Germ-Line Mutations in Mismatch Repair Genes Associated with Prostate Cancer

Eli Marie Grindedal,1 Pål Møller,1 Ros Elees,4 Astrid Tenden Stormorken,1 Inger Marie Bowitz-Lothe,2 Stefan Magnus Landro,1 Neal Clark,1 Rune Kvåle,3 Susan Shanley,4 and Lovise Maehle1

1Section for Inherited Cancer, Department of Medical Genetics, Rikshospitalet University Hospital; 2Department of Pathology, Ullevål University Hospital, The Cancer Registry of Norway, Oslo, Norway and Translational Cancer Genetics Team, Institute of Cancer Research and Cancer Genetics Unit, The Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom

Abstract

Genetic predisposition to prostate cancer includes multiple common variants with a low penetrance (single nucleotide polymorphisms) and rare variants with higher penetrance. The mismatch repair (MMR) genes MLH1, MSH2, MSH6, and PMS2 are associated with Lynch syndrome where colon and endometrial cancers are the predominant phenotypes. The purpose of our study was to investigate whether germ-line mutations in these genes may be associated with prostate cancer. One hundred and six male carriers or obligate carriers in these genes may be associated with prostate cancer. One hundred and six male carriers or obligate carriers of MMR mutations were identified. Nine had contracted prostate cancer. Immunohistochemical analysis was done on tumor tissue from eight of the nine tumors. Absence of gene product from the mutated MMR gene was found in seven of eight tumors. Expected number of prostate cancers was 1.52 compared with 9 observed (P < 0.01). Mean age of onset of prostate cancer was 60.4 years compared with 66.6 expected (P = 0.006); the number of men with a Gleason score between 8 and 10 was significantly higher than expected (P < 0.00001). Kaplan-Meier analysis suggested that cumulative risk by 70 years in MMR mutation carriers may be 30% (SE, 0.088) compared with 8.0% in the general population. This is similar to the high risk associated with BRCA2 mutations. To our knowledge, this study is the first to indicate that the MMR genes may be among the rare genetic variants that confer a high risk of prostate cancer when mutated. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2460–7)

Introduction

The purpose of this study was to investigate if germ-line mutations in the mismatch repair (MMR) genes may be associated with prostate cancer and, thus, if prostate cancer may be a part of Lynch syndrome. This question has been addressed through immunohistochemical analysis of prostate cancer tumor tissue from known carriers of MMR mutations and by assessing the incidence, age of onset, grade (Gleason score), and lifetime risk in this group compared with the general population.

Several studies have shown that prostate cancer may show familial aggregation (1). Risk of prostate cancer increases with increasing number of affected close relatives (2) and with early onset in the affected relatives (3), indicating that a genetic component is involved. It has been proposed that this genetic component is composed of both rare high-risk alleles and more common alleles with moderate lifetime risk (4, 5). Linkage analyses have mapped loci for prostate cancer susceptibility to several chromosomes, and putative candidate genes have also been suggested, but their significance remains unknown (6). The International Consortium for Prostate Cancer Genetics recently reported strong evidence for a prostate cancer gene at chromosome 22q12.3 by linkage, but no coding mutations were found (7). It has also been described that rare mutations in BRCA2, BRIP1, CHEK2, and NBS1 may confer an increased risk of prostate cancer, but mutations in these genes explain only a small part of hereditary prostate cancer (8-11).

The methods that have thus far been used to identify alleles causing familial aggregation of prostate cancer would make it hard to discover prostate cancer as part of a multicancer syndrome. However, studying prostate cancer as part of a multicancer syndrome has led to the observation that the BRCA2 gene involved in hereditary breast and ovarian cancer also confers an increased risk of prostate cancer when mutated (8, 12, 13). It has been reported that 2% of men diagnosed with prostate cancer at 55 years or younger carry a mutation in BRCA2 (8).

