

Minireview

Risk of Prostate Cancer in Lynch Syndrome: A Systematic Review and Meta-analysis

Shae Ryan, Mark A. Jenkins, and Aung Ko Win

Abstract

It has been controversial that men carrying a DNA mismatch repair (MMR) gene mutation (Lynch syndrome) are at heightened risk of prostate cancer given that an increased risk is likely to be modest and the prevalence of prostate cancer is high. We used PubMed to search for "molecular studies" that reported MMR-deficiency status of prostate cancer tumors in men with an MMR gene mutation, and "risk studies" that reported prostate cancer risk for men known or suspected to have an MMR gene mutation relative to that for noncarriers or the general population. Of the six molecular studies, 32 of 44 [73%, 95% confidence intervals (CI), 57%–85%] prostate cancer tumors in carriers were MMR deficient, which equates to carriers having a 3.67-fold increased risk of prostate cancer (95% CI, 2.32–6.67). Of the 12 risk studies, we estimated a 2.13-fold increased risk of prostate cancer (95% CI, 1.45–2.80) for male carriers in clinic-based retrospective cohorts, 2.11 (95% CI, 1.27–2.95) for male carriers with a prior diagnosis of colorectal cancer, and 2.28 (95% CI, 1.37–3.19) for all men from mutation-carrying families. The combination of evidence from molecular and risk studies in the current literature supports consideration of prostate cancer as part of Lynch syndrome. *Cancer Epidemiol Biomarkers Prev*; 23(3); 437–49. ©2014 AACR.

Introduction

Lynch syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC), is a disorder characterized by cancer predisposition in families. The risk of disease follows an autosomal dominant pattern of inheritance, and is due to a germline mutation in one of the DNA mismatch repair (MMR) genes: *MLH1* (1, 2), *MSH2* (3), *MSH6* (4, 5), and *PMS2* (6, 7); or constitutional 3' end deletions of *EPCAM* (8, 9). The frequency of pathogenic mutations in MMR genes in the general population has been estimated to be approximately 1:3,100 to 1:370 (10–12).

MMR proteins detect and excise DNA mismatches occurring during cell division. Tumors are more likely to develop from cells lacking any of the four MMR proteins, as a consequence of germline mutation and/or somatic loss of the MMR gene function. Excess of early-onset colorectal cancer and endometrial cancer are the most commonly observed phenotypes in Lynch syndrome, along with increased risks, albeit to a lesser degree, of extracolonic cancers—ovary, stomach, small bowel, ureter, and renal pelvis (13–15).

Some studies have suggested that risk of prostate cancer may be increased for men with Lynch syndrome. The majority of this evidence is from studies of prostate cancers in men known or suspected to be carriers of an MMR gene mutation, in which they have shown absence of MMR protein expression in prostate tumors by immunohistochemical (IHC) analysis, and the presence of a substantial change (contractions or expansions) in the length of short repetitive DNA sequences in tumor compared with normal tissue (microsatellite instability; MSI) in prostate tumors by PCR-based analysis (16–21). However, because the proportion of prostate tumors exhibiting MMR deficiency is inconsistent across studies, and MMR deficiency alone does not constitute proof that the tumor was caused by the germline mutation, MMR germline mutation testing in men diagnosed with prostate cancer is not currently recommended.

Attempts have been made to directly estimate the risk of prostate cancer in Lynch syndrome using studies of cancer history of men from Lynch syndrome families (14, 15, 19, 22–36). These studies have generally been limited in terms of size and analytic methods used, so as a consequence, estimates are imprecise and inconsistent. Because of the inconsistent evidence of prostate cancer being part of Lynch syndrome, screening for prostate cancer is not currently recommended for Lynch syndrome families (37). Without being tailored to people at high risk, prostate cancer screening by detection of prostate-specific antigen (PSA) is considerably inaccurate and represents significant harms for an individual (38). If men with Lynch syndrome are shown to be at increased risk for prostate cancer, they may as an

Authors' Affiliation: Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia

Corresponding Author: Aung Ko Win, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Level 3, 207 Bouverie Street, The University of Melbourne VIC 3010, Parkville, Victoria, Australia. Phone: 61-3-9035-8238; Fax: 61-3-9349-5815; E-mail: awin@unimelb.edu.au

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identifiable group benefit from such screening. Our aim was to synthesize all published molecular and epidemiologic studies to determine the evidence for prostate cancer risk being increased by a germline mutation in an MMR gene.

Materials and Methods

Identification of studies

We used PubMed (39) to search for all relevant studies of prostate cancer associated with Lynch syndrome that were published by May 9, 2013 using the following combinations of key terms: "Lynch syndrome or HNPCC or MMR" and "prostate cancer or extracolonic cancer or cancer risk." No language restrictions were imposed. References from relevant articles, letters, reviews, and editorials were searched to identify any additional relevant studies. Studies were reviewed initially on the basis of title and abstracts, and then all full manuscripts for those that appeared relevant were obtained and checked for eligibility. Studies were categorized as either "molecular studies" that reported MMR-deficiency status of prostate cancer tumors of MMR gene mutation carriers or "risk studies" that investigated risk of prostate cancer for confirmed or suspected MMR gene mutation carriers.

Eligibility criteria

Molecular studies were eligible if they analyzed and reported MMR-deficiency status either by MSI and/or immunohistochemistry of prostate cancer tumors in confirmed MMR gene mutation carriers. Molecular studies that did not conduct germline testing and confirm MMR gene mutation were excluded, as were studies that observed these measured molecules in external cell lines.

Risk studies were eligible if they were case-control studies or retrospective or prospective cohort studies that estimated the risk of prostate cancer for men confirmed or suspected to have an MMR gene mutation relative to that for noncarriers or to the general population. Risk studies were excluded if they did not genetically or clinically or pathologically define the sample, if they did not report prostate cancer diagnoses, or limited investigation of risk to specific allelic variants, or were editorials or literature reviews.

