Second Primary Cancers after Sporadic and Familial Colorectal Cancer[1]

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Abstract

Second cancers were studied among 68,104 cases of colorectal cancer (CRC) from the Swedish Family-Cancer Database. A total of 1,113 patients received a diagnosis of second CRC; 25 of them had a family history of CRC. Cases of second CRC with a family history were diagnosed up to 10 years before sporadic cases. The relative risk (RR) of all second CRCs was 2.21 compared with the first CRC. Familial second CRCs had a 2-fold risk compared with the sporadic forms. Age of onset was the most important covariate of second CRCs; the relative risk at ages 15–39 years was 27 compared with the first CRC. Familial CRC was associated with a high risk of small-intestinal, endometrial, and gastric cancers apart from CRC, all typical of hereditary nonpolyposis CRC (HNPCC). Among familial cases, 36% of second CRCs and 100% of endometrial cancers came from families that fulfilled the Bethesda criteria for HNPCC. Only 12 families conformed to the Amsterdam criteria; in family members, the risk of second CRC was 127-fold and that of endometrial cancer 257-fold. Other sites that were in excess among all second cancers were many cancers linked to HNPCC and, additionally, breast, prostate, thyroid and other endocrine, skin, and genital cancers. The high risk of second cancer after early-onset CRC calls for evaluation of family history and clinical surveillance.

Introduction

More than 90% of CRCs[3] are adenocarcinomas but carcinoids are common at a young age (1). The incidence rate of CRC has increased earlier in the western countries but the rate has been stable or even decreased recently (2–4). Migrant studies have shown that environmental factors are important in CRC (5). According to a recent twin study, 60% of the variation in CRCs was attributed to random environmental effects and 35% to heritable factors; shared environmental effects accounted for 5%, which was not statistically significant (6). Among the environmental factors, diet, and particularly the intake of vegetables, is assumed to be important (7). Physical activity is another environmental factor linked to the risk of CRC. Insulin and the insulin-like growth factor system are physiological factors modulating the effects of diet and physical activity, and the levels of these factors are related to the levels of risk of incurring CRC (8). Among the heritable causes of CRC, two autosomal dominant syndromes of high penetrance, familial adenomatous polyposis coli (FAP) and HNPCC, as well as several rarer conditions, are recognized (9–15). HNPCC, which is attributable to mutations in the mismatch DNA repair genes, is the most common of these, accounting for some 3% of CRC (16). Mutation carriers are prone to developing multiple primary CRCs and tumors at extracolonic sites, including the endometrium, ovary, small intestine, biliary tract, urinary tract, stomach, kidney, and nervous system (16, 17), and probably the skin when nonmelanomatous skin cancer is involved. In mutation carriers, the risks of CRC and endometrial cancer have been >60 times higher than the population rate (16). Multiple primary cancers are common in HNPCC families (18–20). HNPCC is characterized by microsatellite instability, but this condition is also found in sporadic CRC (21).

Improvements in cancer survival result in increasing proportions of patients with diagnoses of second primary cancer. The interest in second cancers can be of two kinds. Firstly, second cancers may indicate the effects of treatment for the first cancer (22, 23), and secondly, they may be caused by the same environmental or genetic factors that caused the first cancer (24). Concordant second cancers may be particularly informative of polygenic cancer risks (25). In some cases, the intense medical scrutiny after the first cancer may lead to overdiagnoses. However, in the Swedish Cancer Registry practically all reported cancers are histologically or cytologically verified, assuring correctness of diagnosis (26). Here we analyze the risk for second primary CRCs and for any discordant neoplasm after the initial CRC in men and women by family history using the nationwide Swedish Family-Cancer Database (27–30). The Database offers unique possibilities for reliable estimates of familial risks, because the data on family relationships and cancers were obtained from registered sources of practically complete coverage (31, 32). We followed second cancers after 68,000 CRCs, compared with 2,200 colon cancer cases followed in the only other previous population-based study on multiple primaries and family history (33).

