

## Risks of Lynch Syndrome Cancers for *MSH6* Mutation Carriers

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- Background** Germline mutations in *MSH6* account for 10%–20% of Lynch syndrome colorectal cancers caused by hereditary DNA mismatch repair gene mutations. Because there have been only a few studies of mutation carriers, their cancer risks are uncertain.
- Methods** We identified 113 families of *MSH6* mutation carriers from five countries that we ascertained through family cancer clinics and population-based cancer registries. Mutation status, sex, age, and histories of cancer, polypectomy, and hysterectomy were sought from 3104 of their relatives. Age-specific cumulative risks for carriers and hazard ratios (HRs) for cancer risks of carriers, compared with those of the general population of the same country, were estimated by use of a modified segregation analysis with appropriate conditioning depending on ascertainment.
- Results** For *MSH6* mutation carriers, the estimated cumulative risks to ages 70 and 80 years, respectively, were as follows: for colorectal cancer, 22% (95% confidence interval [CI]=14% to 32%) and 44% (95% CI=28% to 62%) for men and 10% (95% CI=5% to 17%) and 20% (95% CI=11% to 35%) for women; for endometrial cancer, 26% (95% CI=18% to 36%) and 44% (95% CI=30% to 58%); and for any cancer associated with Lynch syndrome, 24% (95% CI=16% to 37%) and 47% (95% CI=32% to 66%) for men and 40% (95% CI=32% to 52%) and 65% (95% CI=53% to 78%) for women. Compared with incidence for the general population, *MSH6* mutation carriers had an eightfold increased incidence of colorectal cancer (HR=7.6, 95% CI=5.4 to 10.8), which was independent of sex and age. Women who were *MSH6* mutation carriers had a 26-fold increased incidence of endometrial cancer (HR=25.5, 95% CI=16.8 to 38.7) and a sixfold increased incidence of other cancers associated with Lynch syndrome (HR=6.0, 95% CI=3.4 to 10.7).
- Conclusion** We have obtained precise and accurate estimates of both absolute and relative cancer risks for *MSH6* mutation carriers.

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Lynch syndrome, also known as hereditary nonpolyposis colon cancer syndrome (1), is a rare, autosomal, dominantly inherited syndrome caused by germline mutations in DNA mismatch repair genes, which confer substantial risks for cancers of the colorectum and endometrium and increased risks for cancers of the stomach, small intestine, hepatobiliary system, kidney, ureter, ovary, and sebaceous tumors (2,3). Mutations in the mismatch repair genes, *MLH1* and *MSH2*, account for 70%–80% of all Lynch syndrome colorectal cancers (ie, colorectal cancers occurring in people with germline DNA mismatch repair gene mutations) (4–7).

Mutations in *MSH6* account for 10%–20% of Lynch syndrome colorectal cancers and 0.4% of all colorectal cancers (4–7), with the greater proportion of colorectal cancer diagnosed at a younger age (4,6). The prevalence of *MSH6* mutations in women with endometrial cancer who were not selected for family history

is less well established with estimates ranging from 1.0% to 3.8% (8–12).

Few studies have attempted to estimate the age-specific cumulative cancer risk for carriers of germline mutations in *MSH6* (penetrance) (13–18), so information on the consequences of such mutations remains uncertain. Most of these studies (13–16) have analyzed data from families that were ascertained because of a strong family history of cancers related to Lynch syndrome, or preferentially mutation-tested individuals with colorectal cancer over individuals without colorectal cancer, and appear not to have correctly taken into account the ascertainment when deriving their penetrance estimates. Recruiting families from family cancer clinics will result in oversampling of family members who have been diagnosed with colorectal or other cancers, and such recruitment has been shown to result in inflated estimates of cancer risks

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## CONTEXT AND CAVEATS

### Prior knowledge

Germline mutations in *MSH6* account for 10%–20% of Lynch syndrome colorectal cancers and approximately 0.4% of all colorectal cancers.

### Study design

Families of *MSH6* mutation carriers from five countries were identified through family cancer clinics and population-based cancer registries. Mutation status; sex; age; and histories of cancer, polypectomy, and hysterectomy were sought from their relatives. Age-specific cumulative risks of all Lynch syndrome cancers among carriers were estimated.

### Contribution

*MSH6* mutation carriers had high estimated cumulative risks to age 80 years for colorectal cancer, endometrial cancer, and any cancer associated with Lynch syndrome. Compared with incidence for the general population, *MSH6* mutation carriers had an eightfold increased incidence of colorectal cancer that was independent of sex and age. Women who were *MSH6* mutation carriers had a 26-fold increased incidence of endometrial cancer and a sixfold increased incidence of other cancers associated with Lynch syndrome.