Definitions

For molecular studies, we defined a tumor to be MMR deficient if it had a high level of MSI (>30% of markers tested) or absence of expression of any of the four MMR genes by immunohistochemistry. We defined an MMR gene mutation carrier as confirmed if a pathogenic MMR gene mutation was identified.

For risk studies, subjects were defined as either confirmed MMR gene mutation carriers, or suspected as they were untested and a relative of a confirmed MMR gene mutation carrier, or were a member of a family meeting either the Amsterdam (40, 41) or Bethesda (42) criteria.

Data extraction

For molecular studies, we extracted the following data: year of publication, country in which the study was performed, specific MMR gene(s) mutated, ages at diagnoses of prostate cancer, and the MSI and/or IHC status of the prostate tumors.

For risk studies, we extracted the following data: year of publication, country in which the study was performed, recruitment and ascertainment method of mutation carriers and relatives, mutation status, numbers of confirmed or suspected MMR gene mutation carriers, specific MMR gene(s) mutated, observed and expected numbers of prostate cancers, estimates of prostate cancer risk for mutation carriers compared with noncarriers or the general population [expressed as standardized incidence ratio, standardized morbidity ratio, OR, relative risk (RR), or HR], and absolute or cumulative risk of prostate cancer for mutation carriers (expressed as lifetime risk to a specified age or 10-year risk).

Statistical analysis

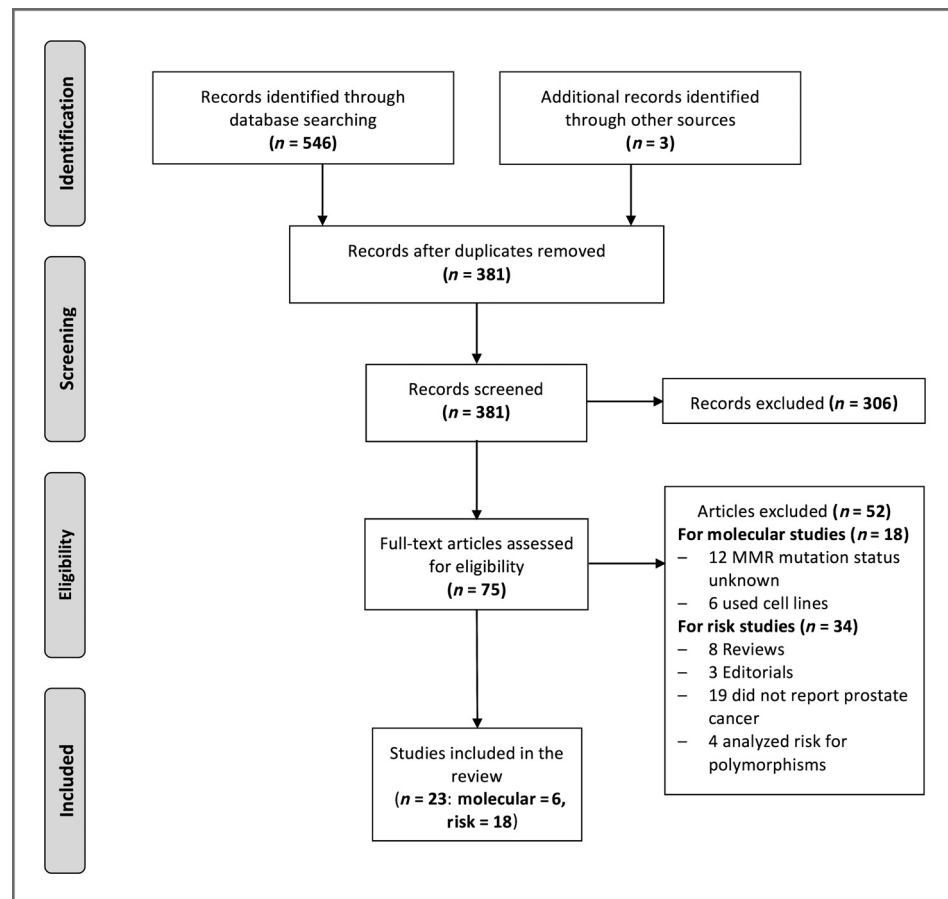
For molecular studies, we divided the total number of MMR-deficient prostate cancers by the total number of prostate cancers in men confirmed to be MMR gene mutation carriers to estimate the proportion of prostate cancers in MMR gene mutation carriers that were MMR deficient. Under the assumption that having a tumor with MMR deficiency meant that the prostate cancer had been caused by the MMR gene mutation, the RR of prostate cancer for men with MMR gene mutations is estimated by $RR = N/(N - n)$, where N is the total number of prostate cancer-affected mutation carriers and n is the number of these for which their tumor exhibited MMR deficiency. The 95% confidence interval (CI) was estimated by assuming that n has a binomial ($N;p$) distribution with $P = n/N$.

For risk studies, we used Stata 12.0 (43) to conduct a meta-analysis generating summary estimates by different study designs (clinic-based retrospective cohorts, population-based retrospective cohorts, retrospective cohorts from both population and clinic sources, prospective cohorts, cohorts of mutation carriers with a prior diagnosis of colorectal cancer, and cohorts of all men who potentially carry a mutation from mutation carrying families). Random and fixed effects models were fitted, and heterogeneity was tested between and within groups using I^2 statistic. A funnel plot was generated to test the evidence of publication bias.

