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MSH2 Mutation Carriers Are at Higher Risk of Cancer Than MLH1 Mutation Carriers: A Study of Hereditary Nonpolyposis Colorectal Cancer Families

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Purpose: Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant disease characterized by the clustering of colorectal cancer, endometrial cancer, and various other cancers. The disease is caused by mutations in DNA-mismatch-repair (MMR) genes, most frequently in *MLH1*, *MSH2*, and *MSH6*. The aims of the present study were to compare the risk of developing colorectal, endometrial, and other cancers between families with the various MMR-gene mutations.

Patients and Methods: Clinical and pathologic data were collected from 138 families with HNPCC. Mutation analyses were performed for all families. Survival analysis was used to calculate the cumulative risk of developing cancer in the various subsets of relatives.

Results: Mutations were identified in 79 families: 34 in *MLH1*, 40 in *MSH2*, and five in *MSH6*. The lifetime risk of developing cancer at any site was significantly

higher for *MSH2* mutation carriers than for *MLH1* mutation carriers ($P < .01$). The risk of developing colorectal or endometrial cancer was higher in *MSH2* mutation carriers than in *MLH1* mutation carriers, but the difference was not significant ($P = .13$ and $P = .057$, respectively). *MSH2* mutation carriers were found to have a significantly higher risk of developing cancer of the urinary tract ($P < .05$). The risk of developing cancer of the ovaries, stomach, and brain was also higher in the *MSH2* mutation carriers than in the *MLH1* mutation carriers, but the difference was not statistically significant.

Conclusion: Pending large prospective studies, the extension of the current surveillance program in *MSH2* mutation carriers with the inclusion of the urinary tract should be considered.

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HEREDITARY NONPOLYPOSIS colorectal cancer (HNPCC) is an autosomal dominant disease characterized by the development of cancer of the colorectum and endometrium and, less frequently, cancer of the stomach, urinary tract, ovaries, small bowel, and brain.¹ It is caused by mutations in DNA-mismatch-repair (MMR) genes, predominantly in *MLH1*, *MSH2*, and *MSH6* and rarely in *PMS1* and *PMS2*.² Most estimates of colon cancer risk are derived from families collected at HNPCC registries and vary between 60% and 85%.^{3,4} A recent study on the cancer risk in mutation carriers identified in a population-based series

of patients with early-onset colorectal cancer reported a significantly lower colorectal cancer risk in female mutation carriers.⁵ The reported risk of developing endometrial cancer is approximately 40% to 50%.³⁻⁵

It is yet to be resolved whether there is a difference in cancer risk between carriers of the various MMR-gene mutations. Knowledge about this possible difference in risk might be important to assist physicians' decisions on surveillance programs.

Previous studies showed that there was no difference in risk of colorectal and endometrial cancer between *MSH2* and *MLH1* mutation carriers.³ However, Danish investigators have reported that the risk of endometrial cancer is significantly lower in families with a specific *MLH1* mutation,⁶ and a recent study by our group suggested that families with *MSH6* mutations seemed to have a higher risk of developing endometrial cancer than families with *MSH2* and *MLH1* mutations.⁷ Regarding the less common extracolonic cancers, one study suggested that patients with *MSH2* mutations have a higher relative risk of developing extracolonic cancers than patients with *MLH1* mutations.³

All studies published at the present time on the cancer risk in HNPCC have been hampered by a relatively small number of patients. We, therefore, evaluated the lifetime risk of developing cancer in a large series of families with identified mutations. The specific aims of the present study were (1) to compare the cancer risk between families with *MLH1*, *MSH2*, and *MSH6* mutations and families with a

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Table 1. Number of Families, Patients With Colorectal and Endometrial Cancer, and Their First-Degree Relatives According to Type of Mutation Detected

	Mutated Gene			Amsterdam Families Without Mutation	Total
	<i>MLH1</i>	<i>MSH2</i>	<i>MSH6</i>		
No. of families	34	40	5	60	139
No. of family members	917	925	107	1,273	3,222
No. of patients with colorectal cancer	137	143	15	209	504
No. of patients with endometrial cancer	26	34	4	16	80
No. of first-degree relatives	754	748	78	1,048	2,638

not-yet-identified mutation who meet the Amsterdam criteria, and (2) to discuss the consequences for surveillance.