### Implications

The elevated risks for Lynch syndrome cancers in *MSH6* mutation carriers differed by sex of the carrier and continued into older age. Screening for Lynch syndrome cancers in *MSH6* mutation carriers is warranted.

### Limitations

No haplotype analysis was done for any of the mutations identified in more than one family.

*From the Editors*

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if this ascertainment is not fully taken into account (19). For population-based studies, the appropriate adjustment for ascertainment is straightforward. A meta-analysis (18) of 10 *MSH6* mutation families extracted from two population-based studies (17,20) estimated that the cumulative colorectal cancer risk to age 70 years was similar for men and women at approximately 35%. For endometrial cancer, the cumulative risk was approximately 35% to age 70 years and 50% to age 80 years. In this analysis, we combined data from 113 families with deleterious germline *MSH6* mutations and estimated the cancer risks for mutation carriers by use of statistical methods that appropriately condition on ascertainment.

## Participants and Methods

### Study Population

The study population was composed of families that carried deleterious *MSH6* mutations, which were defined as variants that were predicted to result in a stop codon, a frameshift mutation, a large insertion or deletion, or a missense mutation that was judged to be deleterious. Families were obtained from four sources: 1) the Colon Cancer Family Registry, which recruited colorectal cancer families from the United States, Canada, Australia, and New

Zealand; 2) a research consortium in the Netherlands; 3) a research group in Scotland; and 4) a research group in Columbus, Ohio. Probands, who were defined as the first person in the family to be identified with a mutation in *MSH6*, were ascertained via population-based cancer registries (ie, population-based probands) or from family genetic services or cancer clinics (ie, clinic-based probands). From these sources, 113 families of *MSH6* mutation carriers were ascertained for this study. Mutation status; sex; age; and histories of cancer, polypectomy, and hysterectomy were sought from the 3104 relatives of the 113 *MSH6* mutation-carrying probands. Written informed consent was obtained, and this research was approved by local institutional review boards at each recruiting source.

**Colon Cancer Family Registry.** Details of recruitment methods have been described previously (21). All probands and families in this study were recruited from January 1, 1997, through December 31, 2002. For clinic-based ascertainment, the probands were selected from multiple-case colorectal or Lynch syndrome cancer families who attended cancer clinics in the United States (Mayo Clinic, Rochester, Minnesota; and Cleveland) and Australasia (Melbourne, Adelaide, Perth, Brisbane, Sydney, Australia; and Auckland, New Zealand). Probands were not required to have colorectal cancer. For population-based ascertainment, probands were defined as patients with newly diagnosed colorectal cancer who were identified by population-based cancer registries in the United States (Puget Sound, Washington; the State of Minnesota; Los Angeles, California; Arizona; Colorado; New Hampshire; North Carolina; and Hawaii), Australia (Victoria), and Canada (Ontario). Most population-based sampling was independent of family history but in some instances was stratified by family history. Relatives were recruited via the probands. Selection of probands for *MSH6* gene analysis was based on the absence of *MSH6* protein expression in tumor tissue. The immunohistochemistry staining protocol has been described previously (22). Mutation analysis of the *MSH6* gene was performed by DNA sequence analysis. Briefly, all 10 exons and flanking intron sequences of *MSH6* were amplified from genomic DNA in eight amplicons divided into two multiplex polymerase chain reactions. Primers were designed from the *MSH6* human genomic sequence (GenBank accession number NT\_022184) and are available from the authors upon request. Polymerase chain reaction multiplex-1 amplified exons 2, 5, 6, 7, and 8–10 and multiplex-2 amplified exons 1, 3, and 4. Electrophoresis was performed on the ABI 3730 (Applied Biosystems Inc, Foster City, CA). Sequence chromatograms were analyzed by use of Mutation Surveyor (SoftGenetics, State College, PA) software. Large insertions and deletions were detected by multiplex ligation-dependent probe amplification (23).

**Netherlands.** Details of recruitment methods have been described previously (24). Probands were selected from families suspected of having Lynch syndrome by the Dutch Lynch Syndrome Study Group from a national registry for families with hereditary non-polyposis colon cancer established in the Netherlands in 1987. Clinical information including age at diagnosis of cancer, site of the tumor, and age at and cause of death was collected by the registry. Most probands were tested for *MSH6* mutations depending

on tumor microsatellite instability or mismatch repair protein expression. Polymerase chain reaction was used to amplify DNA. In most laboratories in the Netherlands, indirect techniques such as denaturing gradient gel electrophoresis, protein truncation test, or more recently high-resolution melting curve analysis are, or were, used to identify DNA variants. The fragments with variants are subsequently analyzed by a direct DNA sequence analysis as described above, and deletions and duplications were identified by use of multiplex ligation-dependent probe amplification (13).

