Tumors associated with Hereditary Nonpolyposis Colorectal Cancer: Defective Mismatch Repair and Familial Risk of Cancer

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Familial Risk of Tumors Associated with Hereditary Non-polyposis Colorectal Cancer: a Swedish Population-based Study

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Background: Familial clustering, which may be due to inherited predisposition, is seen in several common cancer types. The aim of this study was to assess the familial risk of tumors that are associated with hereditary non-polyposis colorectal cancer (HNPCC), a familial cancer syndrome that confers an increased risk of several cancer types, and is associated with a low age at onset. **Methods:** The National Swedish Cancer Registry and population registers were utilized to identify all tumors among the offspring of individuals who had developed any of the diagnoses included in the Amsterdam II criteria for HNPCC. In all, 204,358 offspring of 102,814 individuals with cancer of the colorectum, endometrium, upper urinary tract or small intestine were identified. **Results:** Significantly increased risks for several tumor types were demonstrated. If the parent was below age 50 at diagnosis, the offspring Standard Incidence Ratios (SIRs) were 3.6 for colon cancer, 3.8 for rectal cancer, 2.8 for gastric cancer, and 2.3 for ovarian cancer. Offspring who had both a parent and a sibling with HNPCC-associated cancer showed even higher SIRs for cancer of the colorectum, endometrium, ovary, and urinary tract. The highest values were observed in the subgroup whose parent had developed multiple primary tumors; SIR 34.0 for colon cancer, 17.9 for rectal cancer, 21.8 for endometrial cancer, and 5.8 for ovarian cancer. **Conclusions:** The study demonstrates that there is an increased risk for several tumor types among individuals whose parents developed HNPCC-associated tumors, where a young age at diagnosis and development of multiple tumors in the parents lead to the highest SIRs.

Key words: Cancer of the urinary tract; cancer risk; cohort study; colorectal cancer; endometrial cancer; epidemiology; familial cancer; HNPCC; population-based

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Several common cancer types, such as breast cancer, colorectal cancer, prostate cancer, ovarian cancer, and endometrial cancer, appear in familial forms. Characterization of underlying genetic defects has made genetic testing possible for hereditary cancer syndromes and has thereby facilitated clinical management of these patients (1). However, in many families disease-causing mutations can not be identified, and the majority of the familial cases still constitute familial aggregation that does not fulfill the criteria for any hitherto characterized inherited syndrome. This requires risk estimates based on epidemiological data. Large-scale estimates of familial cancer risk may be used as a basis for decisions on the type and frequency of preventive measures. Previous population-based studies have shown a relative risk of about 2 for colorectal cancer among 1st-degree relatives and of about 1.5–3 for endometrial cancer, with higher risks for individuals whose parents developed cancer at a young age (2–9).

The hereditary non-polyposis colorectal cancer syndrome, HNPCC, is an autosomally, dominantly inherited cancer syndrome that is estimated to affect 1/1000–2000 individuals. HNPCC is caused by a defective mismatch repair (MMR) system, with >90% of the mutations affecting the MMR genes *MLH1, MSH2* or *MSH6* (10, 11). Mutation carriers have an increased risk for cancer of the colorectum (80%–90% life-time risk), endometrium (40%–60% life-time risk), ovary (5%–15%), stomach (5%–15%), urinary tract, small bowel, skin, and brain. Current estimates of the incidence of HNPCC in these tumor types range from 1% to 5%, and HNPCC probably constitutes the major familial colorectal and endometrial cancer syndrome. The syndrome is further characterized by an early age (mean 45 years) at diagnosis and, in about 1/3 of the patients, development of multiple primary malignancies (1, 12–17). Criteria for the classification of HNPCC, the Amsterdam II criteria, have been established and include development of cancer of the colon, rectum, endometrium, small bowel, or the upper urinary tract in at least 3 individuals (in two successive generations), one of whom should be diagnosed before age 50 (18). However, regarding the clinical management, the International Collaborative

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Group (ICG) on HNPCC has concluded that cancer of the stomach, ovaries, brain, skin, and hepatobiliary tract should also be considered part of the HNPCC tumor spectrum (1). Disease-causing mutations are characterized in most families who fulfill the Amsterdam criteria and whose tumors show signs of defective MMR (microsatellite instability (MSI) and/or loss of MMR protein immunostaining). However, in a subset of the HNPCC families and in the vast majority of the HNPCC-like families (with a higher age at onset of colorectal cancer, fewer extra-intestinal tumors and a variable penetrance), no underlying genetic defect can be identified (1).