We have systematically recorded information about families with clustering of different types of cancers in our database for >20 years. This has enabled us to study large multicancer families that span several generations, without limiting our focus to only one type of cancer or one cancer syndrome. In 2003, we reported lack of gene product from the MMR gene MSH2 in tumor tissue from prostate cancer in a carrier of a deleterious MSH2 mutation (14). Soravia et al. (15) reported the same result from...
Materials and Methods

Patients. The patients included in the study belonged to families referred to the Section for Hereditary Cancer at The Rikshospitalet University Hospital in Oslo. All diagnoses in families referred to our clinic were confirmed from the Cancer Registry of Norway or by medical files. On confirmation of diagnoses, the families were classified according to clinical criteria for hereditary cancer syndromes. We searched our family database for all families with a germ-line mutation in one of the MMR genes—MLH1, MSH2, MSH6, or PMS2—and included all men from these families who were found on testing to be carriers or who were or had been obligate carriers of the family's mutation regardless of having had cancer or not. Obligate carriers were defined as being in between relatives that had tested positive for the mutation and/or had shown loss of the relevant gene product by immunohistochemistry of a tumor associated with HNPCC/Lynch syndrome if mutation testing had not been possible. The patients included this way were men who themselves had approached us, or been referred to us, or their male relatives who were not themselves in contact with us, but who were obligate carriers, or deceased relatives who were obligate carriers. One hundred and six men from 34 families were found to be carriers or obligate carriers of a MMR mutation. All diagnoses in the families had been confirmed when the family first was referred to our clinic as described above and continuously as we were informed of new cases of cancer occurring in the family. Nine of the 106 men had contracted prostate cancer. The diagnoses had been made between 1976 and 2004. Immunohistochemical analysis was done on tumor tissue from these cancers. Follow-up years were counted from date of birth until date of prostate cancer diagnosis, date when they were last known not to have contracted prostate cancer, or date of death. The men were followed from birth until a mean age of 50.0 y (range, 20.3-85.0 y). To see whether there were more prostate cancers than expected among all men in the 34 families, we counted number of prostate cancers among the brothers of the 106 men. These men either had tested negative for the family's mutation or had not been tested. Population data on incidence of prostate cancer for specific age groups and time periods were obtained from the Cancer Registry of Norway. When the current study was done, the registry has data up until December 31, 2006. This date was therefore used as date for last follow-up for the men followed longer. Data on Gleason score according to age of diagnosis were obtained from the Norwegian Prostate Cancer Registry, which was established as a subregistry of the Cancer Registry of Norway in 2004.

Immunohistochemistry. Immunohistochemical analysis of the prostate cancer tumors for the presence of MLH1, MSH2, MSH6, and PMS2 gene products was done in one laboratory (Department of Pathology, Ullevål University Hospital). We have previously published results using this method to identify carriers of MMR mutations, where the method is described in detail (19). The percentage of normal staining was in this study graded as follows: complete absence of detectable nuclear staining (0), positive staining in <30% of the tumor cells (1+), positive staining in 30% to 60% of the tumor cells (2+), or positive staining in >60% of the tumor cells (3+). Nuclear staining of normal tissue in the slide was compared with staining of normal tissue in the same slide. Normal staining of normal tissue in the slide was obligatory to score the uptake of stain in tumor tissue in the same slide. The pathologists doing the analysis were blinded for the mutation in the family, and the slides were double read by two pathologists. One pathologist reviewed the histology of all the prostate cancer cases and reported the Gleason score. Unfortunately, we were not able to obtain the paraffin block from the prostate cancer of patient 9.

Statistics. To be able to compare the observed incidence of prostate cancer with what we would expect in a similar group of men without known hereditary predisposition to prostate cancer, we used population data on incidence of prostate cancer according to birth cohort, age, and observation year (1982, 1983, etc.) from the Cancer Registry of Norway. By using these data, we were able to account for the increase in prostate cancer in the general Norwegian population that has been observed since the Cancer Registry started its recordings. We calculated expected incidence for each lived year under observation (incidence when 36 y old in 1982, 37 y old in 1983, etc.) for each of the 106 male carriers or obligate carriers of a MMR mutation. The expected incidence was then summarized for each man and then for all men. Ninety-five percent confidence intervals were calculated based on assumed Poisson distributions.

