Prostate cancer incidence in males with Lynch syndrome

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Purpose: An increased risk of prostate cancer is currently not considered a part of the Lynch syndrome spectrum. The purpose of this study was to retrospectively examine prostate cancer incidence in the Lynch syndrome cohort at the Ohio State University in comparison with that in the general population.

Methods: We included all males diagnosed with Lynch syndrome from June 1998 to June 2012 at the Ohio State University and obtained baseline information including cancer history. If patients had not been seen in the 12 months before June 2012, they were contacted to document changes in their cancer history. We compared prostate cancer incidence among the Lynch syndrome families with that of the general population by using the Surveillance, Epidemiology, and End Results registry 1999–2009.

Results: Of the 188 males identified with Lynch syndrome, 11 males were diagnosed with prostate cancer during the study period. The ratio of observed to expected numbers of prostate cancer cases resulted in a standardized rate ratio of 4.87 (95% confidence interval: 2.43–8.71). Impaired mismatch repair expression and microsatellite instability were seen in one out of two prostate cancer specimens available for testing.

Conclusion: Males with Lynch syndrome had a nearly fivefold increased risk of developing prostate cancer but did not appear to have earlier onset or a more aggressive phenotype.

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Key Words: colorectal cancer; Lynch syndrome; microsatellite instability; mismatch repair deficiency; prostate cancer

INTRODUCTION

Lynch syndrome (LS) is caused by a germline mutation in one of the mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, or *PMS2*. This, followed by a mutation (e.g., chromosomal deletion, point mutation, or epigenetic inactivation by hypermethylation) in a second allele leads to lack of MMR function, causing accumulation of mutations.[1] This can lead to malignant transformation of cells and tumor formation with a hypermutated phenotype and is manifested by microsatellite instability (MSI) and lack of one or more of the four MMR proteins on staining by immunohistochemistry (IHC). A definitive diagnosis is obtained by germline gene sequencing.

LS increases the risk of several cancers, including colorectal, endometrial, ovarian, gastric, small intestinal, pancreatic, ureteral, brain, and sebaceous gland adenocarcinomas,[2] and screening for colorectal cancer (CRC)[3] and prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy have been shown to increase survival of these patients.[4]

Prostate and breast cancer are currently not considered part of the LS tumor spectrum. Some studies have revealed an increased incidence of prostate cancer, especially in patients carrying an *MSH2* mutation,[5–8] whereas others have not shown an increased incidence.[2,9,10] Two studies have shown a lack of MMR protein expression in prostate cancer tumors in patients with LS.[6,11] Other studies have focused on patients with hereditary prostate cancer and have looked for signs of MSI or lack of MMR proteins on IHC. One study found that 3 out of 77 prostate tumors from patients with hereditary prostate cancer harbor MSI.[12] Another study found that 3 out of 31 patients with prostate cancer and a family history of CRC had MSI (two high and one low). IHC confirmed that the MSH2 and MSH6 proteins were missing in one prostate cancer case in which the patient was found to have a *MSH2* mutation.[13] A recent study found 65% of breast cancer tumors from LS patients to lack MMR, indicating that a double hit to MMR genes can potentially lead to breast cancer development.[14]

Prostate cancer is the most common cancer in males in the Western population. Although prostate cancer cells often contain somatic mutations, gene deletions, gene amplifications, chromosomal rearrangements (such as the fusion of the TMPRSS2 (transmembrane protease, serine 2) and the ETS (E26 transformation-specific) transcription factor genes),[15] and hypermethylation of GSTP1 (glutathione S-transferase pi gene) at the time of diagnosis, no gatekeeper mutations that are consistently associated with prostate cancer have been found.[16] Finding an increased incidence of prostate cancer in LS could potentially alter screening guidelines in these patients to allow for earlier detection. Currently, prostate cancer screening

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guidelines for LS patients are the same as those for the general population. The American Cancer Society recommends involving men in the decision-making process and if they decide to be screened, then to start prostate-specific antigen testing with or without digital rectal examination at 50 years of age.[17]

The objective of this cohort study was to assess whether the incidence of prostate cancer is increased above that of the general population in patients with LS by looking at all male patients diagnosed with LS at the Ohio State University (OSU).

