (yrs) 20–49	R/L Ratio		Males and Females		Age (yrs) 50–79	R/L Ratio	
	R	28	0.85			R	45	1.16	
	L	33				L	37		

^a colorectal neoplasia location between males and females 20–49 y.o. and

^b colorectal neoplasia location between males and females age 50–79 y.o. by chi-square analysis. Analysis of cancer neoplasia location by generalized linear, latent and mixed model statistics which adjusted for mutation type, age, and sex, revealed that differences by sex were marginally significant (p=0.09).

Table 5

Dwell time of advanced adenoma and colorectal cancer

	Advanced Adenoma – Mo.	Colorectal Cancer – Mo.
Mean±SD (range)	33.0± 16.2(12–56)	35.2±22.3(7–96)