Results

We identified 381 studies through the literature search, and excluded 306 because they were unrelated to prostate cancer in Lynch syndrome (based on the title and abstract). Of the 75 studies that were retrieved for full assessment for eligibility, 18 molecular studies were excluded because 12 studied MMR-deficiency status of prostate cancer in men whose mutation status was unknown, and six studied cell lines; and 34 risk studies were excluded because eight were literature reviews,

Figure 1. Selection of studies for the systematic review.



three were editorials, 19 did not report prostate cancer (they only estimated risk of cancers already known to be associated with Lynch syndrome), and four studied MMR polymorphisms in prostate cancers. A total of 23 studies were included in the systematic review including six molecular studies and 18 risk studies (one contained data suitable for both molecular and risk; Fig. 1).

Of the six molecular studies, two were single case reports (16, 17) and four were case series (18–21) in which prostate cancer tumors of MMR gene mutation carriers were analyzed for MMR deficiency by MSI and/or immunohistochemistry (Table 1). When all case series were combined, 32 of 44 (73%, 95% CI, 57%–85%) prostate cancers in mutation carriers were MMR deficient. Under the assumption that having a tumor with MMR deficiency meant that the prostate cancer had been caused by the MMR gene mutation, the RR of prostate cancer for men with an MMR gene mutation was estimated to be 3.67 (95% CI, 2.32–6.67).

Of the 18 risk studies, six noted the presence of prostate cancers in a Lynch syndrome cohort but did not quantify the risk (Table 2; refs. 25, 26, 28–31). Of the 12 studies that did quantify the risk, six of these reported a statistically significant increase in prostate cancer for Lynch syndrome (19, 27, 32, 33, 35, 36). The remaining six studies found no evidence for an increased risk of prostate cancer (14,

15, 22–24, 34). Three studies estimated prostate cancer risk using retrospective cohort of family members including relatives of confirmed carriers who were not tested themselves for a germline mutation (24, 27, 35). Eight retrospective cohort studies estimated prostate cancer risk only for mutation carriers using population-based resources (22) or clinic-based resources (19, 24, 32, 34–36) or both population- and clinic-based resources (15). Only one study estimated risk using a prospective cohort design; estimating prostate cancer risk for carriers without a prior diagnosis of any cancer (14). Three studies estimated prostate cancer risk for carriers with a prior diagnosis of colorectal cancer (Table 2; refs. 23, 27, 33).

To account for differences in study designs and the populations to which they apply, we conducted a meta-analysis generating summary estimates by study design. There was no evidence of heterogeneity between studies and we therefore present a fixed-effect model (Fig. 2). Retrospective cohorts were also categorized by ascertainment source for analysis. Compared with men from the general population, these studies together showed a 2.13-fold increased risk of prostate cancer (95% CI, 1.45–2.80) for male mutation carriers in clinic-based retrospective cohorts, 2.11 (95% CI, 1.27–2.95) for male mutation carriers with a prior diagnosis of colorectal cancer, and 2.28 (95%

Table 1. Summary of molecular studies that investigated MMR deficiency status of prostate cancer tumors of men with Lynch syndrome

| | No. of MMR-deficient ^a prostate cancer/No. of confirmed MMR gene mutation carriers | No. of MSI-H tumor/No. of tumor tested for MSI | No. of tumor with absence of MMR protein expression in IHC/No. of tumor tested by IHC | MMR gene mutated |
|--------------------------|--|---|--|-------------------------|
| <i>Single case study</i> | | | | |
| Soravia et al. (16) | 1/1 | 1/1 | 1/1 | <i>MSH2</i> |
| Wagner et al. (17) | 1/1 | 1/1 | 1/1 | <i>MSH2</i> |
| TOTAL | 2/2 | | | |
| <i>Case series</i> | | | | |
| Bauer et al. (21) | 2/2 | 2/2 | NT | <i>MSH2</i> |
| Buttin et al. (18) | 1/2 | 0/1 | 1/2 | <i>MSH6</i> |
| Grindedal (19) | 7/8 | NT | 7/8 | <i>MSH2, MSH6</i> |
| Rosty et al. (20) | 22/32 | 5/10 | 22/32 | <i>MLH1, MSH2, MSH6</i> |
| TOTAL | 32/44 | | | |

Abbreviation: NT, not tested.

^aDisplaying high MSI (MSI-H) and/or absence of MMR protein expression in immunohistochemistry.

CI, 1.37–3.19) for all men who potentially carry a mutation from mutation carrying families. There was no evidence of an increased risk of prostate cancer for male mutation carriers in a prospective study [standard incidence ratio (SIR) 2.49; 95% CI, 0.89–5.87; ref. 14] or a retrospective study using a population-based resource (SIR 2.9; 95% CI, 0.8–7.4; 22) or a retrospective study based from both population and clinic resources (RR 0.92; 95% CI, 0.21–1.63). Funnel plot analysis did not reveal any evidence of publication bias of the studies included in the meta-analysis (Fig. 3).

The mean or median age at diagnosis of prostate cancer for men with Lynch syndrome was reported to be approximately 59 to 60 years in the four studies (14, 19, 26, 32), 64 to 65 years in the four studies (31, 33, 34, 36) and 67 to 69 years in the two studies (15, 35), compared with the median age of 69 years for the U.S. general population (44).

Discussion

We have attempted to elucidate whether prostate cancer should be considered a Lynch syndrome cancer. Through systematic review, we identified 23 studies that reported data on prostate cancer in Lynch syndrome. Molecular evidence, though sparse, indicates that the phenotypic expression of MMR gene mutation operates at the cellular level in these tumors, and if we assume the only cause for MMR-deficient prostate cancers is the genetic mutation in these carriers, then this evidence is consistent with men with Lynch syndrome being two to three times more likely to develop prostate cancer. Risk studies showed an overall increase in risk of prostate cancer in men with Lynch syndrome with or without a prior diagnosis of colorectal cancer, concurrently supporting the molecular literature.