PATIENTS AND METHODS

HNPCC Registry

The Netherlands HNPCC registry was established in 1987. The methods used by the registry have been reported previously.⁸ The aims of the registry on its establishment were to promote surveillance in families with HNPCC and to guarantee follow-up examinations. Families with clustering of colorectal cancer were referred to the registry from all parts of the Netherlands. Pedigree analysis was performed by social workers or clinical geneticists. The pedigrees were traced backward and laterally as far as possible. Most pedigrees contain information on three generations. The data collected at the registry included personal and medical data on each affected and unaffected family member. The information on the cancer diagnosis was verified by medical or pathologic reports. From January to July 2000, a total of 193 families were registered. The collection of information was completed in all 193 families. A total of 116 families met the Amsterdam Criteria I or II, and the other 77 families were suspected of HNPCC.⁹ Mutation analysis has been performed in all families. Also, 58 families suspected of HNPCC known at the Clinical Genetic Centre Radium Hospital (Oslo, Norway) were investigated by mutation analysis.

Molecular Genetics Study

The techniques used in the mutation analysis have been reported previously.¹⁰ In short, the general strategy was to amplify by polymerase chain reaction each of the 16 exons of *MSH2*, the 19 exons of *MLH1* and 10 exons of *MSH6* in a single affected member in each family, and to analyze these products by GC-clamped denaturing gradient gel electrophoresis (DGGE). To determine the molecular nature of the variant, exons with an altered pattern of migration on DGGE were sequenced. When variants were detected, the investigations were extended, if possible to the rest of the family, to verify the segregation of the nucleotide change with the disease phenotype. Southern blot analysis for *MSH2*, *MSH6*, and *MLH1* was done on all patients negative in the DGGE screening.¹⁰

Risk Analysis

The families were subdivided into families with the various MMR-gene mutations and families without a mutation who met the Amsterdam I or II criteria. In all subsets of the families, three groups were regarded as mutation carriers: those relatives affected with cancer of the colorectum or endometrium, called putative carriers (which excluded the colorectal or endometrial cancer patients with a proven noncarrier status); relatives found to be carrying a mutation; and

relatives who were considered to be obligate carriers because of their position in the pedigree in relation to relatives with a mutation. The cumulative risk by age was calculated using Kaplan-Meier survival analysis methods. Only the cancers verified by medical or pathologic reports were included in the calculations. The observation time was from birth until date of diagnosis of cancer, death, or to the end of the study in July 1, 2000. Differences in survival curves were tested for statistical significance on the basis of the log-rank test. With respect to the Norwegian families, only those with an identified mutation were included in the calculations.

RESULTS

Pathogenic mutations were found in 71 Dutch and eight Norwegian families: 34 in *MLH1*, 40 in *MSH2*, and five in *MSH6*. All mutations predicted truncation of the protein-product. Table 1 shows the number of patients with colorectal cancer, endometrial cancer, and their first-degree relatives in the families with or without a mutation. The mean age at diagnosis of colorectal cancer was higher in carriers of *MSH6* mutations (mean age, 50.1 years; range, 26 to 69 years) compared with the age at diagnosis of colorectal cancer in carriers of *MLH1* (mean age, 42.8 years; range, 16 to 81 years) and *MSH2* mutations (mean age, 43.9 years; range, 16 to 90 years).

Table 2 shows the frequency of other cancers observed in the various categories of families. Substantially more cancers were observed in families with an *MLH1* or *MSH2* mutation compared with families with an *MSH6* mutation and families that met the Amsterdam Criteria without an identified mutation. We did not observe any difference in phenotype between families with a null mutation (nonsense mutation and genomic rearrangements) and those with a splice site mutation.

