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Mutation spectrum and risk of colorectal cancer in African American families with Lynch Syndrome

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RSG: study concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript.
AKW: acquisition of data, analysis and interpretation of data and drafting of the manuscript.
CG: acquisition of data and critical revision of the manuscript for important intellectual content.
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Abstract

Background & Aims—African Americans (AAs) have the highest incidence and mortality of colorectal cancer (CRC) in the United States (US). Few data are available on genetic and non-genetic risk factors for CRC among AAs. Little is known about cancer risks and mutations in mismatch repair (MMR) genes in AAs with the most common inherited CRC syndrome, Lynch syndrome. We aimed to characterize phenotype, mutation spectrum, and risk of CRC in AAs with Lynch Syndrome.

Methods—We performed a retrospective study of AAs with mutations in MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) using databases from 13 US referral centers. We analyzed data on personal and family histories of cancer. Modified segregation analysis conditioned on ascertainment criteria was used to estimate age- and sex-specific CRC cumulative risk studying members of the mutation-carrying families.

Results—We identified 51 AA families with deleterious mutations that disrupt function of the MMR gene product: 31 in *MLH1* (61%), 11 in *MSH2* (21%), 3 in *MSH6* (6%), and 6 in *PMS2* (12%); 8 mutations were detected in more than 1 individual and 11 have not been previously reported. In the 920 members of the 51 families with deleterious mutations, the cumulative risks of CRC at an age of 80 y were estimated to be 36.2% (95% confidence interval [CI], 10.5%–83.9%) for men and 29.7% (95% CI, 8.31%–76.1%) for women. CRC risk was significantly higher among individuals with mutations in *MLH1* or *MSH2* (hazard ratio, 13.9; 95% CI, 3.44–56.5).

Conclusions—We estimate the cumulative risk for CRC in AAs with MMR gene mutations to be similar to that of individuals of European descent with Lynch syndrome. Two-thirds of mutations were found in *MLH1*—some were found in multiple individuals and some have not been previously reported. Differences in the mutation spectrum are likely to reflect the genetic diversity of this population.

Keywords

colon cancer; African descent; hereditary non-polyposis colorectal cancer; DNA repair

Introduction

In the United States (US), colorectal cancer (CRC) is the second leading cause of cancer death. African Americans (AAs) have the highest CRC incidence and mortality of all populations[1]. The age of CRC diagnosis in AAs is younger overall[2], and there is higher incidence of proximal and more advanced cancers in this population[3–6]. These epidemiological differences have prompted some to recommend earlier CRC screening for AAs starting at age 45[7,8]. Causes of CRC disparities are not completely understood, and research has predominantly focused on socioeconomic factors. There is a growing body of evidence supporting an important role of biological factors[9], including differences in genetic susceptibility[10, 11] and tumor biology[6, 12–14] between African and European American individuals with CRC. However, knowledge about the most common inherited CRC syndrome, Lynch syndrome, in the AA population is lacking.

Lynch Syndrome, or hereditary non-polyposis colorectal cancer (HNPCC), accounts for 3–5% of all CRC[15] and is caused by mutations in 5 genes: *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*. In addition to CRC, individuals with Lynch Syndrome have an increased risk for uterine, ovarian, gastric, ureter and renal pelvis cancers, pancreas, small bowel, bile duct, brain, and sebaceous skin cancers[16, 17]. Previous clinic-based studies performed in subjects of European descent estimate lifetime risk for CRC between 22.4 to 47%[18, 19] when controlling for ascertainment bias. The overall proportions of *MLH1*, *MSH2*, *MSH6* and *PMS2* mutations in Lynch Syndrome patients of European descent are 32%, 39%, 14%, and 15%, respectively[20].

Although 3 novel MMR mutations (2 *MLH1* and 1 *MSH2*) were described in AA families in 1999[21], there have been no additional reports of Lynch Syndrome in AAs despite higher incidence of early-onset and proximal colon cancers in this population. Moreover, it is not known whether the spectrum of mutations and cancer risks in AAs are the same as in individuals of European descent given different population histories and genetic diversity. Given this gap in the field, we sought to determine the mutation spectrum, phenotype, and risk of cancers in AAs with MMR gene mutations.