The aim of the present study was to assess the cancer risk in children whose parents developed any of the tumor types that have been associated with HNPCC. All children to individuals with at least one of the diagnoses included in the Amsterdam II criteria were identified through Swedish population-based registers. Hence, this study provides data that allow estimates of the cancer risk in offspring of patients with these cancer types, given the parents' age, type and number of tumors, as well as the number of siblings affected.

Materials and Methods

Register data

In the National Swedish Cancer Registry at least 98% of all malignancies diagnosed in Sweden (with a current population of 8.9 million) have been registered since the initiation of the registry in 1958. The registry contains more than 1,200,000 tumors, confirmed by both clinicians and pathologists and arranged according to the International Classification of Diseases (ICD) codes. All individuals with at least one HNPCC-associated diagnosis, as defined in the Amsterdam II criteria (18), were identified in the cancer registry through the ICD version 7 codes. We included the following codes: 152 (small intestine), 153 (colon), 154 (rectum), 172 (corpus uteri), 174 (uterus, part unspecified), 180.1 (renal pelvis), 180.9 (renal part unspecified), 181.1 (ureter), 181.8 (urinary organs, multiple locations), and 181.9 (unspecified location within the urinary organs). Anal cancer, intestinal lymphoma, and carcinoid tumors of the small intestine/colorectum were not included.

Individuals with at least one HNPCC-associated diagnosis constituted potential probands, who, with the help of unique personal identification numbers, could be matched with data from the Swedish Fertility Register and Swedish National Censuses from 1960 and later, in order to identify their offspring. The Swedish Fertility Registry contains data on all births in Sweden since 1961 with identification number of mothers, children and fathers who were married to the mother at the time of birth. The Swedish National Censuses include information about relationships among individuals sharing the same household. Accordingly, children born before 1961 and children to unmarried fathers were obtained from the National Censuses, whereas children born after 1960 with female probands and married male probands were identified by the Swedish Fertility Registry. If an individual had two affected parents, the child was only included once in the study base. Information regarding malignant tumors, emigration, and deaths among the offspring were obtained from the Cancer Registry and from the Swedish Population Registers. Since children who died before 1961 could not be identified by the Swedish censuses, the follow-up started in January 1961, or at birth for children born thereafter. Follow-up was terminated at death or emigration, or in December 1999, when the study was closed.

Standardized incidence ratios and cumulative risks

Standardized Incidence Ratios (SIRs) (observed number of cancer cases divided by the expected number of cases) were calculated for the children. The expected number of cases was calculated by multiplying the person-years at risk by the national Swedish cancer incidence, stratified by sex, calendar year, and 5-year age groups. We assumed that the relative risk is the same before and after the dates of the parents'/siblings' diagnoses. In the analysis of individuals with both a parent and a sibling with HNPCC-associated cancer, a child could be included in the analysis both directly as a cohort member contributing to the follow-up time, and indirectly as part of the exposure. The method for choosing the time-scale and for constructing the cohort of individuals with a parent and at least one sibling with HNPCC-associated cancer has been described earlier in Anderson et al. (19). Confidence intervals and *P* values for the SIRs were calculated assuming that the observed cases were independent and followed a Poisson distribution. However, the assumption about independence is not valid, since there is dependence between siblings. This affects the estimates of the standard errors, and we therefore also calculated confidence intervals and *P* values by a method accounting for dependence (19).