MATERIALS AND METHODS

Study sample

All male patients diagnosed with a mutation in one of the MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) from June 1998 until June 2012 at the OSU were included in this study. This cohort consisted of patients previously included in the Ohio Lynch Syndrome study,[18,19] patients included in the PMS2 study,[20] and patients referred to the genetics clinic for counseling.

The Ohio Lynch Syndrome Project was a prospective cohort study that included 1,566 consecutive colon cancer patients diagnosed in any of the major metropolitan hospitals in Columbus, Ohio. Its purpose was to investigate the incidence of LS.[18] The PMS2 study investigated 99 patients whose tumors lacked PMS2 protein expression on IHC (55 from the OSU, the remaining 44 through research collaborations in Newfoundland, Sweden, the National Cancer Institute–funded Colon Cancer Family Registry, and others), wherein the purpose was to investigate mutations in *PMS2* with a new method using long-range polymerase chain reaction.[20,21]

Data collection

Baseline information on demographics and personal and family history of cancer, including histology reports, were obtained at enrollment in the study or at first visit to the genetics clinic. Patients who had not been seen at the genetics clinic in the 12 months before June 2012 were contacted, and changes to their cancer history were documented.

Follow-up time was defined as the time between detection of the first index cancer, entry into the LS studies, or the first visit to the genetics clinic (whichever came first) until the last date of follow-up or date of death.

Mutation testing, immunohistochemistry, and microsatellite testing

The methods used for germ-line mutation analysis have been previously described in detail.[18] DNA was obtained from blood or normal colon tissue and was directly sequenced with the use of primers. The sequencing of the *MLH1*, *MSH2*, and *MSH6* genes covered the promoter regions (*MLH1* and *MSH2* only), exons, and the intronic regions adjacent to all splice sites. For *PMS2*, conversion to haploidy (GMP Genetics, Waltham, MA) and western blot analysis were used in addition to sequencing.[18] Multiplex ligation-dependent probe amplification assay of *MLH1*, *MSH2*, *MSH6*, or *PMS2* was used if needed (if gene sequencing did not identify a mutation).

Where tumor tissue was available, we stained for MLH1 (Novacastra, Newcastle, UK), MSH2 (Calbiochem, Darmstadt, Germany), MSH6 (Epitomics, Burlingame, CA), and PMS2 (BD Pharmingen, San Jose, CA) proteins with IHC. Microsatellite testing was performed using five mononucleotide markers (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) testing both tumor tissue and unaffected tissue with the Promega fluorescent multiplex polymerase chain reaction kit (Promega, Madison, WI). Results were considered positive when an allelic shift was present in the tumor compared with the unaffected tissue by two or more markers tested.

Statistical analysis

Descriptive statistics (mean, SD, median, range for continuous variables, and frequency for categorical variables) were provided to describe the patient population. SAS for Windows version 9.2 was used (SAS Institute, Cary, NC).

The incidence of prostate cancer was adjusted for age (in cohorts of 5 years) and race and compared with that of the Surveillance, Epidemiology, and End Results registry for 1999–2009.[22] A standardized rate ratio was obtained by