Material and Methods

Family Ascertainment

Academic institutions and the Colon Cancer Family Registry (CCFR)[22] in the US were contacted to contribute population-based and clinic-based families with identifiable mutations in any of the Lynch Syndrome-related genes. Academic centers were identified based on having a clinical registry, membership in the Collaborative Group of the Americas (CGA) and/or requests for participation at CGA and Digestive Disease Week annual meetings. Only families with self-identified African descent from the US were included in

this study, which was approved by the institutional review boards at each participating institution.

Inclusion Criteria

Families were selected for this analysis if they self-reported paternal or maternal AA ancestry and had tested positive by an accredited clinical laboratory for a deleterious mutation, a suspected deleterious mutation (as defined by the laboratory performing the test), or a variant of unknown significance (VUS) in one of the MMR genes. A deleterious mutation refers to one that disrupts function of the gene product.

Personal History and Family History

Medical records were reviewed for all participants. For individuals with a personal history of cancer and/or positive genetic test, original reports were used to confirm cancer diagnoses and/or the type of mutation, when available. Data on colonoscopy screening before and after Lynch syndrome was also obtained when available. Family history information (including incidence of colorectal, endometrium, and other cancers; age at diagnosis; and relationship to the proband) was retrieved from genetic consult notes and/or from pedigrees. Medical records and/or death certificates were gathered when possible, although most family members' diagnoses were not confirmed.

For all probands, the predicted likelihood of carrying a MMR mutation was generated using the prediction model PREMM(1,2,6)[23], and the Amsterdam Criteria II were evaluated. Revised Bethesda Guidelines for testing colorectal tumors for MSI were also evaluated for individuals diagnosed with CRC.

Mutation Nomenclature and Assessment of Pathogenicity

The variants identified in this study were named according to the GenBank, following the instructions provided by the Human Genome Variation Society[24]. The *MLH1*, *MSH2*, *MSH6* and *PMS2* reference sequence were NM_000249.3, NM_000251.1, NM_000179.2, and NM_000535.5, respectively. In addition, we checked the nomenclature by using version 2.0 of the Mutalyzer sequence variation nomenclature checker[25], as well as analyzed if the mutations were already reported in the International Society for Gastrointestinal Hereditary Tumours (InSIGHT)[26] database and Mismatch Repair Genes Variant Database[27]. Suspected deleterious results typically are treated clinically as positive tests; therefore, they were analyzed along with deleterious mutations. Patients with VUS were analyzed separately using two different computational algorithms (sorting intolerant from tolerant [SIFT][28] and polymorphism phenotyping [PolyPhen][29]) to predict the functional impact of VUS results in this study. Recurrent mutations were defined as the same DNA change found in unrelated individuals. Mutation testing using Sanger sequencing and large rearrangement testing was performed by a variety of commercial laboratories as per the individual centers' practices.

Statistical Analysis

Hazard ratios (HR), i.e. the age- and sex-specific cancer incidence for carriers divided by that for the AA general population were estimated using modified segregation analysis [30, 31]. Age- and sex-specific cancer incidences for the general AA population were obtained from

the SEER database[1]. Of note, genetic testing had not been done in all family members with and without cancer who are presumed to have deleterious mutations because these mutations are present in the proband. Models were fit by maximum likelihood with the statistical package MENDEL version 3.2 [32]. Estimates were appropriately adjusted for the clinic- and population-based ascertainment of families using a combination of retrospective likelihood and ascertainment-corrected joint likelihood[18, 30, 33, 34], in which each pedigree's data were conditioned on the proband's genotype, cancer status and age of onset (for population-based families) or on the proband's genotype and the affected statuses and ages of onset of all family members at the time the proband was found to be a MMR mutation carrier (for clinic-based families).