The lifetime risk of developing cancer at any site was significantly higher ($P < .01$) in *MSH2* mutation carriers than in *MLH1* mutation carriers (Fig 1). The cumulative risk of developing colorectal cancer by age in *MLH1* and *MSH2* mutation carriers is shown in Fig 2. The risk of developing colorectal cancer was higher in *MSH2* mutation carriers than in *MLH1* mutation carriers ($P = .13$). Overall, the risk of developing colorectal cancer in male mutation carriers was higher than the risk of colorectal cancer in female mutation carriers, but the difference was

Table 2. Number of Other Cancers in Patients With Colorectal and/or Endometrial Cancer and Their First-Degree Relatives According to Type of MMR Gene Mutation

Type of Mutation	<i>MLH1</i>			<i>MSH2</i>			<i>MSH6</i> No.	Amsterdam Families Without Mutation		
	No.	Mean Age (years)	Range (years)	No.	Mean Age (years)	Range (years)		No.	Mean Age (years)	Range (years)
No. of families	34			40			5	59		
Site of cancer										
Stomach	6	53	39-74	15	51	23-82	0	8	68	36-77
Urinary tract	4	63	52-72	14*	56	40-72	0	3	50	37-70
Small bowel	9	50	25-67	7	51	31-69	0	3	54	39-65
Ovary	6	51	35-75	13	45	37-58	0	5	43	19-57
Brain	3	45	21-78	10	41	2-73	0	3	56	36-69

*One patient had two primary urinary tract cancers.

only statistically significant for *MSH2* mutation carriers ($P < .01$) (Fig 3). The cumulative risk by age of developing endometrial cancer is shown in Fig 4. The risk of developing endometrial cancer was higher in *MSH2* mutation carriers than in *MLH1* mutation carriers ($P = .057$).

Table 3 shows the cumulative risk of developing various cancers by age 70 in the putative mutation carriers. *MSH2* mutation carriers were found to have a significantly higher risk of developing cancer of urinary tract (cumulative risk by age 70, 12%; $P < .05$). The risk of developing cancer of the stomach, ovary, and brain was also higher in the *MSH2* mutation carriers than in the

MLH1 mutation carriers, but the difference was not statistically significant. There was no difference in the risk of developing cancer of the small bowel between the two groups of mutation carriers. Altogether, 21 cases of urinary tract cancer were observed in 20 patients from 17 families (of which 15 were in putative gene carriers). There was one family with three cases of urinary tract cancer and two families with two cases in each. In the other families there was one case in each family. In addition, a total of 24 cases of ovarian cancer were found in 20 families (of which 13 were in putative gene carriers). In four families there were two cases, and in the remaining families there was one case per family.

