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Long term follow-up of HNPCC gene mutation carriers: Compliance with screening and satisfaction with counseling and screening procedures

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Abstract

Hereditary Non Polyposis Colorectal Cancer (HNPCC) is a hereditary predisposition to colorectal and endometrial cancer, caused by mutations of the mismatch repair (MMR) genes *MSH2*, *MLH1* and *MSH6*. Regular colonoscopy reduces the incidence of colorectal cancer in mutation carriers dramatically. The aim of this study was to evaluate the use of colonoscopy by proven HNPCC mutation carriers. We also evaluated the satisfaction with the counseling and screening procedures at the long term. A questionnaire survey was performed among 94 proven MMR gene mutation carriers. Data were analyzed using univariate and multivariate analysis. The average time of follow-up was 3,5 years (range 0.5-8.5 years). The response rate was 74%. The proportion of unaffected mutation carriers under colonoscopic screening increased from 31% to 88% upon genetic testing, and for gynecological screening from 17% to 69%. However, more than half of the responders experienced colonoscopy as unpleasant or painful. About 97% felt well informed during counseling, and 88% felt sufficiently supported. Ten percent of the responders reported a high cancer worry, that was significantly ($p=0.007$) associated with a high perceived cancer risk. Six responders (9%) regretted being tested. Remarkably, of 4 of these 6 a close relative died recently of cancer. Problems with obtaining a disability or life insurance or mortgage were experienced by 4 out 10 healthy carriers opting for these services. In conclusion, genetic testing for HNPCC considerably improves compliance for screening, which will result in a reduction of HNPCC related cancer morbidity and mortality in mutation carriers. Most HNPCC gene mutation carriers cope well with their cancer susceptibility on the long term.

Introduction

Hereditary Non-Polyposis Colorectal Cancer (HNPCC, OMIM #114500) is an autosomal dominantly inherited predisposition to colorectal and endometrial cancer. It is caused by germline mutations of mismatch repair (MMR) genes, particularly *MSH2*, *MLH1* and *MSH6* [1-4]. MMR gene mutation carriers have cumulative lifetime risks of colorectal and endometrial cancer of 70-90% and 30-40%, respectively [5-8]. Also cancers of the stomach, ovaries, small bowel, urinary tract, skin and brain occur in mutation carriers, but the cumulative lifetime risks of each of these tumors do not exceed 15% [5-8].

The identification of MMR gene mutations in HNPCC enabled genetic testing within families with HNPCC. In the context of a known mutation in the family,

identification of individuals with or without the mutation is possible by DNA testing. Non-mutation carriers will be relieved from anxiety and can be dismissed from regular screening programs, while individuals with the mutation may benefit from these procedures. Colonoscopy was shown a potent tool for the detection and treatment of premalignant adenomas or early colorectal carcinomas in individuals at risk of HNPCC. Järvinen et al. [9] reported a decrease of overall mortality of about 65% by regular colonoscopy within this group. However, colonoscopy is an invasive screening technique with a clear burden and some risk [10]. The efficacy of screening for extra-colonic tumors in HNPCC carriers, like gynecological screening, is controversial [11, 12]. To date little is known about cancer screening practices among proven MMR gene mutation carriers. At a follow-up of 12 months Hadley et al. [13] reported a slight increase (41% to 53%) of colonoscopic screening among 17 MMR gene mutation carriers.

Here we evaluate the use of regular colonoscopy by proven MMR gene mutation carriers on the long term. In view of the significant psychosocial impact of genetic testing and related surveillance strategies, we simultaneously evaluated the long-term satisfaction with the counseling procedure and the screening program.

Patients and methods

Between November, 1994 and December, 2002, 115 MMR gene mutation carriers were identified at the Department of Clinical Genetics of Erasmus MC. Questionnaires were sent to carriers with known addresses and who were still alive on May 2003.