Estimated cumulative risks (penetrance) of cancers to age *t* years for carriers were calculated from the USA AA population incidences $\lambda_0(\tau)$ at age τ years multiplied and the estimated HR θ with the formula:

$$1-\exp\left(-\int_0^t \theta\lambda_0(\tau)\,d\tau\right)$$

For each cancer group, 10-year risks of CRC for carriers who have not previously been diagnosed with the disease were estimated as $[R(t + 10) - R(t)]/[1 - R(t)]$, where *t* is the carrier's age in years and $R(t)$ and $R(t + 10)$ are the relevant cumulative risks to ages *t* and *t* + 10 years, respectively.

Observation time for each subject started at birth and ended at age at diagnosis of CRC or other cancer, last follow-up or death, whichever occurred first. The mean and standard deviation (SD) of the age at diagnosis of cancers were calculated using Stata 13.0[35].

Results

Study population

Fifty-seven AA families met eligibility criteria for this analysis from 13 academic institutions in the US of which 4 families were identified through the CCFR (Supplementary Figure 1). Of the 57 probands (54 clinic-based and 3 population-based ascertainment), 51 (89%) had deleterious mutations (Supplementary Table 1) and 6 (11%) had a VUS (Supplementary Table 2). The following data will focus only on the 51 probands carrying deleterious mutations and their families that will be designated as Lynch Syndrome families.

Characteristics of African American Probands With Lynch Syndrome

Table 1 shows the characteristics of probands with Lynch Syndrome. Of 51 probands, 35 (69%) were female, 48 (94%) had personal history of cancer and 21 (41%) developed more than 1 primary tumor. The majority of probands 42 (82%) had CRC, of which 7 (14%) had at least 2 CRC primaries. Lynch Syndrome-related cancers were found in 16 (31%) of probands. Amsterdam Criteria II and revised Bethesda guidelines were met in 31 (61%) and 45 (89%) of probands, respectively. Median score by PREMM(1,2,6) model was 28.5% (range 2–99.8%), including 3 patients with score < 5%, who were all diagnosed with proximal CRC with no first-degree relatives with CRC.

In total, 51 CRCs were diagnosed in 42 AA probands. Characteristics of CRC in these patients are shown in Table 2. Of cases with available data, CRC was predominantly right-sided (30/42, 71%) and showed MSI-H (16/18, 89%) and/or loss of staining by IHC (21/24, 88%). Additional tumor characteristics included presence of mucinous features (9/16, 56%), infiltrating lymphocytes (1/6, 17%) and well- or moderate differentiation (12/17, 71%). Of 28 tumors with data on clinical stage, 3/28 (11%) were in situ, 8/28 (29%) stage I, 9/28 (32%) stage II, 6/28 (21%) stage III and 2/28 (7%) stage IV. Partial colectomy was performed in 28/30 (93%) of cases for which surgical data was available.

Spectrum of Deleterious Mutations

Of 51 Lynch Syndrome families, 31 (61%) had *MLH1* mutations. Of the remaining families, 11 (21%) had *MSH2* mutations, 3 (6%) had *MSH6* mutations, and 6 (12%) had *PMS2* mutations (Figure 1). Eight recurrent mutations accounted for 37% of all deleterious mutations: 6 in *MLH1* [c.117-2A>G (2x), c.199G>A (2x), c.381-1G>A (5x), c.677G>A (2x), c.1772_1775delATAG (2x), c.793C>T (2x)] and 2 in *MSH2* [c.2047G>A (2x), c. 942+3A>T (2x)]. Of 39 distinctive mutations, 11 have not been described either in the InSIGHT[30] or MMR database[27], including 6 in *MLH1* (EX6_8del, EX6_10del, c.962insAG, c.1219C>T, c.1667+1G>A, c.1923delT), 3 in *MSH2* (c.34insG, c.832delG, c.860insG) and 2 in *PMS2* (EX13del, c.2182_2184delACTinsG). The majority of the mutations (19/51, 37%) were frameshift (Table 1).