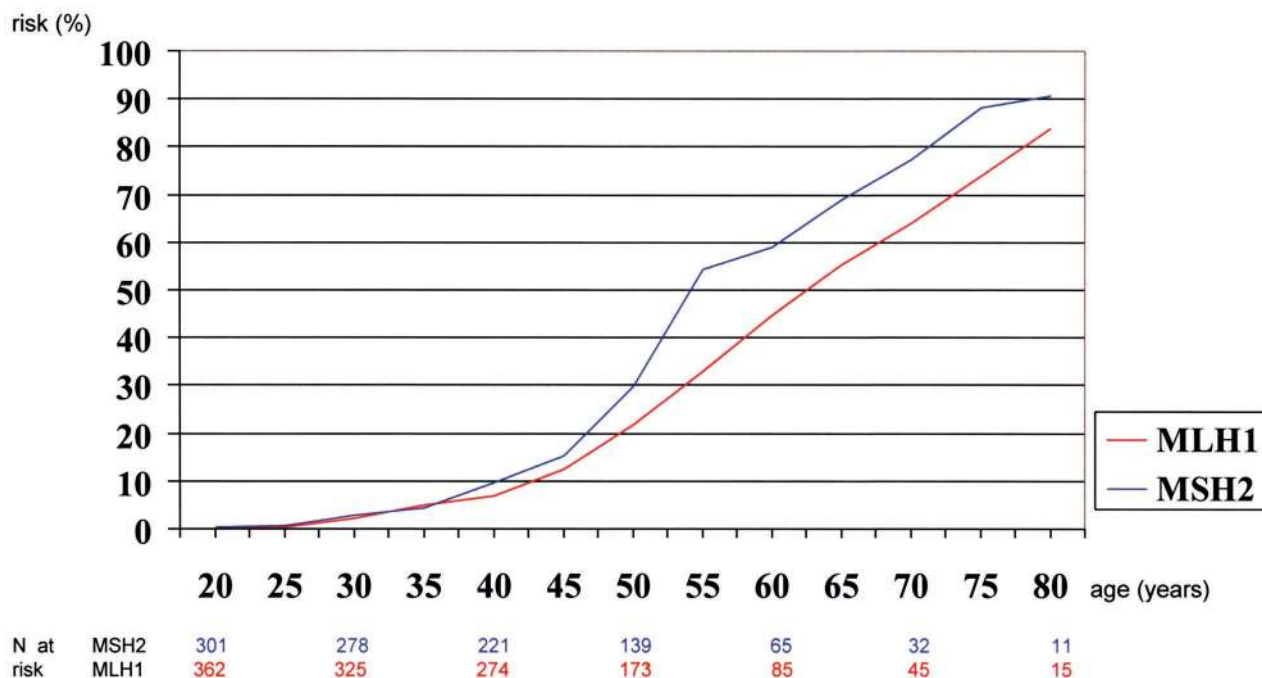


Figure 1. Cumulative risk of developing any cancer by age in putative carriers of mutations in *MLH1* and *MSH2*.