**Scotland.** Details of recruitment methods have been described previously (6). All probands and families in this study were recruited from January 1, 1999, through December 31, 2003. Probands were identified from the Scottish Cancer Registry and were defined as patients with newly diagnosed colorectal cancer or endometrial cancer who were younger than 55 years when diagnosed and whose cancer was diagnosed in Scotland. Relatives were recruited via the probands.

All probands were tested for *MSH6* mutations irrespective of tumor microsatellite instability or mismatch repair protein expression. Mutation analysis of the *MSH6* gene was performed by DNA sequence analysis, and large insertions and deletions were detected by multiplex ligation-dependent probe amplification (6).

**Ohio.** Details of recruitment methods have been described previously (5,9). Probands were defined as individuals with newly diagnosed adenocarcinoma of the colorectum or endometrium, regardless of age or family history of cancer, who were treated at one of six major participating hospitals in Columbus, Ohio, including the Ohio State University Medical Center (the James Cancer Hospital and the Ohio State University East), Mount Carmel East, Mount Carmel West, St Ann's Hospital, Riverside Methodist Hospital, and Grant Medical Center. In total, 1566 patients with colorectal cancer were recruited from January 1, 1999, through August 31, 2004.

All probands with colorectal or endometrial cancer with microsatellite instability were tested for germline mutations in *MSH6*. Mutation analysis of the *MSH6* gene was performed by DNA sequence analysis, and large insertion and deletions were detected by multiplex ligation-dependent probe amplification (5,9).

### Data Collection

Information on demography, personal and family history of cancer, cancer screening, and cancer surgery was obtained from all participants by interview, questionnaire, or extraction from clinical records. Efforts were made to verify reported cancer diagnoses by use of multiple sources, including family reporting, pathology reports, medical records, and death certificates. All probands and selected relatives were asked to provide a blood sample for DNA analysis and to sign a consent to allow us to retrieve archived colorectal cancer tissue.

### Statistical Analysis

We estimated the age-specific cumulative risk (penetrance) and the age-specific hazard ratios (HRs) for mutation carriers compared with the population for the following cancer groups: colorectal cancer, endometrial cancer, all other Lynch cancers (ie, gastric,

small bowel, kidney, ureter, brain, and ovarian cancers) combined, all Lynch cancers combined, breast cancer, prostate cancer, all non-Lynch cancers combined, and all cancers combined. For colorectal cancer, we censored each individual at the age of polypectomy (except when it occurred within a year of the diagnosis of colorectal cancer) and, for endometrial cancer, we censored each woman at the age of hysterectomy (except when it occurred within a year of the diagnosis of endometrial cancer).

Penetrance for carriers was estimated with a likelihood-based approach as in Schaid et al. (25). Cumulative risks to age  $t$  years were assumed to be logistic functions of  $t$ ,

$$F(t) = \frac{\exp(\alpha \cdot t + \beta)}{1 + \exp(\alpha \cdot t + \beta)}$$

where estimates for the parameters  $\alpha$  and  $\beta$  and the corresponding standard errors and correlations were obtained by use of asymptotic maximum likelihood theory. A 95% confidence interval (CI) for the cumulative risk to any age  $t$  was obtained by simulation.

The hazard ratio was estimated with a likelihood-based approach that used a model in which the age-specific hazard for a mutation carrier developing any of the above classes of cancer was assumed to be the estimated hazard ratio times the sex-, country-, and age-specific population incidence for the appropriate cancer group. Average age-specific population incidences in 1998–2002 for each country were obtained from *Cancer Incidence in Five Continents* (26). Hazard ratios were estimated for each cancer group, each sex, and each age category (as decades of age or as <50 vs  $\geq 50$  years), type of mutation (point mutations, small insertions or deletions, and large rearrangements), and ascertainment type (population-based vs clinic-based). More than 90% of families were white, making any comparison in risks with non-white populations underpowered.

For both the penetrance and the hazard ratios analyses, we corrected for ascertainment by conditioning the likelihood for each pedigree, which was sampled independently of family cancer history, on the proband's *MSH6* mutation status, cancer status, and age at diagnosis. The likelihood for each clinic-based pedigree (which was assumed to be ascertained because there was a family history of cancer) and for each population-based pedigree (which was ascertained because there was a family history of colorectal cancer) was conditioned on the *MSH6* mutation status of the proband and the cancer status and age at censoring (if unaffected) or diagnosis (if affected) of the proband and all relatives (27). For the analyses, we included all first- and second-degree relatives for population-based families who were ascertained irrespective of family history; for all other families, all available relatives were included.