Estimation of risk of cancers for African American families with Lynch Syndrome

In the modified segregation analysis, we included a total of 920 relatives (466 males and 454 females) from the 51 AA families with Lynch Syndrome. Mutational status was known for 24 relatives (2.6%). Of these families, 48 (94%) were ascertained via family cancer clinics and 3 (6%) were ascertained via population-based cancer registries. In relatives, we observed a total of 123 CRC (70 males and 53 females) whose average ages at diagnosis was 50.3 (SD 13.2) years. Further, there were 6 pancreas, 3 gallbladder, 14 gastric, 3 small bowel, 1 renal, and 2 urinary bladder cancers in male and female relatives, 18 endometrial, 12 ovarian, and 14 breast cancers in female relatives and 8 prostate cancers in male relatives (Supplementary Table 3).

The cumulative risks of CRC for AA carriers are given in Table 3 and illustrated in Figure 2. For all MMR gene mutation carriers combined, the cumulative risk of CRC to age 80 years was estimated to be 36.2% (95% CI = 10.5%–83.9%) for male carriers and 29.7% (95% CI = 8.31%–76.1%) for female carriers. Ten-year risks of CRC for unaffected AA carriers at various ages are given in Supplementary Table 4. For *MLH1* and *MSH2* mutation carriers combined, the cumulative risk of CRC to age 80 years was estimated to be 53.9% (95% CI = 17.4%–95.7%) for male carriers and 45.6% (95% CI = 13.9%–91.5%) for female carriers.

AAs with any MMR gene mutation had 8.08-fold increased risk of CRC (95% CI = 1.99–32.9) compared with the general AA population in the US. Given the possibility that CRC was misclassified as gastric cancer, we performed sensitivity analysis after assuming gastric cancers to be CRC in family members and noted a similar hazard ratio of 7.64 (95% CI = 2.15- 27.2). CRC risk was higher when considering only individuals with mutations in

MLH1 or *MSH2* [HR 13.9 (95% CI = 3.44–56.5)]. We found no evidence for a difference in CRC risks for *MLH1* or *MSH2* mutation carriers between males (HR 16.2, 95% CI = 2.63–99.3) and females (HR 11.3, 95% CI = 1.13–114) (p=0.81), nor between those aged under 50 (HR 11.4, 95% CI = 0.83–157) and those aged 50 years and above (HR 15.0, 95% CI = 3.08–73.2) (p=0.86) (Table 4). For extracolonic cancers, HR point estimates showed increased risks; however, due to the very small numbers of extracolonic cancers and wide confidence intervals, it is very difficult to meaningfully interpret the data (Supplementary Table 5).

Discussion

This is the largest series of AA families with Lynch Syndrome reported to date. The results show a significantly increased risk of CRC in AA Lynch Syndrome patients compared with the general AA population and are in line with previous studies of Lynch Syndrome performed largely in individuals of European descent[17–19, 36]. We found a predominance of mutations in *MLH1* that is distinct from the mutation spectrum reported in previous studies in individuals of European descent[20]. Moreover, there were several recurrent as well as novel mutations in AAs that have not been previously reported in publicly available databases or the literature.

In compiling cases from several US academic institutions and from the CCFR, the moderate number of AA probands and families is noteworthy. Reasons for this could include less referral, access or uptake of genetic counseling and testing among AAs or, alternatively, lower prevalence of Lynch Syndrome among AAs. In a retrospective study, we noted that AAs seen in a referral cancer risk clinic were less likely to be tested for hereditary CRC syndromes and lacked paternal cancer history knowledge compared with Caucasians[37]. Studies of genetic testing in hereditary breast ovarian cancer (HBOC) syndrome have shown that AA women have decreased awareness[38], hold more negative attitudes[39, 40], have lower perception of cancer risk[41] but have greater increase in testing intentions with education and counseling[42]. A prospective study of women at risk for HBOC showed that AAs undergo less genetic counseling and testing which was not explained by risk of carrying a BRCA1/2 mutation, socioeconomic status, risk perception, attitude toward genetic testing or primary care physician recommendation[43]. Based on these studies, reasons why AAs might not be identified with Lynch Syndrome are likely complex and require further prospective study. We acknowledge that the total number of AAs tested for Lynch Syndrome was not available limiting our ability to estimate overall prevalence in this population. With adoption of universal CRC tumor testing using MSI or IHC, it will be important to expand our study in the future to include AA probands detected through tumor screening rather than by clinic referral.