Molecular studies

The two single case studies (16, 17), both documented *MSH2* mutation carriers with prostate cancer that displayed high-MSI and absence of *MSH2* and *MSH6* protein expression through IHC analysis. Both cases were male and had prior cancers. Four studies did provide both MSI/IHC phenotype and MMR mutation genotype (18–21). Overall, 73% of prostate cancers observed in MMR gene mutation carriers were MMR deficient, and absence of MMR protein expression was completely concordant with that of the underlying germline mutation in all cases. Furthermore, the largest case series (20) showed that tumors from *MSH2* mutation carriers had a higher proportion of MMR deficiency (83%, 95% CI, 61%–95%) compared with *MLH1* (40%, 95% CI, 5%–85%) and *MSH6* (25%, 95% CI, 1%–81%) mutation carriers ($P = 0.01$). They also observed that MMR-deficient prostate cancer tumors had increased levels of tumor-infiltrating lymphocytes compared with MMR-proficient tumors, which is commonly observed in other Lynch syndrome tumors (45, 46). These studies strongly support an association of prostate cancer with MMR gene mutations, especially *MSH2*. However, they are limited, though in that we are unable through these methods to understand whether MMR gene mutation is causing cancer, modifying its severity, or having its phenotype activated on account of tumorigenesis via another cause.

Risk studies

A strength of this review is that it incorporates epidemiologic risk studies to augment the association showed by molecular studies. We have attempted to quantify risk of prostate cancer associated with MMR gene mutations with consideration of study designs.

Table 2. Summary of risk studies that investigated risk of prostate cancer for men with Lynch syndrome

| Author | Year | Country | Study population | Study design | Results | Comments |
|----------------------|------|--------------|---|-----------------------|---|--------------------------|
| Zhang et al. (25) | 2005 | China | 53 families fulfilling the Amsterdam-I (40) and four families fulfilling the Amsterdam-II criteria (41). Ascertained families fulfilling the Amsterdam-I or II criteria from 51 regions of China. | Cross-sectional. | O = 2 E = not reported Age at diagnosis = not reported | Unable to calculate SIR. |
| Goecke et al. (26) | 2006 | Germany | 988 members (418 confirmed carriers, 22 obligate carriers ^a , and 548 first- or second-degree relatives) from 281 families with <i>MLH1</i> (<i>n</i> = 124) or <i>MSH2</i> (<i>n</i> = 157) mutations. Families fulfilling the Amsterdam-II Criteria (41) or the original Bethesda guidelines (55) were ascertained through the six German centers. | Retrospective cohort. | O = 10 (eight in confirmed or obligate <i>MSH2</i> mutation carriers, two in untested relatives of <i>MSH2</i> families, and no prostate cancer observed in <i>MLH1</i> families) E = not reported Mean age at diagnosis = 59 y | Unable to calculate SIR. |
| Barrow et al. (28) | 2009 | UK | 839 carriers (249 confirmed carriers, 90 obligate carriers ^b , 331 putative carriers ^c , and 169 assumed carriers ^d) from 121 MMR gene mutation-carrying families (51 <i>MLH1</i> , 59 <i>MSH2</i> , and 11 <i>MSH6</i>). Ascertained from families fulfilling the Amsterdam (41) or Bethesda criteria (42) who attended the Manchester Regional Genetics Service. | Retrospective cohort. | O = 6 E = not reported Age at diagnosis = not reported | Unable to calculate SIR. |
| Stupart et al. (29) | 2009 | South Africa | 200 (102 male) confirmed carriers of <i>MLH1</i> c.C1528T mutation from 17 families. Ascertainment of families was not described. | Prospective cohort. | O = 1 (19 extracolonic cancers in both men and women). E = not reported Age at diagnosis = not reported | Unable to calculate SIR. |
| da Silva et al. (30) | 2010 | Brazil | 2,095 (1,040 male) members from 60 families fulfilling the Amsterdam-I (40) or -II criteria (41). Used families registered in the Oncotree database of the Hereditary Colorectal Cancer Registry of the Pelvic Surgery Department of Hospital AC Camargo, Sao Paulo. | Retrospective cohort. | O = 16 (21% of 77 extracolonic cancers observed in men) E = not reported Age at diagnosis = >70 y in "most of the cases" Author stated, "the age of diagnosis was over 70 years and because of this, prostate cancer is unlikely to be part of LS spectrum of tumors." | Unable to calculate SIR. |

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Table 2. Summary of risk studies that investigated risk of prostate cancer for men with Lynch syndrome (Cont'd)

| Author | Year | Country | Study population | Study design | Results | Comments |
|----------------------------|------|-----------|--|-----------------------|--|--|
| Talseth-Palmer et al. (31) | 2010 | Australia | 78 <i>MSH6</i> mutation carriers from 29 families and seven <i>PMS2</i> mutation carriers from six families. Ascertained from families referred to Hunter Area Pathology Service in Newcastle, New South Wales, for genetic testing due to fulfilling the Amsterdam-II (41) or Bethesda Criteria (42) or MSI or IHC absence of <i>MSH6/PMS2</i> expression. | Retrospective cohort. | O = 7 in relatives of <i>MSH6</i> carriers E = not reported Mean age at diagnosis (SD) = 65 (7.6); calculated from the reported ages (70, 60, 75, 56, and 64, and two missing). | Unable to calculate SIR. |
| Scott et al. (24) | 2001 | Australia | 95 families (22 <i>MLH1</i> , 12 <i>MSH2</i> , 61 unknown) fulfilled the Bethesda Criteria (55) (<i>n</i> = 63) or the Amsterdam Criteria (40) (<i>n</i> = 32). Ascertainment of families was not described. | Retrospective cohort. | For carriers only. O = 1 (<i>MSH2</i> carrier) E = not reported SIR = 1.02 (95% CI, 0.1–13.6) For both carriers and relatives, O = 11 E = not reported SIR = 2.69 (95% CI, 1.2–5.8) Age at diagnosis = not reported | For untested relatives, this cohort may contain noncarriers and therefore likely to underestimate the true risk. |
| Maul et al. (27) | 2006 | U.S. | 65 CRC cases and 509 FDRs from 18 families fulfilling Amsterdam-I criteria (40). Identified through the Utah Population Database. | Retrospective cohort. | For CRC cases, O = 4 E = 1.62 SMR = 2.5 (95% CI, 0.67–6.34) For FDRs, O = 19 E = 8.73 SMR = 2.18 (95% CI, 1.31–3.39) Age at diagnosis = not reported | No ascertainment bias. For CRC cases, the estimates may reflect only for those with a prior diagnosis of CRC. For FDRs, this cohort may contain noncarriers and therefore likely to underestimate the true risk. |