The counseling procedure was as follows. In the search for the causative MMR gene mutation within a family, we initially invited the relatives affected with an HNPCC related tumor for genetic testing. After identification of a pathogenic mutation, the initial counselees were asked to inform all adult first and second-degree relatives of patients with an HNPCC related tumor about the possibility of genetic testing. Written information to distribute among their family members was available to them. This information included facts on the inheritance of the cancer susceptibility in their family, the possibility of genetic testing, the risks of developing cancer, and the options for intervention. Relatives opting for genetic testing received one or more individual pre-test counseling sessions according to the recommendations of the American Society of Clinical Oncology [14]. Psychological support was offered to all subjects throughout the testing procedure. Disclosure of the test results followed within 6-12 weeks after blood sampling. Mutation carriers were referred to

local specialists for follow-up and surveillance. The advised colonic screening consisted of colonoscopy every 1-2 year from the age of 20-25 years on. The procedure was generally prepared by PEG-solution with or without fluid diet and performed under sedation. Female carriers were offered gynecological screening by vaginal ultrasound and CA125-maesurement in blood from the age of 30-35 years on. Additional screening advices for the stomach, duodenum or urinary tract were occasionally given, based on family history.

Our questionnaire addressed sociodemografic characteristics, experience with HNPCC related cancer, compliance with screening, satisfaction with the screening methods and counseling procedure, knowledge and perception of cancer risks, and discrimination by insurance companies. Sociodemographic characteristics included age, gender, marital status, highest level of education, employment and number and age of children. The use of pre- and post-test screening was asked (1=no; 2=yes), including the frequency and method of screening. Satisfaction with the screening methods and counseling procedure was rated on a 5-point scale and classified in 2 groups. Group 1, the *satisfied* group, scored 1, 2, or 3, and group 2, the *unsatisfied* group, scored 4 or 5. Since an HNPCC related colorectal cancer risk of about 80% had generally been counseled, reported colorectal cancer risks for MMR mutation carriers were scored as underestimated or overestimated if lower than 70% and higher than 90% respectively. Perceived colorectal cancer risk was rated on a 5-point scale and classified in 3 groups. Group 1, the *low* risk group, scored 1 or 2, the *intermediate* group scored 3, and the *high* risk group 4 or 5. For the evaluation of cancer worry three questions based on the "cancer worry scale" of Lerman et al. [15] were used, addressing (1) how often the mutation carrier worried about developing colorectal cancer and whether the carrier's (2) mood or (3) daily activities were impaired by these worries. Response scales varied from 1="almost never" to 4="always". Thus, the range of the total score of these three questions was 3-12. The level of worry was interpreted as *low (*when all three questions were answered by "almost never", total score =3), as *intermediate* (total score: 4-6) or as *high* (total score: 7-12). Interference of the genetic status with work and insurance were asked for (1=no; 2=yes), differentiating the type of insurance (health insurance, mortgage, life and disability insurance).

All data analyses were done with the program SPSS for Windows (version 9.0). Differences in sociodemographic characteristics between individuals affected and not-affected with an HNPCC related tumor, differences in compliance with screening before and after genetic testing and differences between reported HNPCC related risk, perceived

risk and cancer worry between groups were tested by Pearson's Chi square test, a Fisher's exact test, or a Mc Nemar Chi square test. Multiple logistic regression analysis was used to determine factors associated with reporting a wrong HNPCC related colorectal cancer risk. All *P* values were two sided. *P* values less than 0.05 were considered significant.

Results

We identified 24 families with a MMR gene germline mutation (11 of *MSH2*, 10 of *MLH1* and 3 of *MSH6*), encompassing 115 mutation carriers. Questionnaires were sent to 94 individuals (the remaining had died or had moved to unknown addresses). Of the 94 questionnaires, 70 were received back, resulting in a response rate of 74%. Of the 70 responders 24 (34%) were male and 46 (66%) were female, and 28 individuals (40%) were already diagnosed with an HNPCC related tumor at the time of testing (17 with colorectal cancer, 8 with endometrial cancer and 3 with both colorectal and endometrial cancer)(Table 1). There was no significant difference in gender and parenthood between the affected and not affected responders (Table 1). However, the responders affected with an HNPCC related tumor were significantly older than the not affected responders ($p<0.001$). The 24 non-responders did not differ significantly from the responders with respect to gender, clinical status, age and parenthood (data not shown). The average time of follow-up from the individual genetic diagnosis was 3,5 years (range 0.5-8.5 years).