The cohort was further analyzed in strata, determined by age at diagnosis in the parent, development of multiple primary malignancies in the parent, or several additional siblings with HNPCC-associated cancers, i.e. factors known to characterize individuals with HNPCC mutations. We defined six disjoint 'HNPCC risk groups':

Parent with HNPCC-associated cancer, diagnosis $\geq$50 years of age, denoted 'onset $\geq$50'.
Parent with HNPCC-associated cancer, diagnosis $<$50 years of age, denoted 'onset $<$50'.
Parent with multiple HNPCC-associated diagnoses, age $\geq$50, denoted 'multiple, onset $\geq$50'.
Parent and sibling with HNPCC-associated cancer, age $\geq$50, denoted 'familial, onset $\geq$50'.
Parent with multiple HNPCC-associated diagnoses, at least one $<$50, denoted 'multiple, onset $<$50'.
Parent and sibling with HNPCC-associated cancer, at least one $<$50, denoted 'familial, onset $<$50'.

Families in the last group fulfilled the Amsterdam II criteria

Table I. Number of offspring in the whole cohort and in the 'HNPCC risk groups' in relation to parental age at diagnosis, occurrence of multiple tumors in parent and number of affected first-degree relatives

Parent/siblings	All	Onset ≥50	Onset <50	Multiple, onset ≥50	Familial, onset ≥50	Multiple, onset <50	Familial, onset <50
No. of individuals	204,358	178,892	17,677	5,542	784	559	904
Person-years total	7,395,224	6,553,655	553,339	205,781	28,964	20,566	32,919
(<age 50)	(6,781,194)	(597,992)	(541,821)	(189,003)	(23,863)	(19,914)	(30,374)
Female (%)	94,727 (46)	82,639 (46)	8,556 (48)	2,529 (46)	337 (43)	255 (46)	411 (45)
No. of affected individuals	8765	7905	395	292	63	28	82
Median age at onset	50	51.5	43	47	51	40	44

if offspring developed HNPCC-associated cancer. Cancer risks were also calculated as a function of each separate HNPCC-associated malignancy in the parent, and for different follow-up-times in offspring, i.e. before and after age 50. The cumulative incidence until the first HNPCC-associated cancer and the risk of a second HNPCC-associated tumor were calculated using the life table method.

Results

Among the 102,814 parents with HNPCC-associated cancer, there were 48,141 colon cancers, 28,542 rectal cancers, 21,589 endometrial cancers, 1473 cancers of the small intestine, and 5,013 cancers of the upper urinary tract. Altogether, 8,855 (9%) of the parents were diagnosed before 50 years of age and 3,058 (3%) of the parents developed multiple HNPCC-associated malignancies (13% of whom had the first diagnosis before 50 years of age). The cohort contained 204,358 children, 7,905 of whom developed cancer; 17,677 children had parents diagnosed before the age of 50, and 395 of these children developed cancer. Of the 559 children in the 'multiple, onset <50' group, 28 children developed cancer. A total of 904 children constituted the 'familial, onset <50' group, and 82 of them developed cancer (Table I). Most (>90%) of the follow-up time was confined to ages below 50. The median age at onset of the first HNPCC tumor in the whole cohort was 50 years, but was lower for individuals with a proband diagnosed before the age of 50.

Offspring cancer risk in the whole cohort

Of the 9337 malignancies in the cohort, 1,317 were classified as HNPCC-associated. Offspring cancer risks were significantly increased in the whole cohort with SIRs of 1.7 for colon cancer, 1.6 for rectal cancer, 1.4 for endometrial cancer, and 1.6 for any HNPCC-associated cancer (Table II). The risk of testicular cancer was also significantly increased (SIR 1.2, 95% CI 1.1–1.4, data not shown), although this tumor type is not considered part of HNPCC. Increased SIR

Table II. Offspring cancer risk in different 'HNPCC risk groups'; number, standard incidence ratio (SIR) and 95% CI