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Table 2. Summary of risk studies that investigated risk of prostate cancer for men with Lynch syndrome (Cont'd)

| Author | Year | Country | Study population | Study design | Results | Comments |
|-----------------------|------|----------------------|---|-----------------------|--|--|
| Barrow et al. (35) | 2013 | UK | 292 male confirmed carriers (130 <i>MSH2</i> , 141 <i>MLH1</i> , and 21 <i>MSH6</i>) and 529 male untested FDRs. Ascertained from the Manchester Regional Genetics Service where referral was due to clustered colorectal cancer and extracolonic cancers. | Retrospective cohort. | For <i>MSH2</i> carriers, O = 4 E = 0.38 RR = 10.41 (95% CI, 2.8–26.65) For untested FDRs of <i>MSH2</i> carriers, O = 3 E = 1.24 RR = 2.41 (95% CI, 0.48–7.03) For untested FDRs of <i>MSH6</i> carriers, O = 1 E = 0.29 RR = 3.36 (95% CI, 0.04–18.67) Median age at diagnosis (range) = 67.3 (54.2–76.0) y | For confirmed carriers, estimate of association may be upwardly biased. ^e For untested relatives, this cohort may contain noncarriers and therefore likely to underestimate the true risk. |
| Aarnio et al. (22) | 1999 | Finland | 360 carriers (265 confirmed and 95 obligate ^b carriers) from 50 families with <i>MLH1</i> (n = 47) or <i>MSH2</i> (n = 3) mutations. Ascertained through the population-based nationwide Finnish Cancer Registry. | Retrospective cohort. | O = 4 E = not reported SIR = 2.9 (95% CI, 0.8–7.4) Age at diagnosis = not reported | No ascertainment bias. |
| Grindedal et al. (19) | 2009 | Norway | 106 confirmed or obligate ^f male carriers (68 <i>MSH2</i> , 19 <i>MLH1</i> , 13 <i>MSH6</i> , and 6 <i>PMS2</i>) from 34 families. Ascertained from families referred to the Section for Hereditary Cancer at The Rikshospitalet University Hospital in Oslo. | Retrospective cohort. | O = 9 (6 <i>MSH2</i> , 2 <i>MSH6</i> , and 1 <i>MSH6</i>) E = 1.52 SIR = 5.9 (95% CI, 4.1–17.1) Cumulate risk to age 70 y = 30% (SE 0.088) Mean age at diagnosis (range) = 60.4 (53–68) y Expected age at diagnosis = 66.6 y | Estimate of association may be upwardly biased. ^e |
| Engel et al. (32) | 2012 | Germany, Netherlands | 2,118 (1,107 male) confirmed carriers (806 <i>MLH1</i> , 1,004 <i>MSH2</i> , 308 <i>MSH6</i>). Ascertained from families fulfilling the Amsterdam-II (41) or Bethesda criteria (42) through the German HNPCC Consortium and the registry of the Netherlands Foundation for the Detection of Hereditary Tumours. | Retrospective cohort. | E = not reported O = not reported SIR = 2.5 (95% CI, 1.4–4.0) Cumulative risk to 70 y: 9.1% (95% CI, 4.4–13.8) Median age at diagnosis (range) = 59 (50–74) y | Estimate of association may be upwardly biased. ^e |

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Table 2. Summary of risk studies that investigated risk of prostate cancer for men with Lynch syndrome (Cont'd)

| Author | Year | Country | Study population | Study design | Results | Comments |
|---------------------|------|-------------------------------------|---|-----------------------|---|---|
| Pande et al. (34) | 2012 | U.S. | 368 (152 male; 165 probands and 203 relatives) confirmed carriers (152 <i>MLH1</i> , 197 <i>MSH2</i> , 16 <i>MSH6</i> , 3 <i>PMS2</i>) from 176 families. Probands ascertained from the gastroenterology and gynecologic oncology clinics and Clinical Cancer Genetics Clinics at MD Anderson Cancer Center. | Retrospective cohort. | For both probands and relatives, O = 3 E = 3.22 SIR = 0.93 (95% CI, 0.19–2.7) For relatives only, O = 2 E = 1.52 SIR = 1.3 (95% CI, 0.15–4.7) Median age at diagnosis = 65 y | Estimate of association may be upwardly biased, especially for estimates of both probands and relatives. ^e |
| Raymond et al. (36) | 2013 | U.S.A. | 8,314 (4,127 male) members from 198 mutation-carrying families (74 <i>MLH1</i> , 101 <i>MSH2</i> , and 23 <i>MSH6</i>). Ascertained through family cancer clinics at the Dana-Farber Cancer Institute, Boston, and University of Michigan Comprehensive Cancer Centre, Ann Arbor. | Retrospective cohort. | Overall HR = 1.99 (95% CI, 1.31–3.03) For ages 20–59 y, HR = 2.48 (95% CI, 1.34–4.59) Cumulative Risk to age 70 y = 17.39 (95% CI, 10.10–24.07) Median age at diagnosis (range) = 65 (38–89) y | Ascertainment bias corrected by conditioning on the proband's genotype and phenotype status. The estimates may reflect only for carriers from family cancer clinics or carriers with a relative with CRC or endometrial cancer. |
| Dowty et al. (15) | 2013 | Australia, USA, Canada | 17,576 members from 166 <i>MLH1</i> and 224 <i>MSH2</i> mutation-carrying families. Ascertained from population cancer registries or family cancer clinics of the Colon Cancer Family Registry. | Retrospective cohort. | For <i>MLH1</i> carriers, O = 45 HR* = 0.79 (95% CI, 0.25–2.5) For <i>MSH2</i> mutation carriers, O = 60 HR = 1.0 (95% CI, 0.47–2.3) Mean age at diagnosis (SD) = 69.6 (10.4) y for <i>MLH1</i> and 68.6 (11.5) y for <i>MSH2</i> | Ascertainment was corrected by statistical methods conditioning the likelihood for each pedigree. The estimates may reflect only for <i>MLH1</i> or <i>MSH2</i> carriers. |
| Win et al. (14) | 2012 | USA, Canada, Australia, New Zealand | 446 confirmed carriers (161 <i>MLH1</i> , 222 <i>MSH2</i> , 47 <i>MSH6</i> , and 16 <i>PMS2</i>). A median 5-year follow-up. | Prospective cohort. | O = 3 E = 1.21 SIR = 2.49 (95% CI, 0.51–7.27) | No ascertainment bias. |