Observed cases of prostate cancer among the 106 known mutation carriers were compared with observed cases among their 68 brothers using Fisher's exact P.
Expected mean age of onset was derived from the same population data on expected incidence according to birth cohort, age, and observation year (1982, 1983, etc.). We calculated the expected number of cancers to occur at all ages (from 0 to 85) for all the 106 men. For each 1-y age stratum, we summarized the number of expected cancers. We then derived the mean age of onset with the following formula:

\[ \text{Mean age} = \frac{\sum_{i=1}^{85} n_i \cdot \text{age}_i}{\sum_{i=1}^{85} n_i} \]

where “i” designates the 1-y age stratum ranging from 1 to 85, “n” is the number of expected cancers in each stratum, and “age” is the age in years for each stratum. Observed and expected mean age of onset was compared using a one-sample \( t \) test.

Data on Gleason score for prostate cancers diagnosed in men <70 y of age in the general Norwegian population were obtained from the Cancer Registry of Norway. We compared population data on number of cancers diagnosed with Gleason score <8 and between 8 and 10 with the observed number in the study group using Fisher’s exact \( P \).

The Kaplan-Meier algorithm was used to calculate the cumulative risk of prostate cancer by age in the study group. Males who were carriers or obligate carriers were scored as affected at time of diagnosis or censored as unaffected at last observation or at death if dead for another reason. Data from the Cancer Registry of Norway were used to calculate the cumulative risk of prostate cancer in the Norwegian population in 2006 and in the period between 1997 and 2001.

Data were kept in our medical files, which are on Oracle10g database, manipulated by Delphi2007 and TOAD, and statistical calculations were done by Systat10 and StatXact5 as appropriate. Pedigrees were constructed by use of Cyrillic2.1. No named data were exported from the medical files, and no research registry including patient names was erected.

**Ethics.** All activities were part of the public health care system. All diagnoses were verified with written permission from living patients or with permission from descendants of dead patients. Informed consent for mutation analyses of blood and tumor tissue was obtained in writing. If the patient was dead, descendants gave their consent to genetic testing.

**Results**

One hundred and six men from 34 families were found to be carriers or obligate carriers of a MMR mutation. Sixty-eight had a mutation in \( MSH2 \), 19 had a mutation in \( MLH1 \), 13 had a mutation in \( MSH6 \), and 6 had a mutation in \( PMS2 \). Nine men from eight families had been diagnosed with prostate cancer. Four of the families are illustrated in Figs. 1–4. Six of the nine men had a mutation in \( MSH2 \), two in \( MSH6 \), and one in \( PMS2 \) (Table 1). No cases of prostate cancer were found among carriers of \( MLH1 \) mutations. The diagnoses had been made between 1976 and 2004. The 106 men were followed from birth until a mean age of 50.0 years (range, 20.3-85.0 years).

The 106 male mutation carriers had altogether 68 brothers. No cases of prostate cancer were reported among them \( (P = 0.01) \). Twenty-nine of these had tested negative for the family’s mutation, and 39 had not been tested.

The frequency with which prostate cancer occurred in mutation carriers was 9 of 106 (8.5%) in the whole group, 6 of 68 (8.8%) for \( MSH2 \), 2 of 13 (15.3%) for \( MSH6 \), 1 of 6 (16.7%) for \( PMS2 \), and 0 for \( MLH1 \). The expected number of prostate cancers to occur by chance in the 106 men was 1.52 compared with 9 observed (95% confidence interval, 4.1-17.1; \( P < 0.01 \)). This gives a standardized incidence ratio of 5.9.
Kaplan-Meier analysis showed that cumulative risk of prostate cancer by 60 years of age was 9.8% (SE, 0.047) among the MMR mutation carriers. At 70 years, it was 29% (SE, 0.088) compared with 8% in the general Norwegian population for 2006 (Fig. 5). Mean age of onset of prostate cancer among MMR mutation carriers was 60.4 years (range, 53-68) compared with 66.6 expected ($P = 0.006$).