Subjects and Methods

The Swedish Family-Cancer Database includes all persons born in Sweden after 1934 with their biological parents, totaling over 9.6 million individuals (28). Cancers were retrieved from the nation-wide Swedish Cancer Registry from years 1958 to 1996. The completeness of colon and rectal cancer registration in the 1970s was estimated to be 96.4 and 98.0%, respectively, and is now considered to be close to 100%. The percentage of cytologically or histologically verified cases for colon cancer was 98%, and for rectal cancer was 99% (26). A four-digit diag-

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[3] The abbreviations used are: CRC, colorectal cancer; HNPCC, hereditary nonpolyposis CRC; RR, relative risk; SIR, standardized incidence ratio; CI, confidence interval.

Table 1 Number and familial proportion of first and second primary CRCs in men and women

	Men		Women	
	First primary cancer	Second primary cancer	First primary cancer	Second primary cancer
All cases				
Number	36,755	628	31,329	485
Mean age ± SD	66.15 ± 12.08	69.82 ± 11.23	64.84 ± 13.51	71.32 ± 10.30
Familial cases				
Number	450	18	441	7
Mean age ± SD	54.38 ± 15.35	59.06 ± 15.03	53.85 ± 15.48	68.29 ± 11.97
Familial proportion (%)	1.22	2.87	1.41	1.44

Table 2 Risk for second primary CRC and familial cancer in men and women

Sex	First primary cancer				Second primary cancer									
	Familial				Sporadic (1)				Familial (2)				SIR ratio	
	O[a]	E	SIR	95% CI	O	E	SIR	95% CI	O	E	SIR	95% CI	(2):(1)	95% CI
Men	450	286	1.57	1.43–1.72	610	293.94	2.08	1.91–2.24	18	2.20	8.18	4.84–12.40	3.94	2.47–6.30
Women	441	276	1.60	1.45–1.75	478	210.78	2.27	2.07–2.48	7	1.67	4.19	1.66–7.87	1.85	0.88–3.90
All	891	562	1.59	1.48–1.69	1088	504.72	2.16	2.03–2.29	25	3.87	6.46	4.18–9.24	3.00	2.02–4.45

[a] O, observed number of cases; E, expected number of cases.

nostic code according to the 7th revision of the International Classification of Diseases (ICD-7) was used. ICD codes 153.0–154.9 were used for CRCs, apart from code 154.1, which was used for anus. A "second CRC" was included if the time difference between first and second primary cancer was at least 1 month. The analysis presented in Table 4 additionally included the condition that the second CRC was diagnosed at a different anatomical subsite, as defined by the fourth digit in ICD-7. For discordant sites other than CRC, even synchronous cancers were included.

Family history information was collected on all first-degree relatives (parents, siblings, and offspring). The effect of family history was not separately considered by the type of relationship, because of the limited number of familial cases among second cancers; however, an analysis separating the parental and sibling probands has been carried out for first CRCs (34). No molecular diagnostic data were available. A patient was included in the follow-up only once, irrespective of the number of affected relatives. Clinical diagnosis of HNPCC was based on the Amsterdam or Bethesda criteria (11, 35). The Bethesda criteria encompass all of the families fulfilling the Amsterdam criteria. However, because data were lacking on colorectal adenomas and some histological types, only the following additional items of the Bethesda criteria were considered applicable: individuals with CRC and with a first-degree relative under the age of 45 years in whom either CRC or any HNPCC-related cancer was diagnosed. The HNPCC-related cancers encompassed colorectal, endometrial, ovarian, gastric, hepatobiliary, small intestinal, and renal tract transitional cell cancers (11).

Follow-up for second cancer was started after the initial diagnosis of CRC. Follow-up was terminated on death, emigration, second cancer diagnosis, or the closing data of the study, December 31, 1996, whichever came first. Age-specific RRs were calculated for CRC. SIRs were calculated as the ratio of observed (*O*):expected (*E*) number of cases. The expected number (*E*) of cases was calculated from 5-year-age-specific, period-specific, sex-specific, and tumor site-specific standard incidence rates in the corresponding general population (36); 95% CIs were calculated assuming a Poisson distribution (36). In Table 2, two SIRs were compared by dividing these with each other to obtain a "SIR ratio."