The majority of deleterious mutations were found in *MLH1* (61%). This is distinct from a previous clinic-based study in European Americans that found higher prevalence of *MSH2* (55%) compared with *MLH1* (37%)[17]. Population-based studies of MMR gene mutations in those of European descent have also found higher rates of *MSH2* (39%) compared with *MLH1* (32%) mutations[20, 44–47]. Among 12 of the 13 centers included in this study for which data was available, the frequency of *MLH1* mutations in individuals of European

descent was 29.5% in line with previous estimates underscoring the distinct mutation spectrum among AAs found in this study. The predominance of mutations in *MLH1* in AAs raises the question of ancestry-specific targeted panels that could be more cost-effective in low-resource settings. However, given genetic diversity of AAs and limited sample size of the current study, full sequencing of MMR genes should remain the gold standard in clinical practice until larger cohorts have been studied.

It is noteworthy that 8 recurrent mutations were found among AAs raising the possibility of founder mutations in this population. Careful review of pedigrees did not suggest relatedness among families carrying identical mutations, although this cannot be excluded as a possibility. Future genetic studies are needed to confirm possible founder mutations through haplotype analysis. Clinicians should be aware of the possibility of finding novel mutations in AAs and contribute this information to international mutation databases in order to expand our understanding of MMR gene mutations in diverse populations.

The risk of Lynch Syndrome-associated cancers, especially CRC, in AAs is elevated compared with the general AA population. Confidence intervals are overlapping with those previously found in Lynch Syndrome patients of European descent but are wide limiting precise risk estimates in the AA population. Nonetheless, cumulative lifetime risk for males and females is nearly the same as in mutation carriers of European descent especially considering studies that correct for ascertainment bias as was done in this study (Supplementary Table 6). Given the moderate sample size, it is not possible to determine whether cancer risk or age of presentation is significantly different in AAs compared with Lynch Syndrome families of European descent. Efforts to increase Lynch Syndrome diagnosis in AAs (as well as other minority populations) will enable better understanding of different cancer risks among populations.

While we were unable to obtain colonoscopy screening data on all AA subjects prior to their Lynch syndrome diagnosis, among those for whom data was available (n=14), 11 (78.6%) patients with CRC underwent their first colonoscopy at the time of the cancer diagnosis and had not been undergoing earlier or more frequent screening based on family history. For women with endometrial cancer (n=3) as their first or only cancer that led to Lynch syndrome testing, colonoscopy screening was done but started only at age 50 according to population screening guidelines. Although screening data is limited, these findings underscore the fact that AA patients present as the index case in a family despite multiple cancer diagnoses in the family suggestive of Lynch Syndrome. Reasons why AA individuals with family history of CRC might not undergo earlier screening could be due to patient as well as provider factors. Previous studies have shown that AA with family history of at least 1 first-degree relative with CRC perceive their personal risk of CRC as lower compared to Caucasians[48]. Moreover, AA also report higher rates of providers not recommending screening when there is a family history of CRC[49].

This study has a number of strengths. It is the largest compilation of AA Lynch Syndrome patients and their family members to date. This was accomplished by collaboration among 13 US referral centers and the CCFR. Cancer risks were estimated using modified segregation analysis in order to control for ascertainment bias. Inclusion of additional

probands and families, especially those identified through universal tumor testing, will help expand our understanding of hereditary CRC in non-European populations in the future.