Thirty-one percent of the unaffected risk carriers had regular colonoscopy before genetic testing (Table 2); 62% every 2 years, and 38% less frequent. The vast majority (79%) of individuals who had no screening prior to genetic testing was not aware of being at increased risk for colorectal cancer. After being identified as a mutation carrier, 88% of the healthy risk carriers indicated to have colonoscopic screening every 1-2 year. Five individuals refrained from colonoscopic screening so far; one because of the burdensome procedure, one because of lack of time due to a busy lifestyle, and three individuals planned to go for screening in the near future. Gynecological screening was performed in three of 18 unaffected female risk carriers (17%) that were over 35 years before the genetic test (Table 2). At the time of the questionnaire 20 of 29 female mutation carriers (69%) over 35 years of age had had gynecological screening. Noteworthy, endometrial cancer had occurred in the families of 7 of the 9 women not opting for gynecological screening. We cannot exclude that some of these women had had hysterectomy for non-malignant reasons.

Fifty-seven percent of the healthy carriers experienced colonoscopy as unpleasant (Table 3), 32% as fearful, 51% as painful, 16% as shameful, and 14% as hazardous. The majority (71%) would prefer a less burdensome screening technique. About 90% of the carriers believed that screening reduced colorectal cancer risk. Ten of the 37 (27%) healthy risk carriers that underwent colonoscopic screening reported the detection of colorectal polyps. No colorectal cancers were detected during the study period.

Eighty-eight percent of the mutation carriers judged the way they were informed about the possibility of genetic testing for HNPCC as appropriate (Table 4). Also, the information about HNPCC given during counseling was judged sufficiently by 97%. However, almost one third of the mutation carriers with a previous HNPCC related cancer and half of the healthy individuals would have liked information about life-style adjustments and/or food supplements to prevent cancer. Also, updates about new developments on the field of HNPCC were appreciated on the long term.

Interestingly, 63% of the respondents affected by an HNPCC related cancer and 37.5% of the unaffected underestimated the HNPCC related cumulative lifetime colorectal cancer risk (Table 5). Reporting an incorrect HNPCC related risk was in the univariate analysis associated with age and being affected with an HNPCC related tumor, but in the multivariate analysis only with age (Table 6). About half of the respondents experienced their own colorectal cancer risk as high (Table 5).

Sixty-nine percent of the mutation carriers reported some degree of cancer worry, of whom 10% a high level (Table 7). This worry was significantly ($p=0.007$) associated with a high perceived colorectal cancer risk. Clinical status, gender, age, parenthood and reporting high or correct HNPCC related colorectal cancer risks, were not significantly associated with cancer worry. However, our study group may be too small to detect more subtle associations. Eight mutation carriers had expected more support from the genetic department (Table 4), mainly with respect to the arrangement of screening and the psychological handling of cancer risks.

Regret of genetic testing was reported by six respondents (9%). They stated that they would not choose for genetic testing for the familial MMR gene mutation with their current knowledge and experience (Table 4). Within this subgroup, four had recently lost a relative because of cancer, three had high levels of cancer worry, three expected to die of cancer despite screening, and one had insurance problems.

Insurance problems regarding disability, life insurance or mortgage, were reported by 4 out of 10 unaffected respondents, who opted for these services (Table 4). None indicated problems with getting a job or health insurance.

Discussion

We show that genetic testing largely improved colorectal and gynecological screening compliance in the studied group of proven HNPCC risk carriers (from 31% to 88% and from 17% to 69% respectively). This can be expected to lead to a considerable reduction in HNPCC related morbidity and deaths in this group.

Although, the vast majority (90%) of healthy risk carriers has faith in the efficacy and safety of the colonoscopic screening, it is certainly experienced as an invasive and burdensome technique. A main effort should be made to improve preventive options in this group of risk carriers that faces a life-long colorectal screening.

Almost two-thirds of the responders affected with an HNPCC related tumor and a third of the not affected report a lower HNPCC related cumulative lifetime colorectal cancer risk than counseled. Also, only about half of the responders perceived their own colorectal cancer risk as high. Underestimation of colorectal cancer risks by HNPCC carriers was previously described by Aktan et al. [16]. It may be due to coping strategies to deal with the personal colorectal cancer risk and to failing memory [16, 17]. Less accurate recollection of risks is also correlated with age. Since the affected responders are significantly older than the not affected, this may be an explanation for the difference in reported HNPCC related colorectal cancer risks between the responders affected and not affected with an HNPCC related tumor.