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Table 2. Summary of risk studies that investigated risk of prostate cancer for men with Lynch syndrome (Cont'd)

| Author | Year | Country | Study population | Study design | Results | Comments |
|----------------------|------|-------------------------------------|---|-----------------------|--|---|
| Hemminki et al. (23) | 2001 | Sweden | Ascertained from population cancer registries or family cancer clinics of the Colon Cancer Family Registry. 4,794 CRC cases from 88 families fulfilling the Amsterdam (40, 41) or modified Bethesda criteria (23). Identified through the Swedish Family-Cancer Database. | Retrospective cohort. | Median age at diagnosis (range) = 54 (50–62) y O = 1 E = not reported SIR = 3.52 (95% CI, 0.00–13.81) Age at diagnosis = not reported | No ascertainment bias. The estimates may reflect only for those with a prior diagnosis of CRC. No ascertainment bias. |
| Win et al. (33) | 2012 | USA, Canada, Australia, New Zealand | 764 confirmed carriers (316 <i>MLH1</i> , 357 <i>MSH2</i> , 49 <i>MSH6</i> , and 42 <i>PMS2</i>) with a prior diagnosis of CRC. Ascertained from population cancer registries or family cancer clinics of the Colon Cancer Family Registry. | Retrospective cohort. | For all carriers, O = 19 E = 9.25 SIR = 2.05 (95% CI, 1.23–3.01) Median age at diagnosis (range) = 64 (55–77) y For <i>MLH1</i> carriers, O = 3 E = 3.44 SIR = 0.87 (95% CI, 0.00–2.19) For <i>MSH2</i> carriers, O = 15 E = 4.15 SIR = 3.62 (95% CI, 2.07–5.36) For <i>MSH6</i> carriers, O = 1 E = 1.16 SIR = 0.86 (95% CI, 0.00–3.03) | No ascertainment bias. The estimates may reflect only for carriers with a prior diagnosis of CRC. |

Abbreviations: LS, Lynch syndrome; O, observed number of prostate cancers; E, expected number of prostate cancers; SMR, standard morbidity ratio; FDR, first-degree relative; CRC, colorectal cancer.

^aObligate carrier was not defined (26).

^bObligate carrier was defined because of their position in the pedigree in relation to a confirmed MMR gene mutation carrier (22, 28).

^cPutative mutation carriers were first-degree relatives of a confirmed mutation carrier with a Lynch syndrome–related cancer (colorectal, endometrial, ovarian, gastric, brain, biliary, small bowel, and sebaceous adenocarcinoma; ref. 28).

^dAssumed mutation carriers were half of the untested first-degree relatives with non-Lynch syndrome spectrum cancers; or a proportion of untested, unaffected first-degree relatives with no cancers calculated on the basis of the proportion of unaffected relatives who tested positive of the total number of individuals actually tested for each age group (28).

^eEstimates of prostate cancer risk are likely to be upwardly biased if any of the family members attended family cancer clinics because of a family history of prostate cancer (see text for details).

^fObligate carrier was defined as being in between relatives who were confirmed mutation carriers and/or had shown loss of the relevant gene product by immunohistochemistry of a Lynch syndrome–associated tumor if mutation testing had not been possible (19).