To gauge the number of mutation carriers in our study, we estimated the number of carriers in the 131 families by using the laws of Mendelian inheritance to calculate carrier probabilities for every ungenotyped individual that was based on the known family structure and mutation statuses of relatives. The estimated number of carriers was calculated by summing the number of known carriers and the carrier probabilities of the ungenotyped relatives.

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

with the pedigree analysis program MENDEL [Lange et al. (28)] and other calculations in Stata (Stata Corp, College Station, TX) version 10 (29).

## Results

Among the probands of the 113 families with an identified mutation in *MSH6*, 31 carried a point mutation, 77 carried a small insertion or deletion, and five carried a large insertion or deletion. There were 74 distinct mutations of which, 22 were observed across more than one family (range=two to six families) (Supplementary Table 1, available online).

Among the 113 probands, 42 were sampled from population-based sources that were independent of their family history or cancer status, six were sampled from population-based sources because of family history of cancer, and 65 were ascertained from clinic-based sources. The personal cancer history of the probands included 61 with colorectal cancer only, 33 with endometrial cancer only, 10 with colorectal and endometrial cancers, two with ovarian cancer only, two with colorectal and ovarian cancers, one with endometrial and ovarian cancers, one with small bowel cancer, and three with no cancer. Mean age at colorectal cancer diagnosis of affected probands was 52 years (SD=10 years; range=26–82 years). Mean age at endometrial cancer of affected probands was 51 years (SD=9 years; range=31–69 years).

The 48 population-based families included an average of 18.5 relatives per proband and contributed 15 742 person-years for an estimated 346 mutation carriers; the 65 clinic-based families included an average of 19.8 relatives per proband and contributed 35 544 person-years for an estimated 697 mutation carriers (Table 1). In total (excluding probands), the families contain an estimated 1043 mutation carriers who contributed 51 286 person-years. Definitive mutation status was known for all probands and for 278 relatives who were carriers and 247 who were noncarriers.

The colorectal cancer family history of the first- and second-degree relatives of the 42 population-based probands who were ascertained independent of their family cancer history was as follows: 18 (43%) had no affected relative, 14 (33%) had one affected relative, seven (17%) had two affected relatives, and three (7%) had three or more affected relatives. Thirty had a family cancer history that did not meet the Amsterdam II criteria (30), and of the remaining 12 (29%) who had a family cancer history meeting the Amsterdam II criteria, four met the Amsterdam I criteria (30).

Among the relatives of all 48 population-based *MSH6* mutation probands, 37 had colorectal cancer (an average of 0.8 per family), 22 had endometrial cancer (an average of 0.5 per family), and 19 had another Lynch syndrome cancer (an average of 0.4 per family), for a total of 78 Lynch syndrome cancers (an average of 1.6 per family) (Table 2). Among the relatives of all 65 clinic-based families, 111 had colorectal cancer (an average of 1.7 per family), 49 had endometrial cancer (an average of 0.8 per family), and 28 had another Lynch cancer (an average of 0.4 per family), for a total of 188 Lynch syndrome cancers (an average of 2.9 per family).

Table 3 and Figure 1 show that, by age 70 years, we estimate that 22% (95% CI=14% to 32%) of *MSH6* mutation carriers who were men would be diagnosed with colorectal cancer compared with 10% (95% CI=5% to 17%) of *MSH6* mutation carriers who were women. By age 80 years, we estimated that 44% (95% CI=28% to 62%) of *MSH6* mutation carriers who were men would be diagnosed with colorectal cancer, and this was greater than the estimate of 20% (95% CI=11% to 35%) of *MSH6* mutation carriers who were women. The 10-year risks of colorectal cancer for *MSH6* mutation carriers without a previous colorectal cancer diagnosis at age 70 years were 28% (95% CI=16% to 45%) for men and 11% (95% CI=4% to 23%) for women. The 10-year risks at other ages were 6% (95% CI=3% to 9%) at age 50 years and 14% (95% CI=8% to 22%) at age 60 years for men and 3% (95% CI=1% to 5%) at age 50 years and 5% (95% CI=3% to 11%) at age 60 years for women (Table 4).

The two regions contributing the greatest number of population-based families were Scotland (n=21) and North America (n=27). We estimated that the cumulative risk to age 70 years for Scottish men and women who were *MSH6* mutation carriers was 33% (95% CI=17% to 54%) and 15% (95% CI=7% to 32%), respectively, compared with the corresponding cumulative risks for North American *MSH6* mutation carriers of 18% (95% CI=8% to 36%) and 4% (95% CI=1% to 21%), respectively. These differences in cumulative risk by geographic region were not, however, statistically significant ( $P=.4$ ).