Gleason score was done on eight of the tumors. Five (62.5%) were found to have a score from 8 to 10 compared with 17% in men diagnosed before 70 years of age in the general population ($P < 0.00001$). Two of the eight cases were scored based on biopsies, one on a bone metastasis, and the rest on prostatectomy specimens. Three of the five tumors with Gleason score between 8 and 10 were scored based on prostatectomies, one on biopsy, and one on bone metastasis.

Immunohistochemical analysis was done on eight of the nine prostate tumors. In seven of the tumors, complete absence of gene product from the gene mutated in the patient was found (Table 1). In tumor tissue from four of the six carriers of an $MSH2$ mutation, absence of gene product from $MSH6$ was also seen. In patient 8, who had an $MSH6$ mutation, no staining of gene product from this gene was found in either tumor or normal tissue. This was registered as an inconclusive result.

**Discussion**

The results in this study indicate that the germ-line MMR mutations may cause prostate cancer and that prostate cancer therefore might be considered as a part of Lynch syndrome.

Watson and Riley (21) has suggested two ways to consider whether a specific type of cancer is associated with Lynch syndrome. The first is to assess if the cancer arises as a direct result of the mutation the patient carries. We observed lack of MMR gene product of the relevant gene in tumor tissue from prostate cancer in men with germline MMR mutations. According to previous studies, this would not be the expected result in a similar group of sporadic prostate tumors (22-24). The second premise suggested by Watson and Riley requires that there is a definite increased risk of the cancer type in patients with Lynch syndrome compared with the general population. We found a significantly higher incidence of prostate cancer in MMR mutation carriers compared with the general population (9 observed compared with 1.52 expected).

In addition to this, we observed a lower age of onset, a higher Gleason score, and a higher cumulative risk at 70 years in MMR mutation carriers than expected in the general Norwegian population. Whereas we observed no cases of prostate cancer diagnosed after 70 years of age, lifetime risk in the general population increases strongly after this age. In 2006, risk increased to 18% at 80 years and 23% at 85 years. All the findings mentioned above indicate that prostate cancer may have been caused by the germ-line MMR mutations in the patient.

The number of observations in our study was, however, limited and the retrospective data set may have ascertainment bias. Families with additional cancers to those belonging to the syndrome were more likely to be ascertained. Prostate cancer may have been one of the reasons for the referral of the family, and this may have

**Figure 2.** Individuals affected with cancer included in the Lynch syndrome are colored. Individuals that have tested positive and negative for the MMR mutation in the family are marked with “+” and “−,” respectively. The pedigrees have been altered (without altering the message of the article) to maintain confidentiality.
contributed to an overestimation of risk in the mutation carriers. Scott et al. (25) found no evidence of increased risk of prostate cancer in 22 MLH1 and 12 MSH2 mutation-positive families but reported an increased risk in families fulfilling the Amsterdam criteria who had screened negative for mutations in these two genes. These results may fit with our observations as we report no cases of prostate cancer in MLH1 mutation carriers, and prostate cancer is observed with the highest frequency among carriers of MSH6 and PMS2 mutations, for which the families in Scott et al.'s report were not screened. Goecke et al. (26) found that among carriers of MSH2 mutations, prostate cancer was the most common cancer type that did not belong to the established Lynch spectrum and recommended that this should be taken into consideration clinically. Similar to our observations, they found no cases of prostate cancer among carriers of MLH1 mutations. Differences in cancer expression between the MMR genes have been noted in several studies (27, 28).