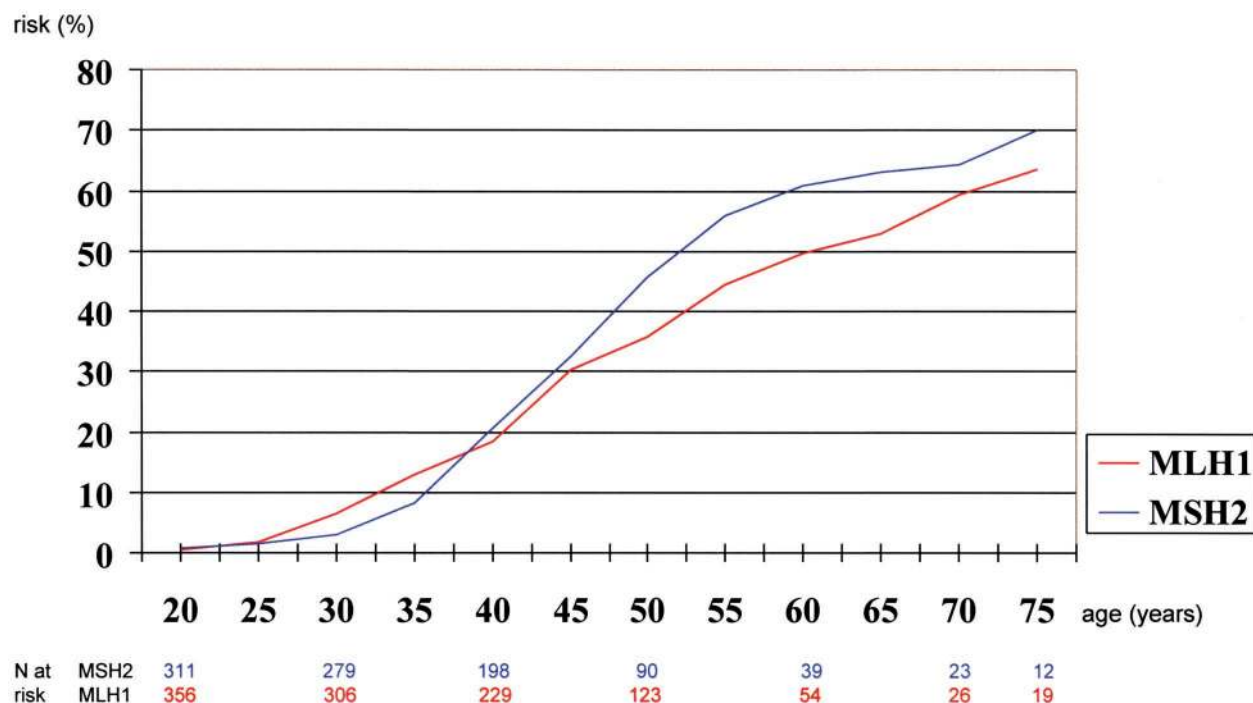


Figure 2. Cumulative risk of developing colorectal cancer by age in putative carriers of mutations in *MLH1* and *MSH2*.

DISCUSSION

In the present study, we compared the incidence of cancer between HNPCC families with *MLH1*, *MSH2*, and *MSH6* mutations and those without a known mutation who met the Amsterdam Criteria I or II. We found a significantly increased overall risk for developing cancer in *MSH2* mutation carriers compared with carriers of *MLH1* mutations. In addition, in *MSH2* mutation carriers there was a significantly higher risk for cancer of the urinary tract (renal pelvis and ureter) than was the case in *MLH1* mutation carriers. Also, compared with the risk in *MLH1* mutation carriers, the risk of endometrial, ovarian, stomach, and brain cancer was greater in *MSH2* mutation carriers. However, this difference was not statistically significant.

There was some evidence for clustering of urinary tract and ovarian cancer in some families. This phenomenon was also described by Watson and Lynch.¹¹ Possible explanations for this variation in expression among families are the presence of modifying genes or the influence of environmental factors.

The results of our study might have been biased in different ways. First of all, the criteria for referral to the National HNPCC registry were familial clustering of colorectal cancer. Therefore, the ascertainment of the families might have led to overestimation of the risk of developing

colorectal cancer. However, we don't expect that the estimated risk of extracolonic cancers and the observed differences in risk of developing colorectal cancer between the various groups of mutation carriers were biased by the way of ascertainment of the families. Secondly, the outcome of the present study might be influenced by the fact that only patients who survived were available for mutation analysis, which led to overrepresentation of tumor types with a favorable prognosis, such as tumors of the endometrium and colorectum, and underrepresentation of tumors with a less favorable prognosis, such as tumors of the brain and stomach.

Recently, Aarnio et al¹² assessed the cancer risk in a large series of Finnish HNPCC families. Although the results of the two studies cannot properly be compared, as the cancers in the Finnish families mainly resulted from *MLH1* mutations (47 of the 50 families), there were several conspicuous differences between them. The reported risk of cancer of the stomach was substantially higher in the Finnish families than the risk of these cancers in the Dutch *MLH1* mutation families. In addition, patients with small bowel cancer were not observed in the Finnish families. The same environmental factors that are responsible for the higher incidence of stomach cancer in the general population of Finland compared with the Dutch population may be responsible for the