Parent/siblings Cancer type in offspring		All	Onset ≥50	Onset <50	Multiple, onset ≥50	Familial, onset ≥50	Multiple, onset <50	Familial, onset <50
Colon	No.	619	504	33	41	11	16	26
	SIR	**1.7**	**1.5**	**3.6**	**4.3**	**3.9**	**34.0**	**18.2**
	(95% CI)	**(1.6–1.9)**	**(1.4–1.7)**	**(2.4–5.0)**	**(3.1–5.8)**	**(1.9–6.7)**	**(19.5–55.3)**	**(11.9–26.6)**
Rectal	No.	340	292	20	13	4	5	8
	SIR	**1.6**	**1.4**	**3.8**	**2.2**	2.2	**17.9**	**9.2**
	(95% CI)	**(1.5–1.7)**	**(1.3–1.6)**	**(2.3–5.8)**	**(1.2–3.7)**	(0.6–5.6)	**(5.8–41.7)**	**(4.0–18.1)**
Endometrial	No.	287	244	10	14	2	6	12
	SIR	**1.4**	**1.3**	1.8	**2.5**	1.5	**21.8**	**13.8**
	(95% CI)	**(1.3–1.6)**	**(1.1–1.5)**	(0.9–3.4)	**(1.4–4.0)**	(0.2–5.3)	**(8.0–47.5)**	**(7.1–24.1)**
Small intestine	No.	22	19	3	0	0	0	0
	SIR	1.1	1.0	4.6	0.0	0.0	0.0	0.0
	(95% CI)	(0.7–1.6)	(0.6–1.5)	(1.0–13.5)	(0.0–6.36)	(0.0–28)	(0.0–123)	(0.0–43.4)
Upper urinary tract	No.	49	39	1	2	3	0	4
	SIR	1.2	1.0	1.0	1.8	**11.2**	0.0	**29.6**
	(95% CI)	(0.9–1.5)	(0.7–1.4)	(0.0–5.6)	(0.2–6.6)	**(2.3–32)**	(0.0–147)	**(8.1–75.9)**
Any HNPCC-associated	No.	1317	1098	67	70	20	27	50
	SIR	**1.6**	**1.4**	**3.1**	**3.1**	**3.1**	**25.0**	**14.7**
	(95% CI)	**(1.5–1.7)**	**(1.3–1.5)**	**(2.4–3.9)**	**(2.4–3.9)**	**(1.9–4.8)**	**(16.5–36.4)**	**(11.0–19.4)**
Gastric	No.	159	136	13	7	1	1	2
	SIR	0.9	0.8	**2.8**	1.5	0.7	4.1	2.8
	(95% CI)	(0.8–1.0)	(0.7–1.0)	**(1.5–4.8)**	(0.6–3.0)	(0.0–3.6)	(0.1–22.6)	(0.3–10.4)
Ovarian	No.	322	274	25	11	4	3	5
	SIR	1.1	1.1	**2.3**	1.4	2.5	**5.8**	**3.9**
	(95% CI)	(1.0–1.3)	(0.9–1.2)	**(1.5–3.4)**	(0.7–2.5)	(0.7–6.3)	**(1.2–16.7)**	**(1.3–9.0)**

HNPCC = hereditary non-polyposis colorectal cancer; SIR = standard incidence ratio.

values of borderline significance were observed for cancer of the pancreas (SIR 1.1, 95% CI 1.0–1.3), breast (SIR 1.1, 95% CI 1.0–1.1), ovary (SIR 1.1, 95% CI 1.0–1.3), malignant melanoma (SIR 1.1, 95% CI 1.0–1.2), and cancer of the nervous system (SIR 1.1, 95% CI 1.0–1.2). Decreased risks of borderline significance were seen in the whole cohort for laryngeal cancer (SIR 0.7, 95% CI 0.5–1.0), cancer of the trachea, bronchus, and lung (SIR 0.9, 95% CI 0.8–1.0), bladder cancer (SIR 0.9, 95% CI 0.8–1.0), and for bone and soft tissue malignancies (SIR 0.9, 95% CI 0.7–1.0).