There are also some limitations. While great effort was made to include subjects from large US registries and the CCFR, the moderate sample size limits estimates of colonic and extracolonic cancer risk resulting in larger confidence intervals. However, point estimates of CRC risk are overlapping with those reported in populations of European descent. Inclusion of convenience samples predominantly from tertiary referral centers might not reflect population-based data as these subjects might be phenotypically different from population-based mutation carriers. It is also acknowledged that ascertainment bias cannot be controlled for in estimates of descriptive characteristics. In most cases, family cancer diagnoses could not be confirmed through medical records. While knowledge of family cancer history has been shown to be accurate overall[50] and previous studies have utilized similar patient-reported family cancer history for risk estimation[17], we acknowledge that this knowledge might be reduced in AAs [37, 51] and could impact risk estimates. Since lack of family history knowledge is more common among AAs, it is possible that cancer risk in AA mutation carriers is an underestimate. We performed sensitivity analysis assuming misclassification of CRC as gastric cancer and did not find different CRC risk estimates. Regarding information about adherence to Lynch syndrome screening, we were unable to obtain reliable data possibly because data was not collected, patients did not get screened at a tertiary care center and/or there was loss to follow up. Finally, while self-identification of race/ethnicity is the preferred strategy used by the US national census[52], we acknowledge that this could limit choices for individuals who identify as multiracial.

In summary, we report results on the largest series of AA Lynch Syndrome patients and families from the US. We found a predominance of mutations in *MLH1* with several recurrent and novel mutations. There is significantly elevated risk of CRC as well as other Lynch Syndrome-associated tumors in this population. The overall paucity of AA families in referral centers is notable and requires additional study to understand factors that could impact Lynch Syndrome identification (or lack thereof) in this population. Inclusion of AAs (and other minorities) in studies of hereditary cancer syndromes is needed to better understand their contribution to overall cancer burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAs	African Americans
AA	African American
CCFR	Colon Cancer Family Registry
CRC	colorectal cancer
HR	hazard ratios
MMR	mismatch
MSI	microsatellite instability
SD	standard deviation
VUS	variant of unknown significance

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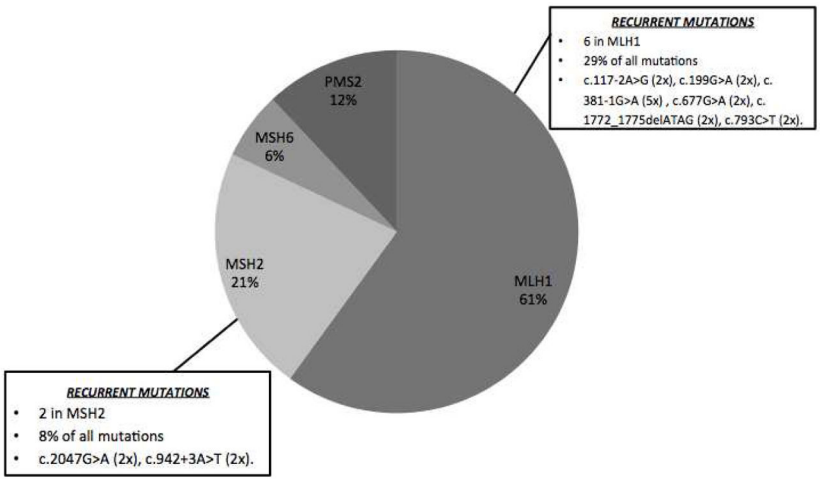

Figure 1.
Spectrum of deleterious mutations in African Americans with mismatch repair gene mutations.

