Attributable Risks of Familial Cancer from the Family-Cancer Database[1]

Kari Hemminki[2] and Kamila Czene

Department of Biosciences at Novum, Karolinska Institute, 141 57 Huddinge, Sweden [K. H., K. C.], and Division of Molecular Genetic Epidemiology, German Cancer Research Center, 69120 Heidelberg, Germany [K. H.]

Abstract

Population attributable faction (PAF) shows the proportion of the disease that could be prevented if the cause could be removed. PAFs for most types of familial cancer have not been determined. We used the Swedish Family-Cancer Database on 10.2 million individuals and 688,537 parental and 116,741 offspring cancers to calculate familial risks, proportions of affected individuals, and familial PAFs for 28 neoplasms among 0–66-year-old offspring. The data were calculated by an exact proband status in the nuclear families. The familial risks for offspring cancer were increased at 23 of 28 sites from the same cancer in only the parent, at 17 sites from a sibling proband and at 12 sites from a parent and sibling proband. The highest PAFs by parent were for prostate (9.01%), breast (3.67%), and colorectal (5.15%) cancer. However, considering that in gender-specific cancers, the familial effect may originate from grandparents, the PAFs for prostate and breast cancer could be multiplied by 2. The PAFs for the sibling history of prostate, breast, and colorectal cancers were 1.55, 2.85, and 1.23% and for the parent and sibling history 0.99, 0.42, and 0.48%, respectively. Because of mutually exclusive proband definition, the PAFs were additive, giving a total PAF of 20.55% for prostate, 10.61% for breast, and 6.87% for colorectal cancer. The present PAF values give an estimate of the heritable single locus or additive effects for cancer in nuclear families. The data show that the familial PAF of prostate cancer was 20.55%, and breast cancer 10.61%, but for most other sites, it was between 1 and 3%.

Introduction

Familial cancer may be attributable to shared genes, habits, or environment among family members. Family studies are informative of cancer etiology and they guide genetic research in its gene identification and quantification efforts (1). Estimates of familial risk are important in clinical counseling. PAF[3] of familial risk defines the proportion of a particular cancer that is related to familial clustering and that could be gained if familial cancer could be prevented, which may be a science and health policy issue (2). In practice, familial cancers cannot be completely prevented, but PAF shows the weight of familial causes compared with other causes of cancer. Familial cancer can be defined through different probands, parents, siblings, offspring, their combinations, or all first-degree relatives, with genetic and clinical implications. Any recessive effects would be seen only among siblings, and if the sibling risks are higher than the risk between parents and offspring, different genetic or environmental mechanisms may underlie (3). Unfortunately, the ambiguous term first-degree relative has been widely used in genetic epidemiology of cancer. Although some studies have considered the number of affected family members, practically no study has compared independent groups of probands. Such independent groups of probands are needed for an unbiased calculation of PAFs. These definitions have also clinical significance: the doctor sees a sibling or a child of a proband, not his or her first-degree relative. The son's risk for prostate cancer is 2.7 if only the father is affected, but it is 23.7 if a brother is additionally affected, a difference with profound effects for clinical counseling (4).

Numerous family studies have been carried out; alone on breast cancer, 52 studies were recently reanalyzed (5), and on prostate cancer, >30 case-control and cohort studies are available (6–8). Family studies usually report familial risks, but they rarely estimate PAFs. Among the numerous family studies, only a few are population-based cohort studies, believed to be the most reliable type of epidemiological study, and almost all of them are based on reported rather than medically verified cancers in family members, which may be a source of serious bias (9, 10). Many of these problems can be avoided if family-based population databases can be linked to cancer registers, as has been accomplished in a few instances (11–13). The Swedish Family-Cancer Database is unique in this regard because it includes practically the whole population in families starting from year 1932 and identifying all cancers in the family members based on the nationwide Cancer Registry. The Family-Cancer Database has been updated several times, and familial risks have been published from some of its previous versions (4, 14, 15). Here we use the 2001 update of the Database, covering now 10.2 million individuals and >1 million tumors to quantify familial risks of all main types of cancer in offspring by three mutually exclusive family relationships, using a parent only, a sibling only, or both as probands, to respond to the clinical counseling situation. These familial risks are used to calculate PAFs for these cancers, most of which lack any previous data. The results define the proportion of invasive

Received 3/22/02; revised 8/30/02; accepted 9/16/02.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] The work was supported by David and Astrid Hagelen's Foundation, The Cancer Society, and The King Gustaf V's Jubileefund. The Family-Cancer Database was created by linking registers at Statistics Sweden and the Swedish Cancer Registry.
[2] To whom requests for reprints should be addressed, at CNT Novum, 141 57 Huddinge, Sweden. Phone: 46-8-6089243; Fax: 46-8-6081501; E-mail: Kari.Hemminki@cnt.ki.se.

[3] The abbreviations used are: PAF, population attributable faction; SIR, standardized incidence ratio; CI, confidence interval.

cancer at different sites for a 0–66-year-old population that can be ascribed to familial causes within nuclear families.

Subjects and Methods

The Swedish Family-Cancer Database, updated in 2001, includes people born in Sweden after 1931 with their biological parents, totaling over 10.2 million individuals (16, 17). The Database is organized in 3.2 million families, with parents and offspring. Cancers were retrieved from the nationwide Swedish Cancer Registry from years 1958 to 1998. In the 2001 update, the number of invasive cancers in the second generation, offspring, was 157,000. A four-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7) was used together with histology codes. Cancer sites and the corresponding ICD-7 codes are shown in tables. Oral cancer included lip, mouth, tongue, pharynx, and larynx. The specific histologies were considered for small intestine, where only carcinoid tumors were included, and for colorectum, where only adenocarcinoma was included. Skin cancer only included squamous cell carcinoma.