We have not in any way advised men in Lynch syndrome families to be tested for prostate-specific antigen (PSA). Three of the prostate cancer cases were diagnosed between 2002 and 2004. They were diagnosed as a result of regular PSA testing, and the men were asymptomatic at time of diagnosis. We do not know if these men would have been diagnosed had they not attended screening, and the fact that they were diagnosed through screening when asymptomatic may have contributed to an overestimation of risk in MMR mutation carriers. The remaining six cases were diagnosed between 1976 and 1993. We cannot exclude that these men had an elevated concern of cancer based on their family history and may have sought health care earlier than men without a family history of cancer would have. However, all these tumors were aggressive (Gleason score of $\geq 8$) and were thus clinically significant. Although they may have sought health care at an early stage, this has most likely not caused an overdiagnosis of cancers. The incidence of prostate cancer in Norway increased with 3.9% per year between 1988 and 1999 mainly because of PSA testing (29). In 1999, it was recommended that PSA testing should not be done routinely on asymptomatic men in Norway (30). Despite this, its use has become more common since then, and this has contributed to the observed increase in cumulative risk at 85 years from 19.6% in the period of 1997 to 2001 to 23% in 2006. When we calculated expected numbers of cancers to occur by chance, we used data from the Cancer Registry of Norway on incidence at a specific age in a specific year, and the increase in use of PSA testing in the general population was therefore accounted for. This may have reduced the possible overestimation of risk of prostate cancer in MMR mutation carriers caused by the fact that three of the cases were diagnosed by PSA testing in asymptomatic men. Moreover, reducing the nine cancers to six would still be within the 95% confidence interval, and the difference between observed and expected incidence would nevertheless be significant. Interestingly, the men diagnosed through PSA testing had tumors with

![Figure 3](image1.png)

Figure 3. Individuals affected with cancer included in the Lynch syndrome are colored. Individuals that have tested positive and negative for the MMR mutation in the family are marked with "+" and "−" respectively. The pedigrees have been altered (without altering the message of the article) to maintain confidentiality.

![Figure 4](image2.png)

Figure 4. Individuals affected with cancer included in the Lynch syndrome are colored. Individuals that have tested positive and negative for the MMR mutation in the family are marked with "+" and "−" respectively. The pedigrees have been altered (without altering the message of the article) to maintain confidentiality.
lower Gleason score than the remaining six. If our results were to be true, and there is an elevated risk of prostate cancer in MMR mutation-positive men, this could indicate that prostate cancer in these men could be diagnosed at an early stage through screening. However, it might as well be that the PSA-detected are more likely to be less aggressive.

Gleason score in the study group was higher than that expected. It has been reported that ~40% of prostate biopsies are undergraded compared with prostatectomy specimens in terms of Gleason score (31). About 75% of the Gleason scores reported in the population were based on biopsies. Gleason score in the MMR mutation carriers might have been lower if the diagnoses had been based on biopsies. However, three of the five specimens with a Gleason score of ≥8 were based on prostatectomies. Moreover, only 6% of the Gleason scores reported from the performed prostatectomies in Norway during the period 2001 to 2004 were of ≥8 (31). Thus, it is unlikely that a higher Gleason score in the prostatectomy specimen than in the biopsy would have had any major effect on the results.

Standardized incidence ratio of prostate cancer in MMR mutation carriers by 70 years of age was observed to be 5.9. Relative risk of prostate cancer in BRCA2 mutation carriers has been reported to be 4.65 (32) Low age of onset and advanced stage have also been noted as a characteristic of prostate cancer in men with BRCA2 mutations (33, 34). Our observations indicate that prostate cancer in MMR mutation carriers may be similar to BRCA2-associated prostate cancer. However, this needs to be confirmed in other studies.

Patient 8 (Table 1) in Family 7 (Fig. 3) carried a missense mutation in MSH6, c.2906A>G. Suchy et al. (35) has reported that the mutation seems to be pathogenic, but the pathogenicity is not fully clarified. We did immunohistochemistry on tumor tissue from this patient’s colon cancer and found no expression of MSH6 gene product in the colon cancer of the mother and brother with only one cancer. That brother carried the mutation and his colon cancer also showed MSI. This brother has later tested positive for the mutation. In the tumor from the brother with three primary cancers, we found normal MSH6 expression. His blood was not available for mutation testing, and none of his three children had the mutation.