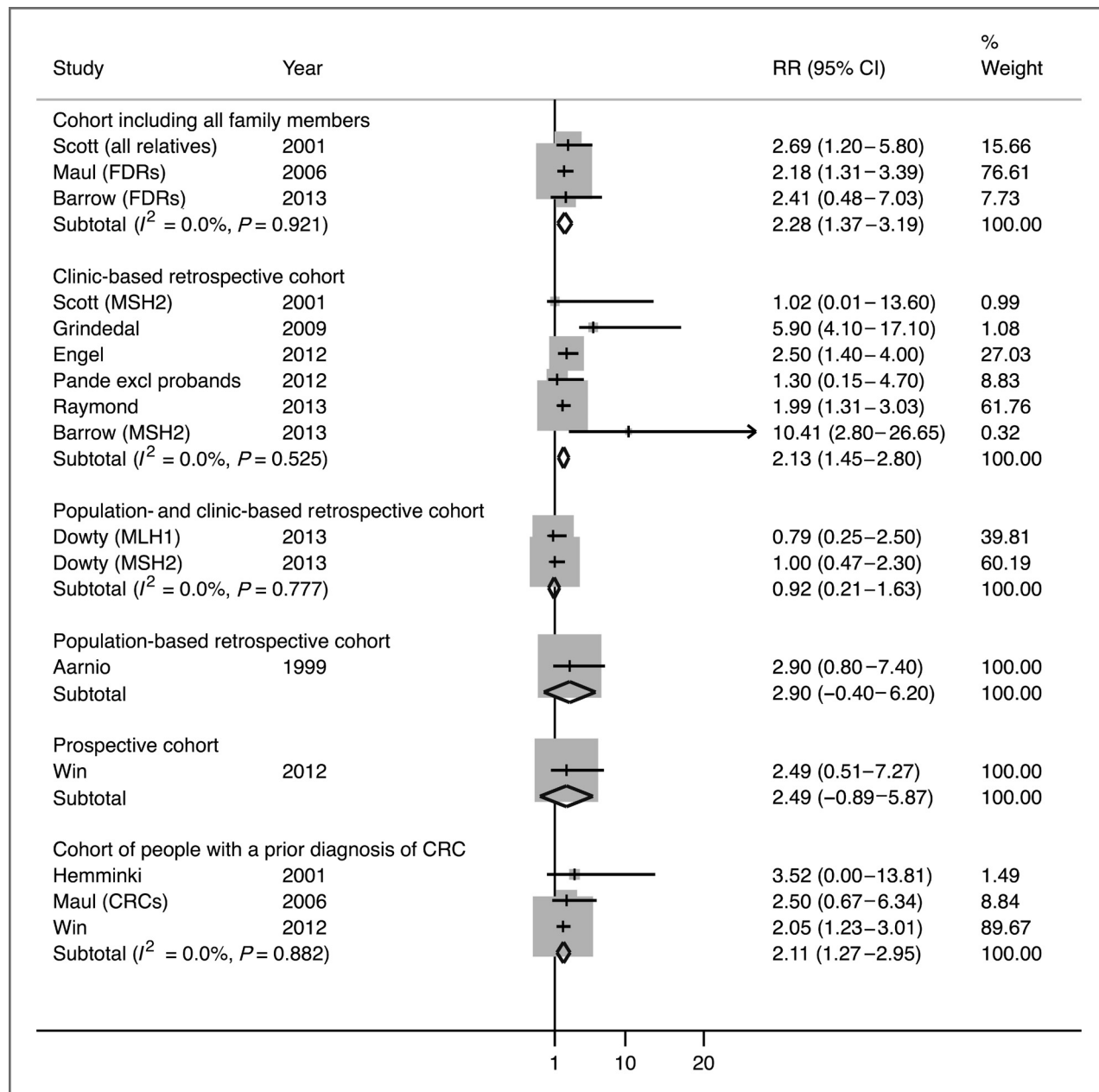


Figure 2. Meta-analysis of studies investigating prostate cancer risk for men with Lynch syndrome stratified by different study designs. Horizontal lines represent 95% CI. Each box represents the RR point estimate, and its area is proportional to the weight of study (the inverse variance of each study's effect). The diamond represents the combined summary estimated RR, with 95% CI given by the width of the diamond. The unbroken vertical line is at the null value (RR = 1). CRC, colorectal cancer; FDR, first-degree relative.

Three of the studies included in the meta-analysis (24, 27, 35) estimated prostate cancer risk using retrospective cohort of all family members, that is, including carriers as well as relatives who were not tested for germline mutation status. As a proportion of these untested relatives will on balance of probability be noncarriers, these studies will underestimate the penetrance if it is increased by germline mutation. Of note, one of these studies (35) did not observe a significant increase in risk of prostate cancer.

Eight retrospective cohort studies estimated prostate cancer risk only for carriers using population-based resources (22), clinic-based resources (19, 24, 32, 34–36), or both population- and clinic-based resources (15). Two studies (19, 22) included obligate carriers as well as confirmed. This should be of no consequence, as by definition their carrier status is locked in by the status of other family members relative to their pedigree. However, Grindedal and colleagues (19) also classified as "obligate carriers" those that had MMR-deficient tumors, thus potentially

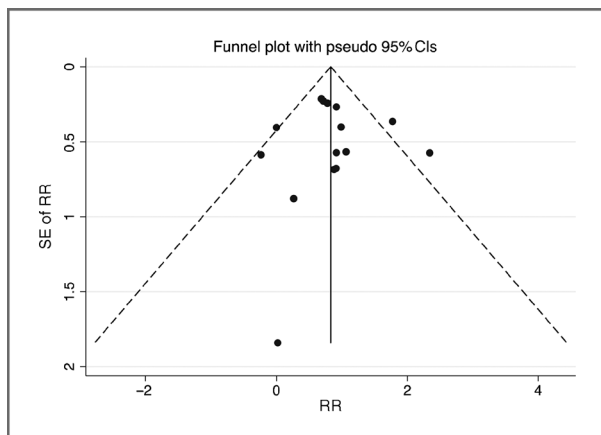


Figure 3. Funnel plot for the meta-analysis of studies investigating prostate cancer risk for men with Lynch syndrome. The vertical line in the funnel plot indicates the fixed-effects summary estimates (using inverse-variance weighting). The sloping lines indicate the expected 95% CIs for a given standard error assuming no heterogeneity between studies. Asymmetry in the funnel plot indicates a systematic underreporting of smaller and negative studies (publication bias) or a systematic difference between smaller and larger studies that arises from inherent between-study heterogeneity.

inflating the estimate of penetrance if MMR-deficient prostate cancers can have an alternate etiology.