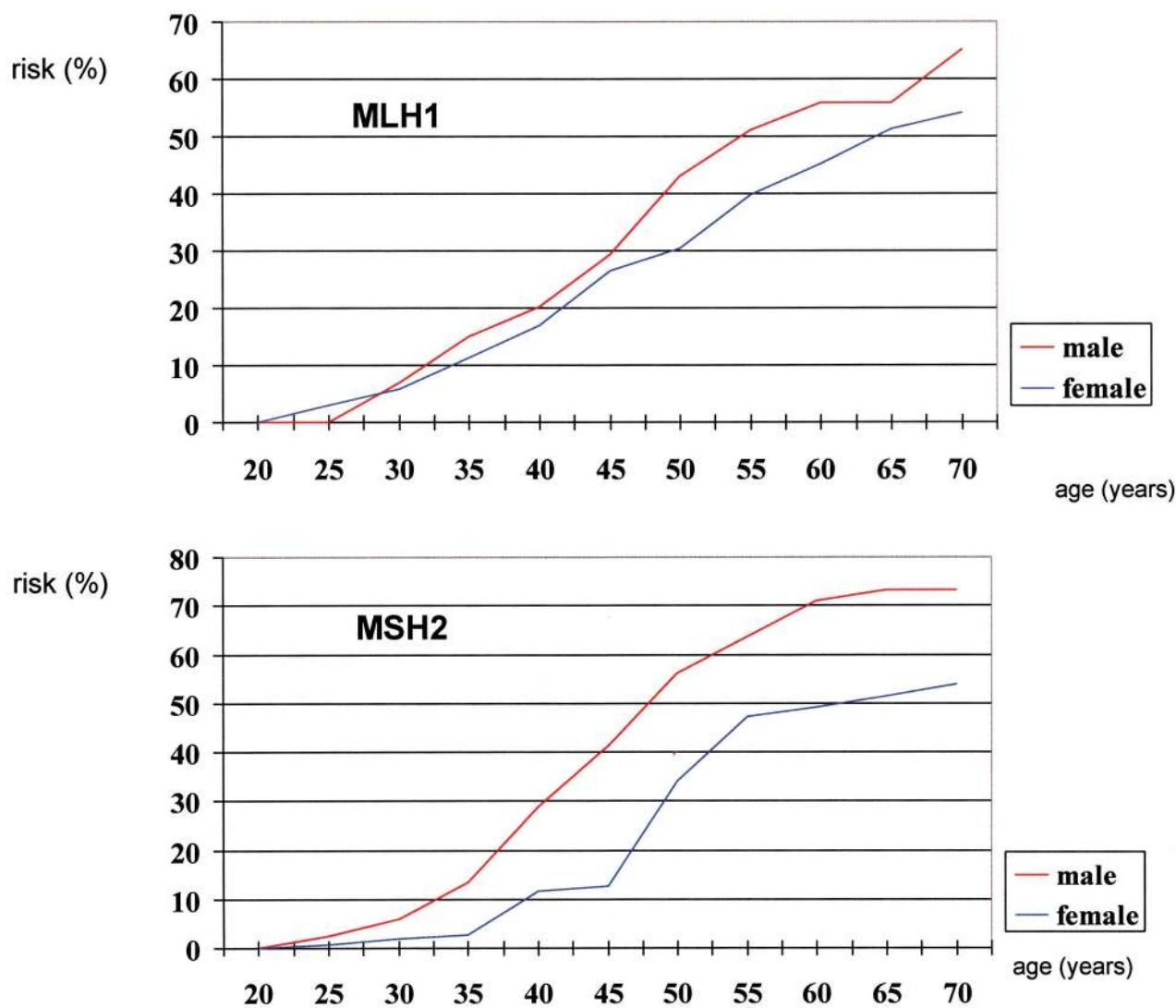


Figure 3. Cumulative risk of developing colorectal cancer by age and sex in putative carriers of mutations in *MLH1* and *MSH2*.

differences in incidence between the Dutch and Finnish *MLH1* families. Similar differences have been observed between Dutch and Korean HNPCC families.¹³

