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CANCER RISK IN MUTATION CARRIERS OF DNA-MISMATCH-REPAIR GENES

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Excessive incidence of various cancers is a challenging feature of the hereditary-non-polyposis-colorectal-cancer (HNPCC) syndrome. This study estimated the cancer incidences in HNPCC compared with the general population. Individuals in a cohort of 1763 members of 50 genetically diagnosed families were categorized according to their genetic status as mutation carriers, non-carriers, or individuals at 50 or 25% risk of being a carrier. Incidences of cancers in these groups were compared with those in the Finnish population overall. In 360 mutation carriers, standardized incidence ratios (SIR) were significantly increased for colorectal [68; 95% confidence intervals (CI), 56 to 81], endometrial (62; 95% CI, 44 to 86), ovarian (13; 95% CI, 5.3 to 25), gastric (6.9; 95% CI, 3.6 to 12), biliary tract (9.1; 95% CI, 1.1 to 33), uro-epithelial (7.6; 95% CI, 2.5 to 18) and kidney (4.7; 95% CI, 1 to 14) cancers and for central-nervous-system tumours (4.5; 95% CI, 1.2 to 12). The SIR increased with increasing likelihood of being a mutation carrier. The cumulative cancer incidences were 82, 60, 13 and 12% for colorectal, endometrial, gastric and ovarian cancers respectively. For other tumours associated with increased risk, corresponding incidences were below 4%. Interestingly, the incidence of endometrial cancer (60%) exceeded that for colorectal cancer in women (54%). The tumour spectrum associated with germline mutations of DNA-mismatch-repair genes involves 8 or more organ sites, suggesting a need to develop methods to screen for extra-colonic cancer also. *Int. J. Cancer* 81:214–218, 1999.

Germline mutations in any of 5 DNA-mismatch-repair genes, *MSH2, MLH1, PMS1, PMS2* or *MSH6* (Rhyu, 1996; Miyaki *et al.*, 1997) cause hereditary non-polyposis colorectal cancer (HNPCC), also known as the Lynch syndrome. Pre-symptomatic genetic testing of members of HNPCC families allows targeting of cancer prevention and screening to mutation carriers only, and relieves non-carriers of any extra cancer risk. The risk of colon cancer in mutation carriers can be managed reasonably well if colonoscopy is repeatedly undertaken or, in selected cases, prophylactic colectomy is performed (Järvinen *et al.*, 1995; Vasen *et al.*, 1996*b*).

Many other types of cancer appear to occur in excess in HNPCC families, *e.g.*, cancers of the endometrium, stomach, ovaries, urinary tract and kidneys, biliary tract, pancreas, small intestine, brain and skin (Vasen *et al.*, 1990, 1996*a;* Mecklin and Järvinen, 1991; Watson and Lynch, 1993; Aarnio *et al.*, 1995). Risk has been estimated in large numbers of individuals in HNPCC families simply by determining percentages of various types of tumour, or by calculating risk ratios in comparison with the general population. It would seem that a parent with an extra-colonic tumour can transmit the HNPCC trait to offspring. However, in most studies, estimates of risk of extra-colonic tumours are affected by uncertainty about mutation status.

To determine the risks of various extra-colonic cancers in HNPCC families, we studied the genetic and cancer status of members of 50 Finnish HNPCC families with known mutations of *MLH1* or *MSH2*.

MATERIAL AND METHODS

The cohort studied consisted of members of 50 HNPCC families in which a mutated *MLH1* gene (47 families) or *MSH2* gene (3 families) had been detected (Table I). The Central Population Register and local parish records cover all Finnish citizens. Pedigrees can be determined 2 to 4 centuries back. A genealogic family data base was created, starting from the index patients in each of the 50 families. The pedigrees included all siblings and their children in each consecutive generation. Branches of the family members were not traced further if 2 consecutive generations had exhibited no cancer of the colorectum, endometrium or stomach. Tracing of family members was systematic. All members of each sibship were included, even those who had died in infancy from any cause, whether or not related to HNPCC or other cancers. In all, 1,763 family members (894 men and 869 women) were identified and included in the family data base.