Offspring cancer risk in different 'HNPCC risk groups'

The risks for colon cancer, rectal cancer, and endometrial cancer were significantly increased in most groups, whereas the increased relative risks for gastric cancer and ovarian cancer were found only in patients with early age at diagnosis in the parent (Table II). Cancer of the upper urinary tract was significantly increased only in the 'familial' groups, whereas cancer of the small intestine was not significantly altered in any of the groups. Overall, higher SIR values were found in offspring whose parents were diagnosed before age 50 (Table II). Furthermore, higher SIR values were found in 'multiple, onset <50' group compared to the 'family, onset <50' group (Table II).

Offspring of parents with both parents affected by HNPCC-associated cancer were at significantly increased risks only for colon cancer (SIR 1.9, 95% CI 1.1–1.3) and endometrial cancer (SIR 2.4, 95% CI 1.3–4.3).

Offspring cancer risk depending on age and type of malignancy in parent

Diagnosis before age 50 in the parent conferred a higher risk for cancer in the offspring.

Colon cancer and endometrial cancer in the parent were linked to an increased risk of colon cancer, rectal cancer, and endometrial cancer in the offspring, whereas rectal cancer in the parent predisposed only to cancer of the colon and rectum (Table III).

Offspring cancer risk for different follow-up ages

The children's age at follow-up was important if the proband had a diagnosis before age 50, whereas the risk estimates were similar at different follow-up ages if the proband had been diagnosed after the age of 50. In the group 'multiple, onset <50', the SIRs for colon cancer were 40.6 before age 50 and 19.0 after age 50, for rectal cancer 29.4 before age 50 and 0 after age 50, and for endometrial cancer the SIRs were 25.6 and 16.8 before and after age 50, respectively. In the group 'familial, onset <50'; SIRs for colon cancer were 28.8 and 7.1 (before and after age 50 in offspring, respectively) and the corresponding figures were 17.1 and 2.1 for rectal cancer and 26.6 and 4.0 (not significant) for endometrial cancer.

Table III. Offspring cancer risk depending on type of malignancy in parent; person years, number, standard incidence ratio (SIR) and 95% CI

Proband cancer type		Colon		Rectal		Endometrial		Small intestine		Upper urinary tract	
Cancer type in offspring		Diagnosis ≥50	Diagnosis <50	Diagnosis ≥50	Diagnosis <50	Diagnosis ≥50	Diagnosis <50	Diagnosis ≥50	Diagnosis <50	Diagnosis ≥50	Diagnosis <50
Person-years		3,199,565	229,606	1,954,770	134,607	1,364,574	185,735	95,394	11,854	354,628	21,535
All tumors, excluding HNPCC-associated diagnoses	No.	3676	133	2150	64	1414	169	102	8	424	11
	SIR	1.0	1.1	1.0	0.9	1.0	**1.4**	1.1	1.5	1.1	1.0
	(95% CI)	(1.0–1.1)	(1.0–1.4)	(1.0–1.0)	(0.7–1.2)	(1.0–1.1)	**(1.2–1.6)**	(0.9–1.3)	(0.7–1.3)	(1.0–1.2)	(0.5–1.8)
Colon	No.	322	30	166	10	81	15	6	0	20	2
	SIR	**1.9**	**8.9**	**1.6**	**4.8**	**1.3**	**3.7**	1.5	0	1.2	6.9
	(95% CI)	**(1.7–2.1)**	**(6.0–12.8)**	**(1.4–1.9)**	**(2.3–8.9)**	**(1.1–1.7)**	**(2.0–6.0)**	(0.5–3.2)		(0.7–1.8)	(0.8–25)
Rectal	No.	164	11	105	5	41	10	7	0	10	1
	SIR	**1.6**	**5.6**	**1.7**	**4.2**	1.1	**4.2**	**2.8**	0	1.0	6.3
	(95% CI)	**(1.3–1.8)**	**(2.9–10.3)**	**(1.4–2.0)**	**(1.4–9.8)**	(0.8–1.5)	**(2.0–7.7)**	**(1.1–5.7)**	0	(0.5–1.8)	(0.2–35)
Endometrial	No.	116	13	72	1	83	10	3	0	18	0
	SIR	1.2	**6.8**	1.3	0.8	**2.4**	**4.0**	1.3	0	1.8	0
	(95% CI)	(1.0–1.4)	**(3.6–11.7)**	(1.0–1.6)	(0.02–4.4)	**(1.9–2.9)**	**(1.9–7.4)**	(0.3–3.8)		(1.0–2.8)	
Small intestine	No.	12	1	3	1	4	1	0	0	0	0
	SIR	1.2	4.2	0.5	6.7	1.1	3.6	0	0	0	0
	(95% CI)	(0.6–2.1)	(0.1–23)	(0.1–1.5)	(0.2–37)	(0.3–2.8)	(0.09–20)				
Upper urinary tract	No.	18	1	17	0	11	0	1	0	4	0
	SIR	0.9	2.9	1.4	0	1.6	0	2.1	0	2.0	0
	(95% CI)	(0.5–1.4)	(0.07–16.0)	(0.8–2.3)		(0.8–2.8)		(0.05–11.9)		(0.5–5.2)	