For *MSH6* mutation carriers, the estimated risks for colorectal cancer among men relative to those among men in the general population (HR=8.6, 95% CI=5.5 to 13.4) were not statistically significantly different from those among women (HR=6.4, 95% CI=3.6 to 11.4;  $P=.4$ ). When we combined men and women who were *MSH6* mutation carriers, the increased risk for colorectal cancer, relative to that of the general population, over all ages was

**Table 1.** Data for the penetrance analysis by country and ascertainment method of recruitment of the proband

Region	Population-based ascertainment		Clinic-based ascertainment	
	No. of families	Estimated No. of carriers*	No. of families	Estimated No. of carriers*
United States†	24	182	7	93
Canada†	3	35	2	23
Australia	0	—	15	88
Scotland	21	130	0	—
Netherlands	0	—	41	493
Total	48	346	65	697

\* Values were based on genetic relatedness to known *MSH6* mutation carriers and noncarriers. The values do not include probands.

† Three Canadian and three US families had population-based ascertainment but were treated in analysis as ascertained on family history because of sampling method used.



**Table 2.** Characteristics of individuals with cancer known to be *MSH6* mutation carriers and of individuals with an *MSH6* mutation carrier probability of 0.25 or higher (excluding probands) in *MSH6* mutation-carrying families by ascertainment

Cancer	Sex	Population-based families (n=48)			Clinic-based families (n=65)		
		No. of diagnoses	Mean age at diagnosis, y (SD)	Median age at diagnosis, y (range)	No. of diagnoses	Mean age at diagnosis, y (SD)	Median age at diagnosis, y (range)
Colorectal	Male	24	62.6 (9.8)	59 (47–85)	69	56.1 (13.3)	58 (30–85)
	Female	13	60.7 (15.1)	60 (36–82)	42	56.8 (12.3)	56 (30–90)
Endometrial	Female	22	53.9 (11.7)	51 (32–80)	49	53.4 (9.8)	53 (33–82)
Other Lynch cancers	Male	6	51.2 (7.6)	51 (43–65)	15	60.9 (15.1)	57 (32–84)
	Female	13	55.4 (9.4)	55 (39–72)	13	46.1 (14.8)	46 (21–75)
Ovary	Female	8	52.2 (9.6)	52 (39–72)	4	41.0 (10.2)	44 (27–49)
Stomach	Male	5	52.2 (8.0)	51 (43–65)	8	65.6 (14.4)	61 (43–84)
	Female	3	63.0 (2.6)	64 (60–65)	2	54.0 (5.7)	54 (50–58)
Small intestine	Male	0	—	—	1	40.0 (—)	40
	Female	0	—	—	0	—	—
Kidney	Male	0	—	—	2	69.5 (9.2)	69 (63–76)
	Female	1	65.0 (—)	65	3	52.3 (19.7)	43 (39–75)
Ureter	Male	0	—	—	1	59.0 (—)	59
	Female	0	—	—	0	—	—
Brain	Male	1	46	46	3	50.3 (16.8)	54 (32–65)
	Female	1	48	48	4	42.5 (19.4)	43 (21–67)
Total Lynch cancers	Male	30	60.3 (10.5)	60 (43–85)	84	56.9 (13.4)	57 (30–85)
	Female	48	56.1 (12.3)	55 (32–82)	104	53.9 (11.8)	54 (21–90)
Other cancers*	Male	34	56.8 (16.3)	60 (16–80)	42	65.3 (14.9)	64 (19–89)
	Female	33	59.7 (16.1)	60 (26–85)	28	57.6 (16.9)	55 (35–87)
Total cancers	Male	64	58.4 (13.8)	60 (16–85)	126	59.7 (14.4)	59 (19–89)
	Female	81	57.6 (13.9)	57 (26–85)	132	54.7 (13.0)	54 (21–90)

\* Other cancers include lung (n=28), breast (n=25), skin (n=13), prostate (n=10), pancreas (n=6), bladder (n=6), testis (n=5), liver (n=4), thyroid (n=4), pharynx (n=3), larynx (n=2), bone (n=2), myeloma (n=2), leukemia (n=5), lymphoma (n=2), eye (n=1), mouth (n=1), biliary tree (n=1), and unspecified (n=14).

statistically significantly elevated (HR=7.6, 95% CI=5.4 to 10.8;  $P < .001$ ). There was some evidence, although not statistically significant ( $P=.15$ ), that the risk for colorectal cancer among carriers younger than 50 years relative to similarly aged men and women in the population (HR=12.0, 95% CI=6.4 to 22.8) was higher than that for carriers 50 years or older relative to similarly aged men and women in the population (HR=6.5, 95% CI=4.2 to 10.0). There was little statistical evidence that the increased risk to carriers differed by mutation type ( $P > .3$ ) or whether the proband was ascertained from a population-based source independent of their family history (HR=7.8, 95% CI=5.3 to 17.4) or from a family cancer clinic (HR=4.5, 95% CI=2.3 to 9.0) ( $P$  for difference=.5).