Family members were classified into 4 categories based on the result of genetic tests performed between 1995 and 1997: (1) individual found to be a mutation carrier (test positive), or an obligate carrier because of position in the pedigree in relation to a test-positive person; (2) first-degree relative (child or sibling) to a test-positive or obligate carrier, *i.e.*, 50% risk of being a carrier; (3) second-(or greater)degree descendant (grandchild or child of a sib, etc.) to a test-positive or obligate carrier (25% or lower risk of being a carrier); (4) individual found not to be a carrier of the known mutation in the family (test-negative) (Table II). Test-negative individuals (243) were uninformative, since there were almost no person-years after genetic testing and very few cases of cancer. Only genetic-testing results, not cancer data, were utilized in classifying family members into these carrier-status categories.

The population-based nationwide Finnish Cancer Registry (FCR) has functioned since 1953. All hospitals, physicians and pathology laboratories are required by law to notify the FCR of all cancer cases that come to their attention. The registry also receives information via all death certificates in which a diagnosis of cancer is mentioned. Coverage of the FCR is almost total. Between 1985 and 1988, more than 99% of some 64 000 solid tumours were recorded (Teppo *et al.*, 1994).

Abbreviations: FCR, Finnish Cancer Registry; CI, confidence intervals; HNPCC, hereditary non-polyposis colorectal cancer; SIR, standardized incidence ratio.

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TABLE I – GERMLINE MUTATIONS IN HNPCC FAMILIES

Site of predisposing mutation[1]	Number of families
MLH1	
Exon 16	30
Exon 6	7
Exon 17	3
Exon 4	3
Exon 12	2
Exon 14	1
Exons 3, 4, 5	1
MSH2	
Exon 10	2
Exon 12	1
Total	50

[1]For exact descriptions of the mutations, see Nyström-Lahti *et al.*, 1995, 1996; Holmberg *et al.*, 1997.

TABLE II – NUMBERS OF SUBJECTS AND PERSON-YEARS OF FOLLOW-UP RISK BY CARRIER-STATUS CATEGORY[1]

Carrier status	Number of subjects	Person-years of follow-up
Test-positive	265	8,855
Obligate carriers	95	1,744
50% risk	625	15,143
25% risk	535	17,909
All	1,520	43,651

[1]243 persons were test-negative and excluded from analysis.

All family members were linked to the FCR by means of the unique personal identification numbers given to everybody living in Finland and alive on January 1, 1967. Family members who died before 1967 were manually linked to the Cancer Registry data files. Follow-up of index patients with colorectal cancer was started after the initial diagnosis of colorectal cancer (index cancer), or from January 1953, whichever came latest. Follow-up of parents of index patients was started from the dates of birth of the index patients or from January 1953, whichever came latest. Follow-up for cancer in children and siblings was started from January 1, 1953 or at birth, whichever came latest. Follow-up was terminated on death, emigration, or the closing date of the study, December 31, 1995. The number of follow-up person-years exceeded 43,000 (Table II).

All tumours that had clear clinical and histological documentation, and that had been reported to the FCR, were included in the study. For brain and ovarian tumours, the histological tumour type was specifically checked, and classified as recommended by the World Health Organization (1993, 1995). Seven brain-tumour specimens out of 13 were available for re-examination; in 4 cases classification was based on pathology data. In 10 ovarian-carcinoma cases, pathology data was available for further review.

Standardized incidence ratios (SIR) were calculated by dividing observed numbers of cancers by expected ones. Selection of types of tumour for evaluation was based on previous reports of suspected associations with HNPCC. Some other common cancers were also studied. Expected numbers were calculated on the basis of person-years at risk, and gender-, age- and period-specific incidence rates of cancer for the population of Finland as a whole. Ninety-five percent confidence intervals (CI) were calculated assuming that numbers of observed cases followed a Poisson distribution. Differences in incidences of cancers were tested for statistical significance using the Chi-squared test.