It would be important to determine whether sporadic prostate cancer commonly shows loss of MMR gene product as a result of somatic mutations in the tumor tissue. This would indicate that our observations from

<table>
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<tr>
<th>Patient and family</th>
<th>Gene</th>
<th>Mutation</th>
<th>Age (y)</th>
<th>Gleason score</th>
<th>Carrier status</th>
<th>Immunohistochemical result</th>
</tr>
</thead>
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<tr>
<td>Patient 1 Family 1</td>
<td>MSH2</td>
<td>c.1076+1G&gt;A</td>
<td>59</td>
<td>10 (5+5)</td>
<td>Carrier</td>
<td>Abnormal MSH2 + MSH6</td>
</tr>
<tr>
<td>Patient 2 Family 1</td>
<td>MSH2</td>
<td>c.1076+1G&gt;A</td>
<td>56</td>
<td>9 (4+5)</td>
<td>Obligate carrier</td>
<td>Abnormal MSH2 + MSH6</td>
</tr>
<tr>
<td>Patient 3 Family 2</td>
<td>MSH2</td>
<td>c.2275G&gt;T</td>
<td>66</td>
<td>10 (5+5)</td>
<td>Carrier</td>
<td>Abnormal MSH2 (inconclusive MSH6)</td>
</tr>
<tr>
<td>Patient 4 Family 2</td>
<td>MSH2</td>
<td>c.1857T&gt;G</td>
<td>56</td>
<td>10 (5+5)</td>
<td>Obligate carrier</td>
<td>Abnormal MSH2 (inconclusive MSH6)</td>
</tr>
<tr>
<td>Patient 5 Family 3</td>
<td>MSH2</td>
<td>c.2038C&gt;T</td>
<td>64</td>
<td>7 (3+4)</td>
<td>Carrier</td>
<td>Abnormal MSH2 + MSH6</td>
</tr>
<tr>
<td>Patient 6 Family 4</td>
<td>MSH2</td>
<td>c.1786_1788delAAT</td>
<td>68</td>
<td>8 (4+4)</td>
<td>Carrier</td>
<td>Abnormal MSH2 + MSH6</td>
</tr>
<tr>
<td>Patient 7 Family 5</td>
<td>MSH6</td>
<td>c.2731C&gt;T</td>
<td>53</td>
<td>6 (3+3)</td>
<td>Carrier</td>
<td>Abnormal MSH6</td>
</tr>
<tr>
<td>Patient 8 Family 6</td>
<td>MSH6</td>
<td>c.2906A&gt;G</td>
<td>62</td>
<td>5 (2+3)</td>
<td>Carrier</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Patient 9 Family 7</td>
<td>PMS2</td>
<td>c.989-1G&gt;T</td>
<td>Not available</td>
<td></td>
<td>Obligate carrier</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Figure 5. Time to prostate cancer visualized as Kaplan-Meier survival functions. Male carriers or obligate carriers included. Each vertical line on the curve marks how long one man has been followed. Each drop in the curve marks one case of prostate cancer.
Prostate Cancer in Male MMR Mutation Carriers