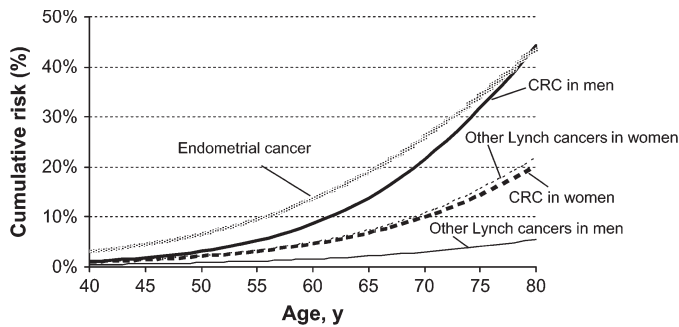
We estimated that 26% (95% CI=18% to 36%) and 44% (95% CI=30% to 58%) of women would be diagnosed with endometrial cancer by ages 70 and 80 years, respectively. The 10-year risk of endometrial cancer for *MSH6* mutation carriers without a previous endometrial cancer diagnosis at age 70 years was 24% (95% CI=14% to 36%). The 10-year risks at other ages were 7% (95% CI=5% to 11%) at age 50 years and 14% (95% CI=9% to 21%) at age 60 years (Table 4). *MSH6* mutation carriers who were women had an endometrial cancer risk that was about 25 times higher than women in the general population (HR=25.5, 95% CI=16.8 to 38.7;  $P < .001$ ).

*MSH6* mutation carriers who were women had a cumulative risk of at least one cancer of the ovary, stomach, small intestine,

**Table 3.** Age-specific cumulative risk from birth (95% confidence intervals [CIs]) for cancer in *MSH6* mutation carriers, for cancer by sex

Cancer type	Sex	Age-specific cumulative risk, % (95% CI)			
		50 y	60 y	70 y	80 y
Colorectal cancer	Male	3 (1 to 7)	9 (5 to 14)	22 (14 to 32)	44 (28 to 62)
	Female	2 (1 to 5)	5 (2 to 9)	10 (5 to 17)	20 (11 to 35)
Endometrial cancer	Female	7 (4 to 11)	14 (9 to 20)	26 (18 to 36)	44 (30 to 58)
Other Lynch cancers*	Male	1 (0 to 6)	2 (0 to 8)	3 (1 to 14)	6 (1 to 25)
	Female	2 (1 to 5)	5 (3 to 9)	11 (6 to 19)	22 (12 to 38)
Any Lynch cancer	Male	4 (2 to 9)	10 (6 to 18)	24 (16 to 37)	47 (32 to 66)
	Female	11 (7 to 16)	22 (16 to 30)	40 (32 to 52)	65 (53 to 78)
Other cancers	Male	4 (2 to 9)	9 (5 to 16)	18 (11 to 29)	33 (19 to 51)
	Female	3 (1 to 6)	6 (3 to 12)	15 (9 to 23)	30 (17 to 47)
Any cancer	Male	8 (5 to 15)	18 (13 to 27)	38 (28 to 51)	65 (51 to 80)
	Female	13 (9 to 19)	27 (21 to 35)	49 (41 to 60)	75 (65 to 86)

\* Other Lynch cancers include cancers of the kidney, stomach, ovary, small bowel, ureter, and brain.



**Figure 1.** Age-specific cumulative risks from birth of Lynch syndrome cancers for carriers of *MSH6* mutations. CRC=colorectal cancer.

kidney, ureter, or brain of 11% (95% CI=6% to 19%) by age 70 years and 22% (95% CI=12% to 38%) by age 80 years. They were at six times the population risk of Lynch syndrome cancers other than colorectal and endometrial cancers compared with the general population (HR=6.0, 95% CI=3.4 to 10.7;  $P < .001$ ). There was no evidence for an increased risk of these cancers for *MSH6* mutation carriers who were men (HR=0.8, 95% CI=0.1 to 8.8;  $P=.9$ ).