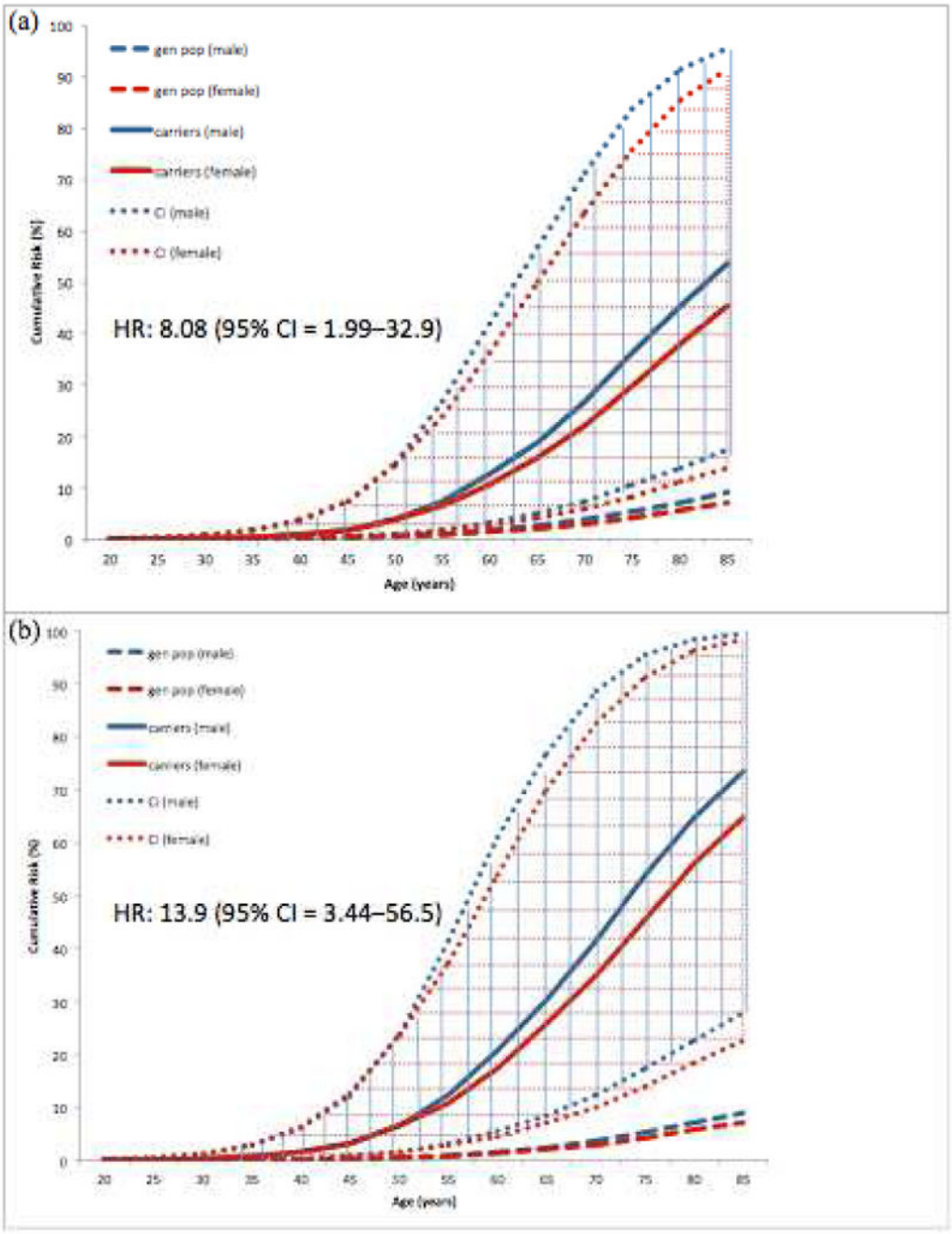

Figure 2.

Cumulative risks % (unbroken lines) and corresponding 95% confidence intervals (CI) (dotted lines) of colorectal cancer for African American carriers of (a) all mismatch repair gene mutations and of (b) *MLH1* and *MSH2* mutations and the African American SEER population-based data (dashed lines). Blue and red colors represent males and females, respectively.

Table 1

Characteristics of African American probands with deleterious or suspected deleterious mutations in mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2*.