Results

The Family-Cancer Database covered years 1958 to 1996 from the Swedish Cancer Registry and included 36,775 men and 31,329 women with primary CRC (Table 1), including 450 men and 441 women with a family history (first-degree relatives: parents, children, and sibs with concordant cancer). Among those affected with second primary CRC, there were 628 men and 485 women, including 18 men and 7 women with a family history of CRC. In women, there was a similar proportion of first and second primary cancer cases among familial cases. In men, the familial proportion with second primary cancer was higher than that in women (2.87 *versus* 1.44%). Compared with all cases, the patients with a family history of CRC had an earlier age of onset by 10 years in both men and women. The total number of second cancers was 5,731, and 83 occurred in patients with a family history of CRC. Total accumulated person-years of follow-up amounted to 349,204; persons with a family history accumulated 5,212 person-years.

Table 2 shows the SIR for familial first primary cancer and SIRs for second primary CRC by family history in men and women. Compared with the sporadic cases, the patients with a family history had an increased risk for second primary cancer. The SIR ratio (familial:sporadic) was 3.94 (95% CI, 2.47–6.30) for men and 1.85 (95% CI, 0.88–3.90) for women.

Age-specific incidence rates were calculated for all cases, as well as for familial first and second primary CRCs among men and women (Table 3). The total number of cases is somewhat less than in Table 1 because, in Table 3, cases were included only if patients were ≥15 years of age. The patients, even without family history, had a much higher incidence rate of second primary cancer compared with first primary cancer. The RRs were >10 for second CRCs when diagnosed before age 50. The overall RR for second CRC was 2.21, and for familial second CRC, it was 2.00. It is noteworthy that a very

Table 3 Incidence rate (cases/100,000 person-years) of first and second primary CRC

Age at diagnosis	First primary cancer		Second primary cancer		RR	95% CI	Second primary cancer, sporadic		Second primary cancer, familial		RR	95% CI
	n	IR[a] (1)	*n*	IR (2)	(2):(1)		*n*	IR (3)	*n*	IR (4)	(4):(3)	
15–39	2,405	2.33	9	63.98	27.43	14.26–52.78	8	59.85	1	212.77	3.55	0.44–28.42
40–49	4,747	13.42	43	199.98	14.90	11.04–20.12	38	187.75	5	395.26	2.11	0.83–5.35
50–59	11,538	40.92	121	240.34	5.87	4.91–7.03	114	232.83	7	505.42	2.17	1.01–4.66
60–69	20,339	101.63	272	285.39	2.81	2.49–3.17	269	284.49	3	395.26	1.39	0.45–4.34
70–79	21,124	199.89	442	390.41	1.95	1.78–2.15	436	387.71	6	787.40	2.03	0.91–4.55
80–	7,803	263.25	226	415.67	1.58	1.38–1.80	223	412.62	3	914.63	2.22	0.71–6.93
All[b]	67,956	144.15	1,113	319.09	2.21	2.09–2.35	1,088	315.48	25	629.56	2.00	1.34–2.97

[a] IR, incidence rate.
[b] All incidence rates were adjusted to the distribution of population for second CRC.