HNPCC = hereditary non-polyposis colorectal cancer; SIR = standard incidence ratio.

Table IV. Cumulative incidence (%) and 95% CI of HNPCC-associated tumors in different 'HNPCC risk groups'

Age	All	Onset ≥50	Onset <50	Multiple and familial, onset ≥50	Multiple and familial, onset <50	Reference*
40	0.1 (0.09–1.2)	0.07 (0.06–0.09)	0.2 (0.2–0.3)	0.3 (0.2–0.5)	1.4 (0.9–2.3)	0.06
45	0.2 (0.2–0.2)	0.17 (0.15–0.20)	0.4 (0.3–0.6)	0.5 (0.3–0.7)	3.3 (2.4–4.6)	0.1
50	0.4 (0.4–0.5)	0.4 (0.3–0.4)	0.7 (0.5–1.0)	0.9 (0.7–1.3)	5.1 (3.9–6.7)	0.3
55	0.9 (0.8–0.9)	0.8 (0.7–0.8)	1.5 (1.0–2.0)	1.5 (1.1–1.9)	6.8 (5.2–8.9)	0.5
60	1.5 (1.4–1.6)	1.4 (1.3–1.5)	2.8 (1.6–4.7)	2.2 (1.7–3.0)	8.7 (6.4–11.6)	1.0
65	2.6 (2.4–2.9)	2.5 (2.2–2.7)	2.8 (1.6–4.7)	4.1 (2.8–5.8)	12.5 (6.7–22.7)	1.7

HNPCC = hereditary non-polyposis colorectal cancer.
*Individuals without a family history of HNPCC-associated cancer.

Table V. Cumulative incidence (%) and 95% CI of a second HNPCC tumor in different 'HNPCC risk groups'

Years after 1st diagnosis	All	Onset ≥50	Onset <50	Multiple and familial, onset ≥50	Multiple and familial, onset <50	Reference*
5	2.6 (1.6–4.2)	2.2 (1.2–3.9)	5.7 (1.3–22.3)	–	7.3 (2.3–21.4)	1.7 (1.5–2.0)
10	5.0 (3.2–7.7)	4.1 (2.4–7.0)	5.7 (1.2–22.3)	7.3 (1.9–26.3)	11.7 (4.3–29.7)	3.2 (2.8–3.7)
15	10.2 (6.7–15.2)	6.7 (3.9–11.6)	41.4 (13.7–85.0)	13.1 (4.3–36.5)	26.4 (11.4–53.9)	4.9 (4.2–5.7)

HNPCC = hereditary non-polyposis colorectal cancer.
*Individuals without a family history of HNPCC-associated cancer.

Cumulative incidence of HNPCC-associated tumors

The cumulative incidences of HNPCC-associated cancer are presented in Table IV The incidences in the two groups 'multiple' and 'familial' were similar, and these groups were therefore combined, although a distinction was made for diagnosis before and after age 50 in the proband. The cancer risks in men and women were similar. The cumulative incidences confirm that, for young individuals, the highest risks are confined to those in the 'familial/multiple, onset <50' group (Table IV).