Cumulative incidences of the various cancers were calculated for the Finnish population (1991 to 1995) as a whole, from Finnish Cancer Registry data, and compared with those in mutation carriers, defined here as the positive and obligate carrier groups combined (Elandt-Johnson and Johnson, 1980).

RESULTS

In the total cohort of 1763 members of 50 HNPCC families, 381 subjects had had at least one malignant tumour diagnosed within the 43-year period covered by the study; 131 subjects had had colorectal cancer only, 195 subjects had had one or more extracolonic cancers, and 55 subjects had had both colorectal and extra-colonic cancers occurring synchronously or metachronously. The total number of separate tumours was 444 (including multiple and metachronous cancers).

The distributions of the various kinds of tumour and the corresponding SIR for genetic risk categories are shown in Table III. In the mutation carriers, significantly increased SIR were observed for 8 types of cancer: colorectal cancer (68; 95% CI, 56 to 81), endometrial cancer (62; 95% CI, 44 to 86), ovarian cancer (13; 95% CI, 5.3 to 25), biliary-tract cancer (9.1; 95% CI, 1.1 to 33), uro-epithelial cancer (7.6; 95% CI, 2.5 to 18), gastric cancer (6.9; 95% CI, 3.6 to 12), kidney cancer (renal-cell adenocarcinoma) (4.7; 95% CI, 1 to 14) and tumours of the central nervous system (4.5; 95% CI, 1.2 to 12). The SIR for colorectal cancer was higher in men (83) than in women (48). The male-to-female ratio was 1.7 (95% CI, 1.2 to 2.7). The incidence of endometrial cancer (SIR = 62) exceeded that for colorectal cancer (SIR = 48) in women. No differences in incidences between men and women were observed in relation to biliary-tract, uro-epithelial, gastric, kidney or central-nervous-system tumours. The SIR for colorectal cancer decreased with decreasing likelihood of being a gene carrier, but was nevertheless as high as 9.8 (95% CI, 6.5 to 14) in those at 25% risk of being a mutation carrier. In the case of endometrial cancer a similar marked tendency was seen. Weaker tendencies were observed in relation to several other cancer sites (Table III). There was no significant increase in the incidence of prostatic (2.9; 95% CI, 0.8 to 7.4), breast (1.4; CI, 0.4 to 3.7) or lung cancer (1.0; 95% CI, 0.2 to 2.8).

The histological types of colorectal, endometrial, biliary-tract, kidney or gastric tumours (all adenocarcinomas) and of uro-epithelial tumours (transitional-cell carcinoma) did not vary greatly and were not studied by sub-type. Ovarian and central-nervous-system tumours were of several histologic types (Tables IV, V). Cystadenocarcinoma and glioblastoma multiforme were the commonest sub-types in the former and latter groups of tumours respectively.

In mutation carriers, cumulative incidence rates at 70 years of age were very high for colorectal cancer and for endometrial cancer, at 82 and 60% respectively, as compared with only 1.6% and 1.3%, respectively, in the Finnish population as a whole (Table VI). The cumulative incidence of colorectal cancer was 100% in men and 54% in women. The corresponding cumulative incidence for gastric cancer was 13%, for ovarian cancer 12%. For uro-epithelial, kidney and bile-duct cancer and for brain tumours cumulative incidences ranged from 2 to 4% by 70 years of age.