There was no evidence for an increased risk of breast cancer (HR=0.6, 95% CI=0.2 to 1.6;  $P=.3$ ), prostate cancer (HR=0.2, 95% CI=0.0 to 1.2;  $P=.08$ ), or any non-Lynch syndrome cancers among men or women. Overall, among those who carry an *MSH6* mutation, we estimate that 24% (95% CI=16% to 37%) of men and 40% (95% CI=32% to 52%) of women will be diagnosed with any Lynch syndrome cancer by age 70 years and that these values will increase to 47% (95% CI=32% to 66%) of men and 65% (95% CI=53% to 78%) of women by age 80 years.

## Discussion

We have assembled, to our knowledge, the largest series of *MSH6* mutation carrier families that has been used to estimate penetrance to date. Among *MSH6* mutation carriers, we estimated that approximately three in 10 men and one in 10 women will be diagnosed with colorectal cancer by age 70 years and that four in 10 men and two in 10 women will be diagnosed with colorectal cancer by age 80 years. In contrast to our findings, a meta-analysis (18) of

**Table 4.** Risk of cancer in 10-year intervals for *MSH6* mutation carriers at ages 50, 60, and 70 years who have had no previous diagnosis of the cancer (or group of cancers) at the beginning of the 10-year period\*

Cancer	Sex	10-y cancer risk at age, % (95% CI)		
		50 y	60 y	70 y
Colorectal cancer	Male	6 (3 to 9)	14 (8 to 22)	28 (16 to 45)
	Female	3 (1 to 5)	6 (3 to 11)	11 (4 to 23)
Endometrial	Female	7 (5 to 11)	14 (9 to 21)	24 (14 to 36)
Any Lynch cancer†	Male	6 (4 to 10)	15 (9 to 24)	31 (17 to 48)
	Female	12 (9 to 17)	24 (17 to 33)	41 (29 to 55)

\* For example, a man with no previous colorectal cancer diagnosis at age 70 years has a 28% risk for development of a colorectal cancer by age 80 years.

† Any Lynch cancers include cancers of the colorectum, endometrium, kidney, stomach, ovary, small bowel, ureter, and brain.

extracted data from just 10 families in two studies (17,20) predicted that three in 10 carriers would be diagnosed with colorectal cancer by age 70 years, with no difference between men and women, and also observed no increase in colorectal cancer risk after age 70 years. We estimated that three in 10 *MSH6* mutation carriers who were women will be diagnosed with endometrial cancer by age 70 years and that four of the 10 carriers will be diagnosed by age 80 years, whereas the meta-analysis (18) estimated that approximately three of the 10 carriers will be diagnosed with endometrial cancer by age 70 years and five of the 10 carriers will be diagnosed by age 80 years.

How do these estimates compare with those for mutations in the other mismatch repair genes—*MLH1*, *MSH2*, and *PMS2*? A meta-analysis (18) of three population-based studies (5,20,31) and one clinic-based study (24) estimated that the risk of colorectal cancer for *MLH1* and *MSH2* carriers was 53% for men and 33% for women (compared with 22% and 10%, respectively, for *MSH6* mutation carriers in this study), and the risk of endometrial cancer was 44% (compared with 26% for *MSH6* mutation carriers in this study) with no substantial increases from age 70 years to age 80 years (compared with a 10-year colorectal cancer risk at age 70 years of 28% among carriers who were men and 11% among carriers who were women in this study, albeit with large confidence intervals). For carriers of *PMS2* mutations, the risk of colorectal cancer to age 70 years was 20% among men and 15% among women and the risk of endometrial cancer was 15% (32).

The major strengths of this study are the size and the statistical methods that we used, which have resulted, to our knowledge, in the most precise and unbiased estimates produced to date and, therefore, of most clinical use of all published estimates. We acknowledge that penetrance may depend on the *MSH6* mutation, the country in which the carrier lives, and other genetic and environmental modifiers of risk; and thus, we have presented the average penetrance of all identified mutations across several countries. There was no statistical evidence of heterogeneity of the penetrance by geographic region when comparing those of Scotland with those of North America. A substantial proportion of the families for this analysis were ascertained because of a relative diagnosed with colorectal cancer at an early age; therefore, these results may be more generalizable to *MSH6* mutation carriers who have a family history of early-onset disease.

A limitation of this study was that no haplotype analysis was done for any of the mutations identified in more than one family, and so it was not possible to conclude founder mutation status. However, mutation c.651\_652insT was identified in five of the clinic-based families from the Netherlands; mutation c.1784delT was identified in four clinic-based families from the Netherlands; and mutation c.3939\_3958dup19 was identified in three population-based families from Scotland, which is consistent with a common founder for each of these mutations.