An intriguing question is why *MSH2* mutations are associated with a higher risk of developing cancer than *MLH1* mutations. The *MSH2* protein forms with other mutS homologues two different mutS protein complexes (*MSH2/MSH6* and *MSH2/MSH3*) that recognize mispaired bases in DNA. The *MLH1* protein forms with *PMS2* a protein complex that interacts with the mutS protein complex bound to the mispaired DNA. After binding of these complexes, excision of the mispaired DNA occurs, followed by DNA resynthesis.¹⁴ In this process both *MSH2* and *MLH1* proteins play a critical role, and mutations in either genes result

in a complete loss of function. However, a difference between *MLH1* and *MSH2* is the role that *MSH2* plays in the control of the homologous recombination of two identical DNA-strands. If the DNA-strands differ more than 1%, the *MSH2* protein prevents recombination.¹⁵ Moreover, *MSH2* seems also to be involved in some pathways of transcription-coupled repair. This diversity in function might be responsible for the variation in cancer risk.

The clinical phenotype of families with *MSH6* mutations is still unknown. The first families reported in the literature were characterized by a late onset of colorectal cancer.^{16,17} Also, in the present study, the mean age at diagnosis of colorectal cancer was higher than the age at diagnosis in families with *MLH1* and *MSH2* mutations. Recent analysis of

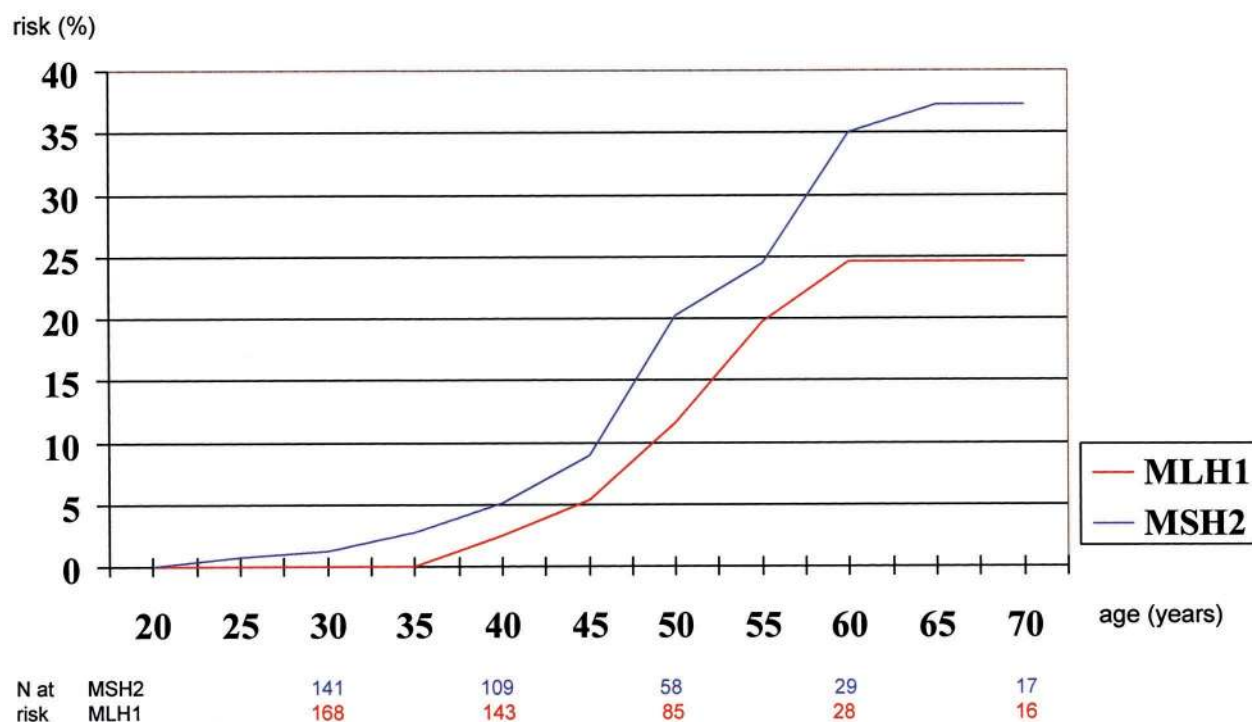


Figure 4. Cumulative risk of developing endometrial cancer by age in putative carriers of mutations in *MLH1* and *MSH2*.

