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

Markku A. Arnio, Risto Sankila, Eero Pukkala, Reijo Salovaara, Lauri A. Aaltonen, Albert de la Chapelle, Paivi Peltonaki, Jukka-Pekka Mecklin and Heikki J. Jarvinen

Divisions of Human Cancer Genetics, Comprehensive Cancer Center, Ohio State University, Columbus, OH, USA

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 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 individual; (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).

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

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*Correspondence to: Second Department of Surgery, Helsinki University Central Hospital, PO Box 260, FIN-00029 Helsinki, Finland. Fax: (358)9-471-4675.
TABLE I – GERMLINE MUTATIONS IN HNPCC FAMILIES

| Site of predisposing mutation | 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                 |
| MSI-positive                  |                    |
| Exon 10                      | 2                 |
| Exon 12                      | 1                 |
| Total                        | 50                |

1For 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

| 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                    |

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 HNPPC. 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).

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 extra-colonic 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 increased 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 prostate (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 HNPPC 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 HNPPC 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., 1996a). 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 HNPPC on the basis of results of an earlier study (Vasen et al., 1996b). An interesting finding in the present investigation was that the cumulative incidence of endometrial
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

| Site of tumour                  | Risk of being carrier |
|--------------------------------|-----------------------|
|                                | 25% risk (n = 535)    | 50% risk (n = 625) | Obligate mutation carriers and test positive (n = 360) |
| 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 1.1–33*   |
| Bladder, ureter, urethra       | 3 2.9 0.6–8.5       | – 0.0 0.0–3.7     | 5 7 2.5–12** |
| Stomach                        | 7 2.5 1.0–5.3*      | 12 3.6 1.8–6.2**  | 12 6.9 3.6–13*** |
| 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 0.0–4.0 |
| 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 |

177 men, 183 women.–*p < 0.05; **p < 0.01; ***p < 0.001.

| 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 |
| 59/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 |

| 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 4 |
| 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 meningio-epithelial and fibroblastic grade 1 |
| 90/MLH1 exon 6         | 25% risk        | 54/M       | Undefined brain tumour         |
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 neuroma). Hamilton et al. (1995), following a study of 14 families with Turcot’s syndrome, suggested a specific association between glioblastoma multiiforme and HNPCC, with cerebellar medulloblastoma as a feature of familial adenomatous polyposis. In accordance with our findings, Vasen et al. (1996a) 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., 1996b). 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. (1996b).

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, 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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