Cumulative incidence of a second tumor in offspring

Overall, 10% of the affected children developed a second malignancy within 15 years after the first diagnosis (Table V). The highest risk of multiple primary tumors was found among individuals whose parent was diagnosed before age 50; 26% of the offspring in the 'multiple, onset <50' and 'familial, onset <50' groups developed an additional cancer within 15 years.

Type of first tumor in offspring

The predominant first cancers in the offspring were colon cancer in males (57% of the cases) and endometrial cancer in females (42% of the cases) (Table VI). In the subgroup 'all, onset <50', colon cancer was the most common first diagnosis also in females (44% of the cases).

Discussion

Hereditary cancers are characterized by young age at diagnosis and an increased risk of multiple primary malignancies. In our material, the observed modification of familial risk by parental age at diagnosis and the occurrence of multiple tumors thus probably reflect hereditary cancer. The excess risks for cancer of the colon, endometrium, rectum, ovaries, and stomach that were pointed out in this study are in line with the HNPCC tumor spectrum. A subgroup of the cohort constituted individuals who had both a parent and a sibling with HNPCC-associated cancer and at least one with onset <50. If

Table VI. Type of first HNPCC tumor in offspring (%) in relation to parental age at diagnosis and offspring gender

Type of 1st HNPCC-associated cancer	All		Onset ≥50		Onset <50		Multiple and familial, onset ≥50		Multiple and familial, onset <50	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Colon	56.6	37.4	55.2	36.5	57.1	44.1	67.5	42.1	65.6	40.6
Rectal	36.3	16.8	37.6	17.4	42.9	17.7	25.0	15.8	25.0	6.3
Endometrial	–	42.0	–	42.5	–	29.4	–	39.5	–	50.0
Small intestine	1.5	1.9	1.7	1.9	0	5.9	0	0	0	0
Upper urinary tract	5.6	1.9	5.6	1.8	0	2.9	7.5	2.6	9.4	3.1

HNPCC = hereditary non-polyposis colorectal cancer.

the offspring in such families developed cancer, the Amsterdam criteria were fulfilled and, accordingly, high relative cancer risks were demonstrated in this subgroup (Table II). Even higher relative risks were demonstrated in offspring whose parent had developed more than one HNPCC-associated cancer with the first diagnosis before age 50 (Table II), which points out the importance of considering multiple malignancies in one individual as suggestive of hereditary cancer.

Individuals whose parents were diagnosed with an HNPCC-associated cancer before age 50 had an increased risk of ovarian cancer and gastric cancer. Although HNPCC mutation carriers have a high risk of developing ovarian cancer and gastric cancer, these tumor types are not included in the Amsterdam criteria (15, 18). Our data suggest that extracolonic tumors should be considered when recommending control programs also for individuals from families that do not fulfill the Amsterdam II criteria.

Cancers in the small intestine and the urinary tract are rare tumors but are included in the Amsterdam II criteria, and the risk in HNPCC patients is increased 25–100-fold compared with in the general population (14, 15, 20). However, the lifetime risk of these tumors in HNPCC patients is less than 5% and, accordingly, the risk analysis herein was partly inconclusive due to a limited number of tumors, with only a few significant SIR values (in the 'onset <50' and 'famlial' groups) (Table II).

Children whose parents developed HNPCC-associated cancers were, besides the risk of colorectal cancer, at a significantly, albeit modest, increased risk also for breast cancer, malignant melanoma, and testicular cancer. These tumor types are not believed to constitute part of the HNPCC tumor spectrum, but may signify other familial cancer syndromes. An association between breast cancer and colorectal cancer has been described within the hereditary breast and colorectal cancer (HBCC) syndrome. The 1100delC mutation in the *CHEK2* gene has been described at increased frequency in such families, but probably does not represent the major underlying cause of HBCC (21). Malignant melanoma occurs in a hereditary form together with pancreatic cancer due to mutations in the *p16* gene (22). Although malignant melanoma has not been associated with the HNPCC phenotype, an increased risk of colorectal and endometrial cancer in the offspring of patients with pancreatic cancer has been demonstrated (23). Testicular cancer has also been described as occurring at increased frequency in individuals whose 1st-degree relatives have been affected, but these findings may also be a manifestation of common lifestyle factors and no specific syndrome or association with other tumor types has been recognized (24). No consistently significantly decreased cancer risks among offspring of individuals with HNPCC-associated cancer were identified in our study, although decreased risks of borderline significance were seen for laryngeal cancer, cancer of the trachea, bronchus and lung, and malignancies of bone and soft tissue. However, a few sarcoma cases have been described in HNPCC individuals and have also displayed MSI, characteristic of MMR-defective tumors (25, 26). Although a reduced risk for lung cancer has been reported, no consistently reduced risks for specific tumor types have been demonstrated in HNPCC (27).