Table 4 SIR for second primary cancer after CRC

Second cancer sites	Follow-up interval								
	<1 year			1–10 years			>10 years		
	O[a]	SIR	95% CI[b]	O	SIR	95% CI	O	SIR	95% CI
UADT	10	1.17	0.56–2.01	79	**1.35**	**1.07–1.66**	31	**1.56**	**1.06–2.16**
Esophagus	3	1.15	0.22–2.82	24	1.36	0.87–1.95	7	1.22	0.48–2.29
Stomach	43	**2.22**	**1.61–2.94**	148	1.08	0.91–1.265	60	1.17	0.89–1.49
Small intestine	55	**33.96**	**25.58–43.53**	45	**3.91**	**2.85–5.14**	10	**2.35**	**1.12–4.02**
Colorectum	125	**2.70**	**2.25–3.20**	678	**2.03**	**1.88–2.19**	310	**2.40**	**2.14–2.68**
Different subsites	108	**3.03**	**2.49–3.63**	625	**2.21**	**2.22–2.60**	300	**2.68**	**2.39–3.00**
Liver	30	**2.41**	**1.62–3.35**	81	0.89	0.71–1.09	41	1.12	0.81–1.50
Pancreas	26	**2.12**	**1.38–3.01**	98	1.11	0.90–1.35	49	**1.46**	**1.08–1.90**
Lung	38	1.30	0.92–1.75	219	1.09	0.95–1.24	82	1.22	0.97–1.50
Breast	49	**1.59**	**1.18–2.07**	284	**1.23**	**1.09–1.38**	112	1.19	0.98–1.42
Cervix	9	**2.71**	**1.23–4.77**	18	0.74	0.44–1.13	4	0.44	0.11–0.97
Endometrium	16	**2.08**	**1.19–3.22**	107	**1.87**	**1.53**–2.24	37	**1.64**	**1.16–2.21**
Ovary	47	**7.39**	**5.43–9.65**	79	**1.68**	**1.33–2.07**	17	0.92	0.53–1.41
Other female genitals	1	0.75	0.00–2.93	22	**2.11**	**1.32–3.09**	9	1.88	0.85–3.31
Prostate	178	**2.51**	**2.16–2.90**	604	**1.22**	**1.12–1.32**	212	**1.20**	**1.05–1.37**
Other male genitals	1	1.43	0.00–5.62	6	1.26	0.45–2.47	6	**3.75**	**1.35–7.35**
Kidney	53	**4.48**	**3.36–5.77**	129	**1.56**	**1.30–1.84**	32	1.10	0.75–1.51
Urinary bladder	36	**1.76**	**1.23–2.38**	192	**1.34**	**1.15–1.53**	63	1.23	0.94–1.55
Melanoma	17	**2.20**	**1.28–3.37**	90	**1.67**	**1.34–2.03**	18	0.94	0.56–1.42
Skin	12	0.80	0.41–1.31	137	**1.23**	**1.03–1.44**	60	1.27	0.97–1.61
Nervous system	24	**2.95**	**1.89–4.25**	64	1.14	0.87–1.43	25	1.30	0.84–1.85
Thyroid gland	8	**3.88**	**1.66–7.04**	22	1.49	0.93–2.18	15	**2.74**	**1.53–4.29**
Endocrine glands	16	**3.20**	**1.82–4.96**	49	**1.37**	**1.01–1.78**	17	1.29	0.75–1.97
Connective tissue	5	2.34	0.74–4.84	19	1.25	0.75–1.88	8	1.44	0.61–2.61
Lymphoma	25	**2.12**	**1.37–3.04**	98	1.17	0.95–1.41	42	1.34	0.97–1.78
Myeloma	3	0.50	0.09–1.23	44	1.02	0.74–1.35	10	0.62	0.29–1.06
Leukemia	22	**2.20**	**1.38–3.22**	72	1.02	0.79–1.26	36	1.36	0.95–1.84
Any cancer	864	**2.33**	**2.18–2.49**	3513	**1.33**	**1.28–1.37**	1354	**1.37**	**1.30–1.44**

[a] O, observed number of cases.
[b] Bold type, 95% CI does not include 1.00.

small proportion of second CRCs can be accounted for by family history because of the small number of cases, 25 from a total of 1113.