The findings of this study indicate that the screening recommendations for *MSH6* mutation carriers may vary slightly from those previously published for Lynch syndrome as a whole (Table 5). We have shown that the risk for colorectal cancer and endometrial cancer continued to increase between the ages of 70 and 80 years, although the confidence intervals for the 10-year risks are large. Our data suggest that screening for colorectal cancers should likely continue

**Table 5.** Management for at-risk members of Lynch syndrome families with *MSH6* mutation

Management	Recently published recommendations for Lynch syndrome as a whole	Levels of certainty* regarding net benefit for Lynch syndrome as a whole	Recommendations for <i>MSH6</i> mutation carriers by authors of this article
<b>Cancer screening options</b>			
Colonoscopy	Every 1–2 y beginning at age 20–25 y (age 30 y in <i>MSH6</i> families) or 10 y younger than the youngest age at diagnosis in the family, whichever comes first (33); every 1–2 y starting at age 20–25 y for men and age 30 y for women (34); every 1–2 y starting at ages 20–25 y (3)	High†	Every 1–2 y beginning at age 30 y‡
Endometrial sampling	Every year beginning at age 30–35 y (33); every 1–2 y starting between ages of 30 and 35 y (34)	Moderate (when combined with transvaginal ultrasound) (35)	Every year beginning at age 30–35 y‡
Transvaginal ultrasound for endometrial and ovarian cancers	Every year beginning at age 30–35 y (33); every 1–2 y starting at age 30–35 y (34); every 1–2 y starting between ages of 30 and 35 y (3)	Poor	Every year beginning at age 30–35 y. Role of serological markers for ovarian cancer screening is uncertain
Urinalysis with cytology	Every 1–2 y beginning at age 25–35 y (33) or beginning at age 50 y (34); every 1–2 y starting between ages of 30 and 35 y if urinary tract cancer runs in family (3)	Poor	Consider every 1–2 y beginning at age 40 y
Gastroduodenoscopy	“Could be offered periodically” (33); every 1–2 y starting at age 30–35 y if it occurs two or more times in the family (34); every 1–2 y starting between ages of 30 and 35 y if gastric cancer runs in family or in countries with high incidence of gastric cancer (3)	Poor	No evidence of increased risks except by analogy to other genes causing Lynch syndrome
<b>Surgical considerations</b>			
Colorectal resection (segmental vs subtotal colectomy vs complete proctocolectomy)	For at-risk persons without colorectal cancer: generally not advised. Discuss as alternative, with preferences of well-informed patient actively elicited. For persons with a diagnosis of colorectal cancer or polyp not resectable by colonoscopy, subtotal colectomy favored with preferences of the well-informed patient actively elicited (33). The option of extensive resection should be discussed with patients younger than 50 y at colorectal cancer diagnosis (3)	Poor	No change in recommendations
Hysterectomy or salpingo-oophorectomy	Discuss as option after childbearing completed (33); may be an option for women as it substantially reduces site-specific cancers (3)	Moderate	No change in recommendations

\* The United States Preventative Services Task Force changed its grade definitions on the basis of a change in methods in May 2007 (36).

† Quality of evidence supports colon examination, but optimal frequency and initiation age have not been adequately addressed.

‡ In the cohort of relatives of the *MSH6* mutation families, three (1.2%) of the 241 colorectal cancer diagnoses occurred at or before age 30 years, zero of the 129 endometrial cancer diagnoses occurred at or before age 30 years, and seven (5.4%) of the 129 endometrial cancer diagnoses were diagnosed between ages of 30 and 35 years.

into advanced years, being discontinued only when the risk of the procedures outweighs the risk of development of a cancer. Careful discussion between doctor and patient will be required to reach an optimal decision on when or if that point has been reached.

For the management of gynecological cancers, the evidence supporting the use of screening is moderate to poor (35) and, therefore, underscores the consideration of risk-reducing bilateral salpingo-oophorectomy and hysterectomy at a premonitory age. Endocervical

stenosis may render annual endometrial sampling increasingly difficult in many postmenopausal women. Cancer screening and prevention in men and women with Lynch syndrome remain a subject in flux, with much promise of noninvasive screening on the horizon for some cancers including ovarian (37) and urothelial (38) cancers.

In conclusion, by aggregating data from 113 families that contained approximately 1000 mutation carriers from five countries and analyzing the data with statistical methods that

allow for conditioning on ascertainment, we have provided the most precise cancer-specific estimates of penetrance to date for carriers of *MSH6* mutations. These results demonstrate that the elevated risks for cancers in *MSH6* mutation carriers differ by sex of the carrier and continue into older age.

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## Notes

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