DISCUSSION

In the present study, incidences of cancers in 360 mutation carriers in the largest reported collection of genetically defined HNPCC families investigated so far were compared with incidences of cancers in Finland as a whole. At least 7 extra-colonic types of tumour were associated with HNPCC syndrome: cancers of the endometrium, ovary, stomach, biliary tract, uro-epithelium (transitional-cell carcinoma) and kidneys (renal-cell adenocarcinoma), as well as tumours of the central nervous system. For most of these types of tumour, associations have already been proposed by studies lacking knowledge of the exact genetic status of the subjects (Watson and Lynch, 1993; Vasen *et al.*, 1996*a*). On the other hand, our mutation-carrier group did not include cases of small-bowel cancer, also considered to belong in the tumour spectrum of HNPCC on the basis of results of an earlier study (Vasen *et al.*, 1996*b*). An interesting finding in the present investigation was that the cumulative incidence of endometrial

TABLE III – NUMBER (n) AND STANDARDIZED INCIDENCE RATIO (SIR) WITH 95% CONFIDENCE INTERVALS (CI) OF CANCERS AT SELECTED SITES AMONG 1520 HNPCC FAMILY MEMBERS BY CARRIER-RISK CATEGORY

Site of tumour	Risk of being carrier								
	25% risk (n = 535)			50% risk (n = 625)			Obligate mutation carriers and test positive (n = 360[1])		
	n	SIR	95% CI	n	SIR	95% CI	n	SIR	95% CI
Colon and rectum	28	9.8	6.5–14***	54	19	13–25***	109	68	56–81***
Endometrium	10	8.5	4.1–15***	15	13	7.5–22***	36	62	44–86***
Ovary	2	1.7	0.2–6.0	3	2.9	0.6–8.3	8	13	5.3–25***
Biliary tract, gallbladder	3	7.0	1.4–20*	2	4.5	0.6–16	2	9.1	1.1–33*
Bladder, ureter, urethra	3	2.9	0.6–8.5	–	0.0	0.0–3.7	5	7.6	2.5–18**
Stomach	7	2.5	1.0–5.2*	12	3.6	1.8–6.2**	12	6.9	3.6–12***
Kidney	–	0.0	0.0–3.4	4	4.0	1.1–10*	3	4.7	1.0–14*
Nervous system	4	2.6	0.7–6.8	6	4.7	1.7–10*	4	4.5	1.2–12*
Pancreas	1	0.8	0.0–4.7	–	0.0	0.0–3.0	3	4.5	0.9–13
Prostate	3	1.6	0.3–4.7	2	1.1	0.1–3.9	4	2.9	0.8–7.4
Non-Hodgkin	1	1.3	0.0–7.2	1	1.5	0.0–8.4	1	2.2	0.1–12
Melanoma (skin)	–	0.0	0.0–4.0	1	1.4	0.0–8.0	1	1.8	0.1–9.9
Breast	4	0.8	0.2–2.0	5	1.2	0.4–2.8	4	1.4	0.4–3.7
Lung	8	1.7	0.7–3.3	5	1.0	0.3–2.4	3	1.0	0.2–2.8
Leukaemia	2	1.9	0.2–6.7	–	0.0	0.0–3.4	–	0.0	0.0–5.9
Small intestine	1	6.9	0.2–39	–	0.0	0.0–28	–	0.0	0.0–131
Thyroid gland	–	0.0	0.0–6.0	–	0.0	0.0–8.1	–	0.0	0.0–46

[1]177 men, 183 women.–*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE IV – HISTOLOGY AND AGE AT DIAGNOSIS IN 13 PATIENTS WITH OVARIAN TUMOURS

Family number/mutation	Genetic status	Age at diagnosis	Type of ovarian tumour
1/*MLH1* exon 16	Mutation carrier	49	Mucinous cystadenocarcinoma
1/*MLH1* exon 16	Mutation carrier	27	Serous cystadenocarcinoma
1/*MLH1* exon 16	50% risk	53	Carcinoma
2/*MLH1* exon 16	Mutation carrier	40	Clear-cell adenocarcinoma
4/*MLH1* exons 3, 4, 5	50% risk	46	Cystadenocarcinoma
11/*MLH1* exon 16	Mutation carrier	56	Clear-cell adenocarcinoma
30/*MLH1* exon 16	Obligate mutation carrier	50	Mucinous cystadenocarcinoma
39/*MLH1* exon 12	Mutation carrier	46	Serous papillary cystadenocarcinoma
39/*MLH1* exon 12	Mutation carrier	47	Serous papillary cystadenocarcinoma
58/*MLH1* exon 16	25% risk	76	Carcinoma
69/*MLH1* exon 16	50% risk	76	Carcinoma
90/*MLH1* exon 6	Obligate mutation carrier	47	Serous papillary cystadenocarcinoma
93/*MSH2* exon 10	25% risk	26	Endometrioid adenocarcinoma