families with *MSH6* mutations revealed a remarkably high incidence of endometrial cancer.^{7,18} The reported series even included families exclusively with endometrial cancer. The observation of predominantly colorectal cancer in the families with *MSH6* mutations reported in the present series might be attributed to the fact that the main criteria for referral of families to the HNPCC Registry was familial clustering of colorectal cancer. More studies—preferably studies that use less strict criteria for the selection of families for mutation

analysis¹⁸—are needed to provide reliable estimates of cancer risk in *MSH6*-associated families.

In our series, we found that the colorectal cancer risk was higher in male mutation carriers than in female mutation carriers. This is in parallel with the higher risk of developing colorectal cancer in males compared with females in the general population in the Netherlands. A sex difference in colorectal cancer risk in carriers of mismatch repair gene mutations was also reported by other investigators.^{5,12,19}

Table 3. Cumulative Risk (%) of Developing Cancer by Age in Carriers of *MLH1* or *MSH2* Mutations

Age (years)	<i>MLH1</i>					<i>MSH2</i>				
	40	50	60	70	95% CI	40	50	60	70	95% CI
Stomach*	—	0.4	2.1	2.1	0-4.7	0.7	1.2	4.3	4.3	0.5-8.1
Urinary tract†	—	—	—	1.3	0-3.9	0.4	1.5	5.4	12	3.5-20
Small bowel‡	—	0.7	4.0	7.2	1.5-12.9	0.8	1.2	4.5	4.5	0.5-8.5
Ovary§	0.6	2.3	3.4	3.4	0-6.8	1.7	6.4	10.4	10.4	3.2-17.6
Brain	—	—	—	—	—	1.2	1.2	1.2	1.2	0-2.6

Abbreviation: CI, confidence interval.

*Stomach: *MLH1* v *MSH2*: *P* = .13

†Urinary tract: *MLH1* v *MSH2*: *P* < .05

‡Small bowel: *MLH1* v *MSH2*: *P* = .8

§Ovarian cancer: *MLH1* v *MSH2*: *P* = .11

||Brain tumor: *MLH1* v *MSH2*: *P* = .06

According to the guidelines proposed by the International Group on HNPCC, surveillance of the colorectum and endometrium (including the ovaries) is recommended for all mutation carriers, and surveillance of other sites (eg, the urinary tract and stomach) for mutation carriers from families that include such types of cancers. In this study, *MSH2* mutation carriers have a significantly increased risk of developing cancer of the urinary tract. An extended surveillance program, including surveillance of the urinary tract, should, therefore, be considered in *MSH2* mutation carriers, pending the outcome of large prospective studies. The recommended protocol of screening for urinary tract cancer includes cytologic examination of the urine and sonography starting at age 30 to 35 years at 1- to 2-year intervals. However, the sensitivity and specificity of these tests are yet unknown.²⁰ The protocol of screening of the endometrium and ovaries includes annual transvaginal sonography and estimation of CA-125 starting at age 30 to 35 years. Prophylactic oophorectomy might be considered

for women older than 40 years with a complete family. Because also the value of surveillance of the endometrium and ovaries is unknown, periodic examination should ideally be performed in the setting of a prospective study. In the follow-up of mutation carriers, it is important to realize that the family members may develop cancer at sites that are not included in the surveillance program. Therefore, clinicians managing HNPCC patients should always be alert when the patient exhibits unusual symptoms.

In conclusion, our study indicates that there are substantial differences in cancer risk between *MLH1* and *MSH2* mutation carriers. On the basis of these results, a more extended screening program might be considered for *MSH2* mutation carriers. Because there is some evidence that other factors, such as environmental/life style factors, and modifier genes play a role in the carcinogenesis, not only the type of the mutated MMR gene but also the phenotype of the disease in the family should be taken into account in the decision as to which surveillance protocol should be recommended.

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