	Total	*MLH1*	*MSH2*	*MSH6*	*PMS2*
All patients	**51 (100%)**	31 (61%)	11 (21%)	3 (6%)	6 (12%)
Male	**16 (31%)**	13	1	2	-
Female	**35 (69%)**	18	10	1	6
CRC diagnosis					
First CRC ≤ 50 yo	**34 (67%)**	26	4	-	4
First CRC > 50 yo	**7 (14%)**	2	2	2	1
At least 2 CRC primaries	**7 (14%)**	7	-	-	-
Lynch Syndrome-related cancers[a]	**16 (31%)**	9	5	1	1
ACII positive	**31 (61%)**	21	6	-	4
RBG positive	**45 (88%)**	31	7	2	5
Median PREMM(1,2,6) score (range)	**28.5% (2–99.8%)**	46 % (5.8–99.8%)	22.4% (2–85.5%)	10.8% (3.3–12.9%)	6.65% (3.9–62.3%)
Type of mutation					
Frameshift	**19 (37%)**	8	6	1	4
Nonsense	**5 (10%)**	4	-	1	-
Missense	**11 (22%)**	7	2	-	2
Splice site	**14 (27%)**	11	3	-	-
Hypermethylation of gene promoter	**1 (2%)**	1	-	-	-
Not available	**1 (2%)**	-	-	1	-
Novel mutation (%)	**11 (100%)**	6 (55%)	3 (27%)	-	2 (18%)

[a]Endometrium, ovarian, stomach, hepatobiliary, small bowel, transitional cell carcinoma of the renal pelvis or ureter. CRC, colorectal cancer; ACII, Amsterdam Criteria II; RGB, Revised Bethesda criteria

Table 2

Colorectal cancer phenotype in probands with mismatch repair gene deleterious or suspected deleterious mutations.

	Number/total number available (%)
Location	
right-sided	30/42 (71%)
left-sided	12/42 (29%)
MSI	
high	16/18 (89%)
stable/low	2/18 (11%)
IHC	
Positive[a]	21/24 (88%)
Negative	2/24 (8%)
undetermined	1/24 (4%)
Colectomy	
partial	28/30 (93%)
total	2/30 (7%)
Clinical stage	
In situ	3/28 (11%)
I	8/28 (29%)
II	9/28 (32%)
III	6/28 (21%)
IV	2/28 (7%)

IHC, immunohistochemistry; MSI, microsatellite instability

[a] loss of at least one of the MMR proteins by immunohistochemistry

Table 3

Age-specific cumulative colorectal cancer risk percentages (95% confidence intervals) for African Americans with any mismatch repair (MMR) gene mutation or only *MLH1* & *MSH2* mutation carriers.

Age (yrs)	Male			Female		
	Gen Pop	All MMR mutation carriers	*MLH1* and *MSH2* mutation carriers	Gen Pop	All MMR mutation carriers	*MLH1* and *MSH2* mutation carriers
30	0.01	0.05 (0.01–0.21)	0.09 (0.02–0.37)	0.01	0.08 (0.02–0.33)	0.14 (0.03–0.56)
40	0.05	0.41 (0.10–1.66)	0.71 (0.18–2.84)	0.06	0.45 (0.11–1.81)	0.77 (0.19–3.08)
50	0.23	1.85 (0.46–7.31)	3.17 (0.79–12.3)	0.24	1.91 (0.47–7.54)	3.27 (0.82–12.6)
60	0.95	7.43 (1.88–26.9)	12.5 (3.23–41.7)	0.83	6.52 (1.65–23.9)	11.0 (2.83–37.6)
70	2.56	18.9 (5.02–57.3)	30.3 (8.52–76.8)	2.11	15.9 (4.16–50.5)	25.8 (7.08–70.1)
80	5.41	36.2 (10.5–83.9)	53.9 (17.4–95.7)	4.27	29.7 (8.31–76.1)	45.6 (13.9–91.5)

Gen Pop, general population

Table 4

Hazard ratios and corresponding 95% confidence intervals (CI) of colorectal cancer risk for African American carriers of all mismatch repair gene (MMR) mutations and of *MLH1* and *MSH2* mutations compared with the African American SEER population-based data.

	Hazard Ratio (95% CI)	
	All MMR mutation carriers	***MLH1* & *MSH2* mutation carriers**
Overall	8.08 (1.99–32.9)	13.9 (3.44–56.5)
Sex		
Male	8.46 (1.31–54.5)	16.2 (2.63–99.3)
Female	7.77 (1.33–45.4)	11.3 (1.13–114)
Age at diagnosis (years)		
<50	11.8 (1.69–82.6)	11.4 (0.83–157)
≥50	6.18 (1.03–36.9)	15.0 (3.08–73.2)