The immunohistochemical analyses at least partly were not a result of the germ-line mutation. Chen et al. (22) studied expression of MLH1, MSH2, PMS2, and PMS1 in prostate cancer cell lines and in tumor tissue from prostate cancer. In both cancer cell lines and tumor tissue, reduction or loss of PMS1 and PMS2 was more common than loss of MLH1 and MSH2 expression. They noted that this is different from what is commonly seen in Lynch syndrome or HNPCC. They found complete loss of MSH2 in one cancer cell line (LNCaP). However, in this cell line, a homozygous deletion of exons 9 to 16 in MSH2 has later been detected (36). Chen et al. (22) also reported loss of MLH1 in one cancer cell line (DU145). A mutation in the splice site between exons 1 and 2 of the MLH1 gene had previously been reported in this cell line (37). These mutations could be germ-line mutations in the individual from whom the cell lines were developed. Velasco et al. (23) did immunohistochemistry on tumor tissue from 73 prostate cancers to look for expression of MSH2. They found that 29% of the samples showed low staining. Complete absence of MSH2 expression was not found in any of the samples. Norris et al. (24) showed increased PMS2 expression in tumor tissue from prostate cancers. In summary, results from studies on MMR gene expression in sporadic prostate cancers are different from what we observed in prostate cancer tumor tissue from known carriers of germ-line MMR mutations. It is therefore likely that lack of expression of the gene product from the gene mutated in the family is, in fact, caused by the germ-line mutation and not by somatic mutations in the tumor tissue.

In four of six patients with a mutation in MSH2, we found complete absence of gene product from both MSH2 and MSH6. This is a result of complex forming between the MSH2 and MSH6 protein and has been reported for other tumors associated with germ-line MMR mutations in several studies (38-40).

Because Lynch syndrome is rare and sporadic prostate cancer is common, the association between prostate cancer and this syndrome on the population level may be difficult to detect. High-frequency MSI (MSI-H) was found in only 3 of 80 prostate tumors from Swedish men from families with hereditary prostate cancer (41). From this, it was concluded that MSI-H tumors are rare in hereditary prostate cancer. Interestingly, two of the men with MSI-H tumors were from families with both hereditary prostate cancer and familial colon cancer. These families had not been tested for mutations in the MMR genes. Germ-line mutation in the MMR genes as a cause of prostate cancer may be a small fraction of hereditary prostate cancer. Screening for MMR mutations in families affected mainly with prostate cancer may therefore give few positive findings. Fredriksson et al. (42) did not find that germ-line MLH1 mutations play a major role in hereditary prostate cancer in Finland. When doing immunohistochemistry on tumor tissue from 11 men with colon and prostate cancers, they found lack of expression of MLH1 in one patient and of MSH2 in another. We did not find any cases of prostate cancer among men with a mutation in MLH1. If mutations in this gene do not lead to increased risk of prostate cancer, the tumors tested in Fredriksson’s study may have been sporadic prostate cancer in colon cancer patients.

We have observed that prostate cancer is significantly more common than expected by chance among MMR mutation carriers (9 observed compared with 1.52 expected). We have previously reported that regular colonoScope surveillance may prevent colon cancer (43). Known mutation carriers therefore have a low risk of dying from this disease but are more likely to contract other cancers belonging to the syndrome. In a retrospective material, the high frequency of colon cancer may be masking the real risk of prostate and other cancers, and lifetime risk of these cancers may change in the future as colon cancer is prevented.

Conclusion

Based on the observations of an association between MMR mutation and lack of expression of the gene product in question in prostate cancer tumor tissue, the significantly higher incidence of prostate cancer among MMR-mutation-positive men, the lower age of onset, and the high Gleason score, we suggest that germ-line mutations in MMR genes are associated with prostate cancer and that prostate cancer is a part of Lynch syndrome or HNPCC. Prostate cancer predisposition is composed of multiple low-risk genetic variants and rarer higher-risk variants. According to our observations, risk of prostate cancer in men with MMR mutations may be as high as 30% by 70 years of age (SE, 0.088). To our knowledge, this study is the first to indicate that the MMR genes should be included in the group of rare genetic variants that may confer a high risk of prostate cancer. The possible risk of prostate cancer should be considered by clinicians caring for men with germ-line MMR mutations. Further investigations and prospective observations are also needed to more accurately assess the risk of prostate cancer among MMR mutation-positive men and possible genotype-phenotype correlations. Prostate cancer surveillance, similar to being investigated for BRCAl/2 mutation carriers in the IMPACT protocol (44), should be considered.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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