Given the potential effect of ascertainment on the estimates of risk, we conducted meta-analysis by the stratifying of cohort studies on the source of their samples. The motivation of attending a family cancer clinic may include having a family history of cancer or a recent diagnosis of cancer, and therefore, mutation carriers identified through clinic attendance may have higher risk of cancer. Of the six clinic-based retrospective studies included in the review, four studies (19, 24, 32, 35) did not attempt to correct for the family history ascertainment in their statistical analyses. This implies that the estimates of prostate cancer risk from these studies are likely to be upwardly biased (47) if any of the family members attended the clinics, or genetic testing for MMR gene mutations was instigated because of a family history of prostate cancer. Pande and colleagues (34) attempted to analyze excluding the probands on the basis that they were ascertained "largely because of being cancer affected," yet neither of the estimates including or excluding probands was statistically significant. In this case, even conditioning on the proband alone may not be sufficient to ensure these populations are representative of all mutation carriers in terms of prostate cancer risk (48).

Two retrospective studies used a statistical method called modified segregation analysis that is capable of producing unbiased estimates of risk by adjusting for ascertainment (15, 36). Raymond and colleagues (36) conditioned on the genotype and cancer status of the proband but did not condition on the cancer status of the relatives, therefore penetrance estimates could be biased if family members attended clinics or were tested for MMR gene mutations because of a family history of prostate

cancer. In contrast, Dowty and colleagues (15) conditioned on the genotype and cancer status of the proband and the cancer status of the relatives for clinic-based families, and therefore produced unbiased estimates of penetrance even if attendance to a family cancer clinic or testing for MMR gene mutations was due to prostate cancer. If families' attendance or MMR gene testing was not due to prostate cancer, the estimates from these studies will still be unbiased but the conditioning may incur a loss of power to detect an increased risk of prostate cancer (49).

There is only one population-based retrospective study (22) that estimated risk by comparing the observed number of prostate cancer in confirmed and obligate carriers with the number expected on the basis of their age, and they found no evidence of an increased risk. They ascertained carriers from a population cancer registry and therefore their estimate is less likely to be upwardly biased because of family history. However, due to the wide CIs on the estimate of RR, conclusions from this study alone are limited.

Referral of families to clinics for investigation of Lynch syndrome may also be hampering the investigation of prostate cancer as part of Lynch syndrome. Where entry into family cancer clinics or genetics clinics is contingent upon meeting Amsterdam-I or -II criteria (40, 41), it is likely that there will be a focus on families with higher levels of colorectal and endometrial cancers and some additional cancers, but not prostate cancer. It is possible that research on existing Lynch syndrome families will therefore miss prostate cancer, as it will be underrepresented.

Although difficult to conduct, prospective studies are immune from these recall and ascertainment biases. The prospective study by Win and colleagues (14) did not provide evidence of an increase but was probably underpowered to detect a moderate increase in prostate cancer risk. Future meta-analyses or pooled analyses are required to incorporate additional prospective studies with the advantage of increased power, particularly if the follow-up time is lengthened.

The final study design for which we estimated prostate cancer risk was as a second primary cancer for carriers with a prior diagnosis of colorectal cancer (23, 27, 33). This is a clinically relevant finding given colorectal cancer cases are subject to cancer surveillance. The strength of the association implicates elevated prostate cancer risk in men who are more susceptible to cancer (given their prior diagnosis of colorectal cancer). This type of study overcomes the bias for primarily observing cancers associated with Lynch syndrome classification.

In addition to the studies reviewed in this analysis, there have been four studies examining the role of single-nucleotide polymorphisms (SNP) that are not considered high-risk mutations on prostate cancer. Langeberg and colleagues (50) observed a SNP in *MLH1* (rs9852810) was associated with an increased risk of prostate cancer, more aggressive cancer, and prostate cancer recurrence. *MLH1*

polymorphisms (51) and *MSH3* polymorphisms (52, 53) have also been reported to be associated with prostate cancer. These studies do provide some additional evidence to the mutation studies for an etiologic role of MMR genes on prostate cancer risk.

Clinical implications

It seems from the evidence provided by molecular studies that testing for MMR protein expression in prostate cancer tumors can be informative for Lynch syndrome in men from a family with a suspected MMR gene mutation where no colorectal tumors are available for testing. However, a formal comparison of prostate tumors from men known not to be MMR gene mutation carrier is needed to confirm the utility of such a test.

The 2- to 3-fold increased risk provided by risk studies may be an important factor in consideration for prostate cancer screening in men with Lynch syndrome. The positive predictive value of PSA screening for prostate cancer in these men may be high enough to warrant recommended screening. Studies on the aggressiveness or nuclear grade of prostate tumor in men with an MMR gene mutation would be relevant to studies on harm-benefit ratio of age-specific screening for such men.

There is some evidence that prostate cancer is more commonly diagnosed in men with an *MSH2* mutation compared with men with a mutation in one of the other MMR genes. Except for the study of Rosty and colleagues (20), most studies have been underpowered to observe any differences in prostate cancer risk by specific MMR gene mutations. Large cohorts will be required to measure separate prostate cancer risks for specific MMR gene mutation carriers. Clarification of the associated risk for

specific gene mutations will increasingly inform optimal screening strategies of prostate cancer.

Given almost all previously published studies were of Caucasian men, and that prostate cancer incidence varies substantially by country (54), the current findings may not be applicable to non-Caucasian populations.

Conclusion

The molecular and epidemiologic risk evidences in combination present a convincing argument for the inclusion of prostate cancer into the Lynch syndrome cancer spectrum. Certainly the available molecular evidence is consistent with, although does not prove, prostate cancer being caused by an MMR gene mutation. Overall, the published risk studies support a moderately increased risk of prostate cancer for men with an MMR gene mutation, although the evidence is not consistent and many of the studies have limitations in design and analysis. Further research that overcomes these limitations is suggested and warranted to finalize the question of prostate cancer is a Lynch syndrome cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Shae Ryan, Mark A. Jenkins and Aung Ko Win

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