Second cancers after CRC were analyzed in men and women combined (Table 4). The follow-up time after the first cancer was divided into three periods: <1, 1–10, and >10 years. The last period may show the effects of treatment. All of the second cancers were increased to a SIR of 2.33 in the first period and to a SIR of 1.3–1.4 in the later periods. The SIR for CRC was >2.00 throughout the follow-up period. Because of some concern that a second CRC might be a recurrence, a separate analysis was carried out for second cancers diagnosed in subsites that were different from the first subsite. In fact, most cancers were located at different subsites, and the SIRs did not materially change. Small intestine and ovarian cancers showed very high SIRs within the first year of follow-up. Among second cancers followed for 1–10 years, SIRs were increased for upper aerodigestive tract, small intestine, colorectum, breast, endometrium, ovary and other female genital, prostate, kidney, urinary bladder, melanoma, skin (squamous cell carcinoma), and endocrine gland cancers. Thyroid gland showed increased SIRs in the first and last period. Among the 45 cases of thyroid cancer, only 2 were medullary cancers. However, because the registration of medullary cancers as a separate histology was introduced in 1985, only 25 of the cases were informative, *i.e.*, 2 of a total of 25 thyroid cancers were medullary thyroid cancers (37).

Table 5 presents SIRs for second cancers after familial

Table 5 SIR for second primary cancer after familial CRC

Second cancer	Follow-up interval								
	0–10 years			>10 years			All		
	O[a]	SIR	95% CI[b]	O[a]	SIR	95% CI	O[a]	SIR	95% CI
Stomach	2	1.99	0.19–5.69	4	**9.08**	**2.36–20.16**	6	**4.15**	**1.49–8.13**
Small intestine	2	**49.95**	**4.71–143.16**				2	**49.95**	**4.71–143.16**
Colorectum	12	**4.85**	**2.49–7.98**	13	**11.97**	**6.34–19.35**	25	**7.02**	**4.54–10.04**
Lung	3	1.90	0.36–4.66				3	1.90	0.36–4.66
Breast	3	1.10	0.21–2.70	2	2.11	0.20–6.04	5	1.36	0.43–2.82
Cervix	2	4.65	0.44–13.33				2	4.65	0.44–13.33
Endometrium	7	**9.37**	**3.71–17.60**	1	4.31	0.00–16.89	8	**8.17**	**3.49–14.81**
Ovary	2	3.08	0.29–8.82				2	3.08	0.29–8.82
Prostate	6	1.73	0.62–3.39	2	1.36	0.13–3.89	8	1.62	0.69–2.93
Kidney	2	7.17	0.68–20.54				2	7.17	0.68–20.54
Skin	2	2.82	0.27–8.08	1	9.17	0.00–35.96	3	3.66	0.69–8.98
Nervous system	2	3.17	0.30–9.08	1	8.74	0.00–34.25	3	4.02	0.76–9.86
Lymphoma	3	4.25	0.80–10.43	1	5.91	0.00–23.16	4	**4.57**	**1.19–10.16**
Leukemia	2	8.86	0.84–25.39				2	8.86	0.84–25.39
Any cancer	57	**2.34**	**1.77–2.98**	25	**2.80**	**1.81–4.01**	82	**2.46**	**1.96–3.03**

[a] O, observed number of cases.
[b] Bold type, 95% CI does not include 1.00.

Table 6 SIR for second primary cancer after CRC from HNPCC families

Second cancer	Follow-up interval								
	0–10 years			>10 years			All		
	O[a]	SIR	95% CI[b]	O	SIR	95% CI	O	SIR	95% CI
Stomach	1	16.00	0.01–62.71				1	16.00	0.01–62.71
Colorectum									
All	4	**28.30**	**7.36–62.84**	5	**22.45**	**7.08–46.43**	9	**24.72**	**11.21–43.51**
Amsterdam criteria	2	**65.43**	**6.17–187.54**	2	**2586.15**	**243.80–7412.23**	4	**127.64**	**33.20–283.37**
Lung				1	8.26	0.00–32.39	1	8.26	0.00–32.39
Breast	1	2.38	0.00–9.32				1	2.38	0.00–9.32
Cervix	1	9.36	0.00–36.68				1	9.36	0.00–36.68
Endometrium									
All	7	**88.74**	**35.18–166.66**	1	14.99	0.01–58.76	8	**54.95**	**23.47–99.62**
Amsterdam criteria	4	**257.84**	**67.06–572.43**				4	**257.84**	**67.06–572.43**
Ovary	2	**22.21**	**2.09–63.65**				2	**22.21**	**2.09–63.65**
Prostate				1	3.52	0.00–13.81	1	3.52	0.00–13.81
Nervous system				1	28.97	0.01–113.58	1	28.97	0.01–113.58
Leukemia	1	45.01	0.02–176.46				1	45.01	0.02–176.46
Any cancer	17	**18.43**	**10.71–28.22**	9	**12.35**	**5.60–21.73**	26	**15.74**	**10.27–22.38**