On the long term most MMR gene mutation carriers tested at our department were able to cope with having this cancer predisposition. The vast majority of proven carriers judged the information and support they received during the counseling procedure as sufficient. Noteworthy, 59% would have appreciated updates on scientific developments regarding HNPCC. High cancer worry regarding their colorectal cancer risk was indicated by 10% of the responders (3 affected and 4 not affected with an HNPCC related tumor). This is comparable to the figures presented by Aktan et al. in 83 MMR mutation carriers at one year of follow-up (8%) [16]. Cancer worry in our study was correlated significantly with a high perceived colorectal cancer risk. During counseling and follow-up an effort should be made to identify subjects with high perceived colorectal cancer risks, and

psychological support should be more actively offered. Even more so, since, in our study, underestimation of the HNPCC related colorectal cancer risk did not influence screening behavior negatively.

Regret of being tested for the familial susceptibility for HNPCC was expressed by 6 respondents (9%). Remarkably, in the families of 4 of the six responders a relative recently died of cancer. Events in the family are known to influence perceived cancer risk [17]. Also, faith in the efficacy of screening may be violated. Tailor-made psychological support may help relatives with coping problems due to newly diagnosed cancer cases or deaths in the family. Since relatives can develop HNPCC related or non-related cancer at any moment in time, it is optimal to have an ongoing follow-up of the MMR mutation positive families. This could be obtained by yearly telephone contact or information gatherings. Also, offering screening to all carriers in a multidisciplinary outpatient facility can improve long-term follow-up and satisfaction.

In the Netherlands employers or insurers are prohibited to exclude individuals with a genetic predisposition for cancer from jobs or health insurance. For life or disability insurance no questions about genetic predisposition may be asked by insurers for insurance below a certain limit; $\in$160.00 for health insurance and $\in$32.000 in the first year of a disability insurance and $\in$22.000 the following years. As a result of these regulations, the studied group experienced no problems with jobs or health insurance. However, almost half of the healthy risk carriers opting for life insurance, disability insurance or mortgage, had some kind of trouble. This represents a potential threat to the accessibility of genetic testing for cancer susceptibilities.

In conclusion, this study indicates that genetic testing for HNPCC considerably improves compliance with screening. Also, most MMR gene mutation carriers can cope with their cancer susceptibility on the long term. We identified a need for updates regarding new developments and for more support of a vulnerable minority that has coping problems at the time of genetic testing or later on. We therefore propose an ongoing access to psychological and counseling facilities for MMR gene mutation carriers, preferably in the setting of a multidisciplinary family cancer clinic.

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Table 1:
Gender, Age and Parenthood in MMR mutation carriers affected and not affected with an HNPCC-related tumor

	Affected (%) n=28	Not affected (%) n=42	Total (%) n=70	P value
Gender: Male	13/28 (46)	11/42 (26)	24/70 (34)	0.081
Female	15/28 (54)	31/42 (74)	46/70 (66)	
Age: 25-50	6/28 (21)	30/42 (71)	36/70 (51)	<0.001
>50	22/28 (79)	12/42 (29)	34/70 (49)	
Children: No	1/28 (4)	7/42 (17)	8/70 (11)	0.093
Yes	27/28 (96)	35/42 (83)	62/70 (89)	

Table 2:
Screening behaviour among MMR mutation carriers without an HNPCC-related tumor *before* and *after* genetic testing.

		Number of carriers (%)	P value
Regular colonoscopy:	*Before* genetic testing	13/42 (31)	<0.001
	After genetic testing	37/42 (88)	
Gynecological screening:	*Before* genetic testing	3/18 (17)	<0.001
	After genetic testing	20/29 (69)	

Table 3:
Satisfaction with colonoscopic screening among the studied MMR gene mutation carriers without an HNPCC-related tumor.