We had no information about possible confounding factors such as shared diet and smoking habits in the families. Thus, it is likely that some of our observed risk estimates could be affected by environmental and lifestyle factors. Exposure to environmental risk factors usually causes a moderate increased risk, whereas hereditary mutations are characterized by a strong increased risk. Accordingly, in the groups with the highest relative risks, the risk estimates would probably only be slightly changed if possible confounding factors were taken into account.

When different diagnoses in the proband were investigated separately, a higher relative risk was found for parental cancer at concordant sites compared to the relative risk in the whole cohort, e.g. the offspring's risk of developing colon cancer or endometrial cancer was higher if the parents had developed colon or endometrial cancer, compared to the risk among offspring whose parents had developed any HNPCC-associated cancer (Tables II and III). The higher SIRs for cancers at concordant sites, compared to those in the whole HNPCC cohort, may reflect site-specific familial cancer syndromes. Alternatively, this observation may reflect variability in tumor spectra between different HNPCC families; extracolonic cancers are less frequent in families with mutations affecting the MMR gene *MLH1,* whereas *MSH6* mutations are associated with endometrial cancer (15, 20, 28, 29). The increased risks of colorectal cancer and endometrial cancer in children whose both parents had developed an HNPCC-associated cancer may indicate recessive mechanisms of inheritance. Overall, part of the familial risks demonstrated in this study may be explained by different patterns of inheritance, such as recessively acting alleles, low-penetrant alleles, or polygenic mechanisms. In a previous study utilizing the Swedish Cancer Registry, Hemminki & Li reported an overall familial risk of colorectal cancer of 2.0 and a population-attributable proportion (i.e. colorectal cancers attributable to a positive family history) of 4.9% (9).

The cumulative cancer incidence in our cohort, which includes patients up to age 60, was 1.5% for any HNPCC-associated cancer (compared with 1.0% among individuals without a family history of these tumor types). In the groups 'multiple' and 'familial, onset <50' the cumulative incidence was 5.1% before age 50 and 8.7% before age 60 (Table IV). If a child in the 'familial, onset <50' group develops cancer, the family fulfills the Amsterdam criteria. The cumulative risk is thus considerably lower than that described in HNPCC. This reflects that sporadic tumors are included in our material, but may also support a role for other inherited cancer syndromes than HNPCC associated with the tumor spectrum studied. Cumulative incidence of a second tumor in the high-risk groups ('multiple' and 'familial', onset <50) was 26% within

15 years of diagnosis (Table V), which is in accordance with the 30% risk of developing a metachronous tumor in HNPCC (17).

In summary, we confirm a familial clustering of HNPCC-associated tumors and demonstrate significantly increased risks of malignancy, compatible with high-penetrant, dominant genes being involved in the pathogenesis of these cancer types. Rather than assessing cancer risk in defined HNPCC families, this study focuses on cancer risk attributable to parental cancer at these sites, thus also including sporadic tumors. The highest risks were observed for cancers of the colorectum, endometrium, ovary, and stomach. Colorectal or endometrial cancer in the parent entailed a more pronounced risk for the offspring, although the combined results of this study point out that any of the HNPCC-associated tumor types included in the Amsterdam criteria should be considered when counseling individuals with a familial aggregation of cancer. The strongest risk factors were occurrence of multiple primary tumors in the parent, both a parent and a sibling affected, and young age at onset in the parent.

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