TABLE V – HISTOLOGY, AGE AT DIAGNOSIS AND GENDER OF PATIENTS WITH A NERVOUS-SYSTEM TUMOUR

Family number/ mutation	Genetic status	Age at diagnosis/gender	Histology of nervous-system tumour
1/*MLH1* exon 16	Mutation carrier	49/M	Glioblastoma multiforme grade 4
11/*MLH1* exon 16	50% risk	49/F	Glioblastoma multiforme grade 4
11/*MLH1* exon 16	50% risk	53/M	Anaplastic astrocytoma grade 3
11/*MLH1* exon 16	50% risk	64/M	Undefined brain tumour
13/*MLH1* exon 6	25% risk	59/F	Meningioma grade 1
24/*MLH1* exon 16	Mutation carrier	57/F	Acoustic neurinoma
39/*MLH1* exon 12	25% risk	1/M	Neuroblastoma (mediastinum)
50/*MLH1* exon 16	Obligate mutation carrier	65/M	Anaplastic astrocytoma grade 3
50/*MLH1* exon 16	50% risk	41/F	Glioblastoma multiforme grade 4
59/*MLH1* exon 16	Mutation carrier	42/M	Anaplastic astrocytoma grade 3
78/*MLH1* exon 16	50% risk	51/F	Glioblastoma multiforme grade 4
83/*MLH1* exon 17	25% risk	40/M	Meningioma fibroblastic grade 1
83/*MLH1* exon 17	50% risk	60/F	Meningioma meningo-epithelial and fibroblastic grade 1
90/*MLH1* exon 6	25% risk	54/M	Undefined brain tumour

cancer was greater than that of colorectal cancer in women. No excess risk was detected in relation to cancers of the breast, prostate or lung. An association of those cancers with HNPCC has hitherto been debated (Itoh *et al.*, 1990; Lynch *et al.*, 1993).

For the most part, the SIR values increased constantly with increasing likelihood of being a mutation carrier, providing ample support of the conclusions. For several tumours the number of cases was low, resulting in wide confidence intervals. Moreover, despite the fact that DNA-mismatch repair requires interaction of the different gene products so that predisposition ensues if any mutation switches the function off (Rhyu, 1996), there may be variation in the tumour spectrum depending on the specific gene and mutation involved. Thus, since the present family material included predominantly mutations of the *hMLH1* gene and many

TABLE VI – CUMULATIVE INCIDENCE RATES (%) UP TO 70 YEARS OF AGE FOR CANCERS IN THE FINNISH POPULATION, 1991 TO 1995, AND IN 360 MUTATION CARRIERS OF HNPCC, 1953 TO 1995, BY SITE

Site of tumour	Finnish population (%)	HNPCC families (%)
Colon and rectum	1.6	82
Endometrium	1.3[1]	60[1]
Stomach	0.8	13
Ovary	1.3[1]	12[1]
Bladder, ureter and urethra	0.7	4.0
Brain	0.9	3.7
Kidney	0.8	3.3
Biliary tract, gallbladder	0.2	2.0

[1]Women only.

families shared a single mutation type, other family series may have different tumour spectra.