		Number of carriers (%)
Colonoscopy*:	unpleasant	21/37 (57)
	fearful	12/37 (32)
	painful	19/37 (51)
	shameful	6/37 (16)
Faith effectiveness of colonoscopy		38/42 (90)
Worry of complication of colonoscopy		6/42 (14)
Wish other screening method		30/42 (71)

*Scored in the 37 healthy carriers who underwent colonoscopy

Table 4:
Long term satisfaction with the counseling procedure and genetic testing in the studied MMR gene mutation carriers.

	Affected (%)	Not affected (%)	Total (%)
Appropriately invited	25/27 (93)	35/41 (85)	60/68 (88)
Sufficiently informed	26/26 (100)	40/42 (95)	66/68 (97)
Sufficiently supported	23/26 (88)	35/40 (88)	58/66 (88)
Regret of testing	2/28 (7)	4/42 (10)	6/70 (9)
Insurance problems	3/4 (75)	4/10 (40)	7/14*(50)

Not all items were scored by all 70 carriers
* only 14 carriers opted for insurance after genetic testing

Table 5:
Reported and perceived HNPCC related cumulative lifetime colorectal cancer risks by the MMR gene mutation carriers.

Reported HNPCC related colorectal cancer risk				
	Over-estimators n=4 (%)	Correct estimators n=31 (%)	Under-estimators n=32 (%)	P value
Age:				
≤50 years	0/35	24/35 (69)	11/35 (31)	<0.001
>50 years	4/32 (12)	7/32 (22)	21/32 (66)	
Affected:				
No	1/40 (2.5)	24/40 (60)	15/40 (37.5)	0.016
Yes	3/27 (11)	7/27 (26)	17/27 (63)	
Perceived colorectal cancer risk				
	High N=34 (%)	Intermediate n=13 (%)	Low n=23 (%)	P value
Age:				
≤50 years	18/36 (50)	7/36 (19)	11/36 (31)	0.91
>50 years	16/34 (47)	6/34 (18)	12/34 (35)	
Affected:				
No	19/42 (45)	9/42 (21)	14/42 (33)	0.7
Yes	15/28 (54)	4/28 (14)	9/28 (32)	

Not all respondents reported an HNPCC related colorectal cancer risk

Table 6:
Comparison of correct vs. incorrect reported HNPCC-related cumulative lifetime colorectal cancer risk in respondents affected with and without an HNPCC-related tumor and according to age.

Reported HNPCC related colorectal cancer risk								
	Correct n=31	Incorrect n=36	Univariate			Multivariate		
			OR	95% CI	P value	OR	95% CI	P value
Age:								
≤50 years	4/35	11/35	1	2.6 -	<0.001	1	1.7 -	0.004
>50 years	7/32	25/32	7.8	23.4		5.8	19.7	
Affected:								
No	24/40	16/40	1	1.5 -	0.008	1	0.6 -	0.27
Yes	7/27	20/27	4.3	12.5		2	7.0	

Not all respondents reported an HNPCC related colorectal risk

Table 7:
Long term cancer worry in the studied MMR gene mutation carriers.

Cancer worry	Low n=22 (%)	Intermediate n=31 (%)	High n=7 (%)	P value
Affected:				
No	11/42 (26)	27/42 (64)	4/42 (10)	0.47
Yes	11/28 (39)	14/28 (50)	3/28 (11)	
Gender:				
Male	8/24 (33)	13/24 (54)	3/24 (13)	0.82
Female	14/46 (30)	28/46 (61)	4/46 (9)	
Age:				
≤50yrs	10/36 (28)	23/36 (64)	3/36 (8)	0.65
>50yrs	12/34 (35)	18/34 (53)	4/34 (12)	
Children:				
No	2/8 (25)	5/8 (62.5)	1/8 (12.5)	0.91
Yes	20/62 (32)	36/62 (58)	6/62 (10)	
Reported HNPCC risk*:				
Underestimated	11/32 (34.5)	18/32 (56)	3/32 (9.5)	0.58
Correct	9/31 (29)	20/31 (64.5)	2/31 (6.5)	
Overestimated	2/4 (50)	1/4 (25)	1/4 (25)	
Perceived risk:				
Low	11/23 (48)	12/23 (52)	0	0.007
Intermediate	4/13 (31)	8/13 (61)	1/13 (8)	
High	7/34 (20.5)	21/34 (62)	6/34 (17.5)	

*Three respondents did not report an HNPCC related colorectal cancer risk