Table 1 Patient characteristics and mutation analysis

	All patients, *n* = 188 (%)	Prostate cancer Dx, *n* = 11 (%)
Median age (years)[a]	46 (Q1;Q4 = 33;56)	61 (Q1;Q4 = 59;71)
Race		
Caucasian	176 (95.1%)	11 (100%)
African American	7 (3.8%)	0
Asian	2 (1.1%)	0
Hispanic	0	0
MMR gene mutation		
MLH1	51 (27.1%)	1 (9.1%)
MSH2	87 (46.3%)	7 (63.6%)
MSH6	24 (12.8%)	2 (18.2%)
PMS2	26 (13.8%)	1 (9.1%)
MMR mutation type		
Del/ins	47 (25%)	2 (18.1%)
Large genomic del/dup	40 (21.3%)	4 (36.5%)
Missense	25 (13.3%)	0
Nonsense	25 (13.3%)	2 (18.1%)
At splice site	51 (27.1%)	3 (27.3%)
Location of index cancer		
Colonic	77 (41%)	5 (45.5%)
Extracolonic	26 (13.8%)	6 (54.5%)
No cancer diagnosed	85 (45.2%)	N/A
Mean follow-up time ± SD (years)	6.2 ± 7.2	6.4 ± 4.8

Dx, diagnosed; MMR, mismatch repair; *n*, number; N/A, not applicable; Q, quartile; SD, standard deviation.

[a]At MMR mutation diagnosis.

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comparing the observed rate with the expected rate by the direct method of standardization. Fisher's exact test was used to compare the incidence of MMR gene mutations in patients with prostate cancer versus that in subjects without prostate cancer. Pathology reports for the prostate cancer diagnosis were obtained when possible.

RESULTS

Patient and mutation characteristics

One hundred and eighty eight males (median age: 46 years, Q1;Q4: 33;56, range: 11–83) were identified as MMR mutation carriers either by testing (95%) or as obligate carriers (5%) in 90 families. Their mean follow-up time was 6.2 years (SD: ±7.2 years), with a total of 1,156 person-years. Table 1 includes further details on patient characteristics, gene mutation, and index cancers.

Table 2 Characteristics of patients with prostate cancer

Patient no.	Age at diagnosis (years)	Stage at diagnosis	Gene	Mutation
1	64	Localized	*MLH1*	Del exon 19
2	68	Not available	*MSH2*	c.942 + 3A>T
3	56	Metastatic	*MSH2*	c.942 + 3A>T
4[a]	65	Locally advanced	*MSH2*	Del exons 1–6
5	55	Localized	*MSH2*	c.942 + 3A>T
6[a]	57	Localized	*MSH2*	Del exon 8
7	55	Not available	*MSH2*	c.2038C>T
8	71	Localized	*MSH2*	c.1906G>C
9	82	Localized	*MSH6*	c.3155_3156delAG
10	74	Not available	*MSH6*	c.3261dupC
11	63	Not available	*PMS2*	Del exons 11–12

[a]Had available prostate cancer tissue for immunohistochemistry and microsatellite instability testing.

Prostate cancer incidence

Eleven patients (5.9%) were diagnosed with prostate cancer during the study period (Tables 1 and 2). In two cases, prostate cancer was the index cancer; in two other cases, it was found at the same time as another cancer; and in seven cases, the diagnosis of prostate cancer was preceded by that of other cancers. One patient was identified as an *MLH1* carrier, seven as *MSH2* carriers, two as *MSH6* carriers, and one as a *PMS2* carrier. There was no significant difference between the incidence of gene mutations in patients with prostate cancer versus that in subjects without prostate cancer (*MLH1*: 9.1% in patients with prostate cancer versus 28.3% in subjects without prostate cancer, $P = 0.29$; *MSH2*: 63.6 vs. 45.2%, $P = 0.35$; *MSH6*: 18.2 vs. 12.4%, $P = 0.64$; *PMS2*: 9.1 vs. 14.1%, $P = 1.0$). The observed rate of 11 cases was compared with that of the expected 2.26 cases, and the standardized rate ratio was calculated at 4.87 (95% confidence interval (CI): 2.43–8.71).

Five patients (72%) were diagnosed with localized disease, one (14%) with locally advanced disease, and one (14%) with metastatic disease (Table 2). In four cases, the stage at diagnosis was unknown. The median age at diagnosis was 64 years. All of the prostate cancer patients had known pathogenic MMR mutations, with no cases of missense mutations. Seven out of 11 patients had not received radiation therapy to the pelvis before their prostate cancer diagnosis; in the other 4 cases, we did not have information on previous treatment.