[a] O, observed number of cases.
[b] Bold type, 95% CI does not include 1.00.

CRC. The first follow-up period is given as 0–10 years because only 2 cancers (prostate cancers) were diagnosed during the 1st year. In addition to CRC, increased risks were found for gastric, small intestinal, and endometrial cancers, all with high SIRs. The risk for all cancers was also substantially increased.

Among the more than 3,000,000 families in the Family-Cancer Database, only 12 (0.0004%) fulfilled the Amsterdam criteria for HNPCC, with all 12 consisting of an affecting parent and two affected offspring. We could only partially apply the Bethesda criteria (see "Subjects and Methods"), but a total of 88 families fulfilled these, including the 12 that fulfilled Amsterdam criteria. Among the offspring generation (ages <62 years), there were the Bethesda-defined HNPCC families with 88 CRCs and a total of 4,794 CRCs among all offspring. Thus, 1.84% of offspring CRC could be ascribed to the strictly defined HNPCC. SIRs for second cancers in these HNPCC families are shown in Table 6. The SIR for second CRC was 24.72 and for second endometrial cancer was 54.95. The respective SIRs for the Amsterdam families were 127.64 and 257.84. Even ovarian cancers were in excess. It is noteworthy that the present strictly defined HNPCC families accounted for 9 of 25 familial second CRCs (see Tables 5 and 6) and all of the 8 familial second endometrial cancers.

Discussion

The causes of second primary cancers can be the same environmental and heritable factors that contribute to first primary cancers, and they include additional treatment-related factors, such as X-rays and chemotherapy agents, with carcinogenic and immunosuppressive effects. The documented treatment-related effects on solid tumors manifest themselves ≥1 decades after the first cancer (22, 23, 38–40). Surgery has been the standard therapy in curable CRC; radiotherapy and chemotherapy have been used as an auxiliary therapy to a variable degree. In the present data, there appeared to be no strong evidence for ther-

apy-induced cancers because the risks were not markedly increased in patients followed-up for more than 10 years. Only pancreatic, male genital, and thyroid cancers increased in incidence in the last follow-up period. During treatment of the first cancer, the patient is under intense surveillance, resulting in early diagnosis of the second cancer. Because practically all cancers are histologically or cytologically verified when reported to the Swedish Cancer Registry, it is unlikely that the diagnostic accuracy would be compromised. Diagnosis of cancers in small intestines, ovary, and kidney during the treatment of the first CRC is the likely explanation for the high risks of these cancers within the year of the first diagnosis. Even synchronous cancers were included at such discordant cancer sites. For CRC, SIRs were increased throughout the follow-up time; however, only nonsynchronous cancers were included.

Overall, the risk of second CRC was 2.21-fold higher than the risk of first CRC. The most important variable that influenced the risk of second CRC was age of onset of first CRC, illustrated in Table 3. The RR was 27 between the first and second CRC when the age of onset of was 15–39 years. Even at ages 40–49 years, the RR was 15. An increased risk in second cancer compared with first cancer may be attributable to genetic effects on a susceptible population. In polygenic and recessive conditions, the affected individuals would be expected to be at a high risk of second events, whereas their relatives would not be at risk. Polygenic models have been evoked in explaining the risk for contralateral breast cancers, and the models could also apply for CRC (25, 41).