Most of the cancers associated with HNPCC exhibit uniform histologies, with particular features pointing to the underlying etiology in individual cases (Mecklin *et al.,* 1986; Jass *et al.,* 1994; Aarnio *et al.,* 1997). In ovarian and brain tumours, however, several histological tumour types were seen. The ovarian cancers were all adenocarcinomas (Watson and Lynch, 1993), but included 4 different sub-types; the most common being serous and mucinous cystadenocarcinomas. Central-nervous-system tumours included 12 brain tumours of different grades of malignancy and 2 other tumours of neural origin (neuroblastoma, acoustic neurinoma). Hamilton *et al.* (1995), following a study of 14 families with Turcot's syndrome, suggested a specific association between glioblastoma multiforme and HNPCC, with cerebellar medulloblastoma as a feature of familial adenomatous polyposis. In accordance with our findings, Vasen *et al.* (1996*a*) observed variable brain tumours in 14 patients from 50 Dutch HNPCC families. The occurrence of 4 glioblastomas in our mutation carrier and 50% risk groups supports the existence of a specific predisposition for glioblastoma, though some brain tumours were of other histological types.

Increased risk of many extra-colonic cancers does not necessarily mean that prophylactic screening is desirable, let alone efficacious or cost-effective. Some reasonable requirements for screening are: (*i*) the tumour in question should be fairly common; (*ii*) outcome should be serious if the tumour is advanced, but the tumour should be readily treatable if detected early; (*iii*) accurate and easy methods for detection of early tumours or pre-malignant lesions should exist (Lambert, 1983). Several of these requirements are non-existent in relation to the extra-colonic cancers associated with HNPCC. Screening for endometrial cancer would appear to be justified simply because of its high cumulative incidence: 60% by 70 years of age in this study and from 30 to 60% in other studies (Watson *et al.,* 1994; Vasen *et al.,* 1996*b*). Endometrial suction biopsy at regular intervals starting from 35 years of age (Aarnio *et al.,* 1995) might be sufficient, with the possible addition of transvaginal ultrasound (Watson *et al.,* 1994). Experience of screening for endometrial cancer is limited. Prospective studies are needed to allow its value to be assessed. However, the potential importance of such screening is further highlighted by our observation that the cumulative incidence of endometrial cancer (60%) exceeded that of colorectal cancer (54%) in the 184 women concerned. Earlier findings by Dunlop *et al.* (1997) in 35 women were similar. Since the cumulative incidence of colorectal cancer was only 54% in women, prophylactic colectomy might be less advisable in women than in men, in whom the cumulative incidence was up to 100% in our study, 90% in the study by Vasen *et al.* (1996*b*).

Gastric and ovarian cancers were the next commonest cancers, with cumulative incidences of 13% and 12% by 70 years of age in mutation carriers. Early detection or prevention of such tumours using ultrasound and endoscopy may be possible, but cost-effectiveness is likely to remain low. The lack of specificity of ultrasound would probably lead to many false-positive findings, often related to benign ovarian cysts. Gastroscopy with biopsy would probably allow more accurate diagnosis of gastric cancer. However, in pernicious anaemia with a 5-fold relative gastric-cancer risk, nearly as high as in the present study in relation to HNPCC mutation carriers (6.9), screening has not been considered useful (Kokkola *et al.,* 1998). It remains doubtful whether screening for ovarian and gastric cancer should be recommended for DNA-mismatch-repair-gene-mutation carriers. For cancers of the small bowel, brain, biliary tract, even of kidney and uro-epithelial cancers, incidence is clearly too low (2–4%) and methods available for screening are too inefficient for routine examinations to be recommended.

The wide variety of types of tumour associated with HNPCC syndrome has implications for the counseling of family members considering genetic testing. Further studies are needed to evaluate whether detailed, potentially anxiety-provoking information should be given about the types of tumour associated with mutation-carrier status and for which no good means of prevention or early detection exist. There may also be a risk of encouraging the fallacy that all cancers can be prevented and treated. Appropriate solutions probably differ among families and situations, and need to be decided on a case-by-case basis by the clinician and the subject. For clinicians managing HNPCC patients, knowledge of the less common types of associated tumours could be important if a patient exhibited unusual symptoms. The most important outcome of genetic testing, however, may be the relief in the case of a negative test result. Optimization of management and screening strategies for test-positive subjects requires more prospective studies, with special emphasis on extra-colonic cancers.

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