Immunohistochemistry and microsatellite testing

Two tumors were available for IHC and MSI testing. Patient 4 (Table 2) was found to have MSH2/MSH6 missing on IHC, in addition to MSI in the prostate tumor. Patient 6 was found to have all MMR proteins intact on IHC, and the tumor was microsatellite stable.

Other cancers

One hundred and three patients were diagnosed with other cancers: 73 (38.9%) had 1 primary tumor during the study

Table 3 Previous studies looking at prostate cancer incidence in Lynch syndrome

Reference	Place	*N* (PrCa)	SIR/SRR	95% CI	Median age at Dx	Gene involved
Aarnio et al.[2][a]	Finland	360 (4)	SIR 2.9	0.8–7.4	NR	NR
Scott et al.[10]	Wales	95 families (1)	SIR 1.02	0.1–13.6	NR	*MLH1* (0), *MSH2* (1)
Goecke et al.[24]	Germany	259 (8)	NR	NR	59	*MLH1* (0), *MSH2* (8)
Grindedal et al.[6]	Norway	106 (9)	SIR 5.9	4.1–17.1	60.4	*MLH1* (0), *MSH2* (6), *MSH6* (2), *PMS2* (1)
Win et al.[5][b]	Australia, Canada, United States	382 (19)	SIR 2.05	1.23–3.01	64	*MLH1* (3), *MSH2* (15), *MSH6* (1), *PMS2* (0)
Pande et al.[9]	MD Anderson	151 (3)	SIR 0.93	0.19–2.7	65	NR
Engel et al.[8]	Germany, The Netherlands	1,107 (17)	SIR 2.5	1.4–4.0	59	NR
Raymond et al.[7]	University of Michigan	412 (15)	HR 1.99	1.31–3.03	65	NR
This study	The Ohio State University	188 (11)	SRR 4.87	2.43–8.71	64	*MLH1* (1), *MSH2* (7), *MSH6* (2), *PMS2* (1)

CI, confidence interval; Dx, diagnosis; HR, hazard ratio; *N*, number; NR, not reported; PrCa, prostate cancer; SIR, standardized incidence ratio; SRR, standardized rate ratio.
[a]Studied *MLH1* (47 families) and *MSH2* (3 families). [b]Studied patients who had a previous history of colorectal cancer.

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period, 22 (11.7%) had 2 primary tumors, 7 (3.7%) had 3 primary tumors, and 1 (0.5%) had 4 primary tumors. The origin of the index cancer was colorectal in 77 (41.0%), dermal in 8 (4.3%), ureteral in 5 (2.7%), upper gastrointestinal in 3 (1.6%), prostatic in 2 (1.1%), and of the brain and other cancers in, respectively, 2 (1.1%) and 6 (3.2%) patients.

DISCUSSION

Prostate cancer incidence was significantly increased—almost fivefold—in this relatively large cohort of LS patients. This is in concordance with the results of most other studies (**Table 3**) that have demonstrated an increased risk, with standardized incidence ratios (SIRs) ranging from 2.0 to 5.9.

The median age of diagnosis for prostate cancer in the Surveillance, Epidemiology, and End Results registry for the period 2005–2009 was 67 years, with 80% having localized disease at diagnosis.[23] Our cohort shows consistent results, with a median age of 64 years and 71% with localized disease at diagnosis, and therefore it does not appear that prostate cancer is being diagnosed at a younger age or at a more advanced stage in LS patients compared with the general population. The incidence was adjusted for both age and race to eliminate the confounding effect of the young age of our cohort on prostate cancer incidence.