According to two previous follow-up studies, a history of CRC in first-degree relatives increased the lifetime risk of CRC to 1.7 (42, 43), in line with the familial risks of 1.6 observed here for the first CRC. However, even higher familial risks have been reported, particularly among siblings (33, 44–46). According to the present study, the familial risk in second CRC was quite similar, 2.00 for all ages, and 3.55 for those whose CRC was diagnosed at an early age, 15–39 years. Interestingly, patients with a family history of CRC presented with their first and second CRC almost 10 years earlier than sporadic CRC patients. Previous studies on second cancers after CRC have observed essentially two types of patterns that have become better understood with the characterization of HNPCC as a manifestation of the Lynch syndrome (13). One type is characterized by cancers that associate with HNPCC, endometrial, ovarian, gastric, renal, biliary tract, pancreatic, urinary tract, small intestinal, nervous system cancer, and, sometimes, skin cancer (14, 16, 20, 47, 48). The second type is an increase in cancers that are not features of HNPCC, such as breast and prostate cancers (49, 50 and the cited references). These were found also in the present study; additionally, an excess of thyroid and other endocrine cancers was observed. Nonmedullary thyroid cancer is a manifestation in the familial APC syndrome, and the increase in non-medullary thyroid cancers suggests the involvement of this disease. Lymphoma was increased, particularly during the 1st year of follow-up. A group of malignancies at UADT, cervix, male and female genitals, and skin (both squamous cell carcinoma and melanoma), were moderately increased. Among these, only squamous cell skin cancer has been sometimes associated with HNPCC, but studies on carriers of mismatch gene mutations have been relatively small in size and unable to detect modest increases in rare cancer types. Common to all of these malignancies is that they are squamous cell carcinomas (apart from melanoma) and that they are associated with a strong environmental cause: tobacco and alcohol for the UADT, UV radiation for the skin, and human papillomavirus for the remaining sites (5). Although mismatch repair is not directly involved in any of the above types of DNA damage (12, 13), more data are emerging on the interactions of various repair and cell cycle control pathways that may eventually link the microsatellite instability in CRC and some environmentally induced cancers (51).

In the present analysis of familial CRC, typical HNPCC-related cancers emerged as second tumors, including small intestine, stomach, and endometrium cancers (Table 5). CRC and endometrial cancer showed very high risks in the putative HNPCC families defined by the Amsterdam or Bethesda criteria. These criteria apply poorly to the present database of essentially nuclear families. Second-degree familial relationships are available only on young generations that have not reached the critical age for cancer. However, the application of even the limited parts of the Bethesda criteria showed that a large proportion [9 (36%) of 25] of familial second CRCs and 100% of familial second endometrial cancers came from HNPCC-type families. The applied Bethesda criteria encompassed 1.84% of all offspring CRC. This is within the range, 1–2.5%, that we have estimated as the proportion of HNPCCs from among all Swedish CRCs with age of onset, 0–61 years (52). The present data agree that double primaries of HNPCC-related cancer may be a sign of HNPCC when there is a family history of CRC (20, 48). In contrast, without family history, the likelihood of HNPCC is lower; *e.g.*, among 40 women with CRC and endometrial cancer, only 18% were positive for the two most common mismatch repair gene mutations (*hMSH2* and *hMLH1*) and an additional 35% showed microsatellite instability in tumors (19). It is likely that the inclusion of individuals with double primaries of any HNPCC-related tumors irrespective of family history, as stipulated by the Bethesda criteria, is too permissive, resulting in the inclusion of false-positive families.

The present results can be used to devise clinical surveillance strategy for patients with CRC. Any patient diagnosed with CRC at a young age is at a high risk of having a second CRC and should be followed-up at regular intervals. The risk of second CRC exceeds the risk for first CRC by 27-fold when first CRC is diagnosed before age 40, 15-fold when diagnosed between 40 and 50 years of age, and 6-fold when diagnosed between 50 and 60 years of age. The family history of the patient should be taken at the first diagnosis of CRC. If the family history is positive for CRC, the above risks should be multiplied by 2 or 3, and a molecular analysis for HNPCC is well motivated (19, 53, 54). In surveillance of these patients, all HNPCC-related sites should be considered.

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