Mutations in *MSH2* appear to be more common in patients who are diagnosed with prostate cancer, and although not statistically significant in our study, most mutations in patients with prostate cancer occurred in *MSH2* (63.6%). Win et al.[5] showed an increased incidence of prostate cancer in patients with previous colon cancer diagnosis (SIR: 2.11; 95% CI: 1.22–3.14) but not in those with previous rectal cancer (SIR: 0.88; 95% CI: 0–3.36). When grouped by gene mutation, only *MSH2* mutations were found to increase the risk of prostate cancer (SIR: 3.62, 95% CI: 2.07–5.36).[5] Aarnio et al.[2] looked at Finnish families, in which the most common mutation occurs in the *MLH1* gene. In fact, 47 of the 50 families included in this study had a mutation in the *MLH1* gene, which could potentially explain why prostate cancer was not increased in this cohort. Goecke et al.[24] found 8 cases of prostate cancer in 333 males carrying the *MSH2* mutation in a population-based study performed in Germany. SIR was not reported, but they noted that there was a marginal association between *MSH2* mutations and prostate cancer and determined that the median age of diagnosis in their cohort was 59 years. Similarly, an increased risk in only *MSH2* mutation carriers was seen in a cohort study conducted in the United Kingdom.[25] It is therefore important to be mindful of the ratio of mutations in the four MMR genes when comparing incidence of cancers across LS studies because they may vary in different populations.

Urothelial carcinoma was found in three patients who were also diagnosed with prostate cancer in our study; this could potentially be due to the association with *MSH2* mutations, which are also known to increase the incidence of urothelial carcinoma, or due to heightened awareness of genitourinary malignancies in patients with a previous diagnosis of a genitourinary cancer.

A study on pooled cohorts from the national LS registries in Germany and the Netherlands revealed an increased incidence, with SIR = 2.5 (95% CI: 1.4–4.0), wherein patients with *MSH2* mutations had an increased risk of developing urothelial and prostate cancer. Median age at diagnosis was 59 years (range: 50–74). The cumulative risk at age 70 was 9.1% (95% CI: 4.4–13.8).[8]

The two patients who provided prostate tumor tissue for testing had mixed results, with the prostate tumor from patient 4 (deletion of exons 1–6 in *MSH2*) exhibiting both loss of protein expression and MSI, whereas the prostate tumor from patient 6 (deletion of exon 8 in *MSH2*) had intact protein expression and microsatellite stability. We conclude that although impaired MMR function may contribute to prostate cancer development in some cases, it is unlikely to do so in all cases.

Although several studies have looked at MMR protein expression by IHC in prostate cancer, no study has looked at the number of accumulated mutations in combination with MMR system inactivation. If MMR protein inactivation (by germ-line mutations) is responsible for prostate cancer development, one might hypothesize that this would happen by the same mechanism, by accumulation of multiple mutations from uncorrected DNA repair errors, leading to a hypermutated phenotype such as the one seen in CRCs related to LS.

The strengths of our study include the fact that all patients had confirmed mutational diagnosis, except for 5% who were diagnosed as obligate carriers with subsequent-generation family members being diagnosed with LS by mutation analysis. Moreover, the study includes consecutive CRC patients enrolled in the Ohio Lynch Syndrome Project; therefore, the cohort has a representation of unselected patients who did not seek care at a genetics clinic, somewhat limiting selection bias. Limitations in our study include patients lost to follow-up (who had to be censored prematurely) and the relatively young age of the cohort.

Our study strengthens current growing evidence that the incidence of prostate cancer is increased in males with LS. We believe that heightened surveillance should be considered in these cases, especially in patients carrying a mutation in *MSH2*. The American Cancer Society currently recommends beginning discussions of screening at age 40–45 in patients at high risk (e.g., African-American men and men with a first-degree relative with prostate cancer <65 years of age),[17] but because prostate cancer does not seem to develop earlier in patients with LS and it is not more aggressive, it is unclear whether these high-risk guidelines are applicable to this group. The IMPACT study, a multicenter observational study initiated in the United Kingdom, is currently investigating the impact of prostate cancer screening on 40- to 69-year-old men with mutations in the breast cancer genes *BRCA1/2* and LS mutations. Patients are offered annual prostate-specific antigen checks, and the threshold for prostatic biopsy is a prostate-specific antigen level >3.0 ng/ml.[26] This study may answer current questions about the benefit of surveillance in these patients.

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