The completeness of cancer registration in the 1970s has been estimated to be >95% and is now considered to be close to 100%. The percentage of cytologically or histologically verified cases of cancer has been close to 100% (18). The Family-Cancer Database has an incomplete linkage from deceased offspring to parents, particularly among those offspring born between 1932 and 1940 who died before 1990. Of a total of 7.0 million offspring, 216,000 have died by the end of follow-up. Parental information was missing from 15,600 dead offspring who had a diagnosis of cancer (9.9% of all offspring cancers). Only families with complete data on both parents were included.

Because there is incomplete information in the Database about death among cancer cases between years 1958 and 1960, we used the follow-up period between January 1, 1961, and December 31, 1998. SIRs were used to measure the cancer risks for offspring according to occurrence of cancers in their family. SIRs were calculated for offspring whose parent only, sibling only, or parent and sibling had the same concordant cancer, *i.e.*, using parents only, sibling only, or parent and sibling as probands. Follow-up was started for each offspring at birth, immigration, or January 1, 1961, whichever came latest, independently of proband diagnosis. Follow-up was terminated on diagnosis of first cancer, death, emigration, or the closing data of the study, December 31, 1998. In the Family-Cancer Database, aging offspring become parents in due course. Such individuals are considered independently, first as offspring, then as parents. Concordant cancers are extremely rare in three generations, and dependence between the individuals has not been of concern in analysis. When more than two affected offspring were found in any family, they were counted as independent event.

Age-specific incidence rates in offspring were calculated by the 5-year diagnosis ages. Parents' ages were not limited but offspring were 0–66 years of age. Data were shown for ICD-7 sites only if at least two familial pairs were identified for the particular proband status. SIRs were used as estimates of relative risk. They were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year-age-, sex-, tumor type-, period- (10-year bands), socioeconomic status- (four groups), and residential area- (two groups) specific standard incidence rates for all offspring lacking family history (19). For each of the 28 types of cancer analyzed, we used three reference datasets for the calculation of expected numbers: (*a*) offspring with no family history in parents; (*b*) offspring with no family history in siblings; and (*c*) offspring with no family history in parents nor siblings. CIs were calculated assuming a Poisson distribution (19). Risks for siblings were calculated using the cohort method, described elsewhere (3).

The PAF of cases with a family history of cancer was estimated as follows: proportion of cases with a family history × (familial SIR-1)/familial SIR, as defined by Miettinen (20, 21). Note that SIR in the present paper was an estimate of relative risk, *i.e.*, the expected numbers were calculated for those lacking a family history. For siblings, the SIRs were calculated only in families of two or more siblings, as given earlier (3). The proportion of cases with a sibling history was obtained by taking the number of affected siblings in families of two or more affected and dividing this by the number of affected siblings in families of at least one affected sibling. The calculation of SIRs for cancer in all families or in families of two or more offspring gave essentially similar results. PAF was calculated separately for each mutually exclusive family history. In gender-specific cancers, calculations are also shown when the PAF from the available parent were multiplied by 2, assuming that both parental lineages contribute equally to the familial risk.

Results

In the Database, there were 688,537 parents and 116,741 offspring with any invasive cancer. There were 4850 affected parent-offspring pairs with only one affected offspring, 1428 sibling pairs without an affected parent, and 190 triplets of an affected parent and two affected offspring. Table 1 shows familial SIRs for offspring when only a parent had the same cancer. In this and subsequent tables, data are shown when at least two familial pairs were identified. Table 1 also shows 95% confidence intervals, number of observed cases, familial proportion, *i.e.*, the percentage of all affected offspring who have an affected parent, and PAF. Of the 28 shown SIRs, all but those for small intestinal carcinoids, liver, pancreas, other female genitals, and connective tissue were significantly increased and bolded in Table 1. The SIR (12.69) was highest for anal cancer but only based on 2 cases; other high SIRs were for thyroid (7.13), testis (4.58), and esophagus (3.82). Endometrial, ovarian, prostate, skin (squamous cell carcinoma) and nonthyroid endocrine gland tumors, melanoma, and myeloma had SIRs in excess of 2.00; the remaining significant increases ranged between 1.50 and 2.00.

Familial proportion ranged from 0.33% for connective tissue tumors to 15.34% for prostate cancer. SIR and familial proportion were used to calculate familial PAF; the calculation was done for each cancer site, irrespective of the significance of the familial risk. The PAFs ranged from 0.10% for connective tissue tumors to 9.01% for prostate cancer. Other cancers with a large PAF were colorectal adenocarcinoma (5.15) and breast (3.67), lung (2.93), and skin (2.11) cancer. In parentheses, we also show the doubling of PAF for gender-specific cancers if it is assumed that both parental lineages contribute equally to the familial risk.

Familial risks and PAFs are shown in Table 2 for offspring who only have a sibling history. Of 21 sites, all but oral, gastric, pancreatic, and skin cancer were significant, and for esophageal and liver, not 2 cases were available. High SIRs were recorded for testicular (10.02), thyroid (7.65), and kidney (5.25) cancers. Even for the other sites of significant increases, the SIRs were higher than those shown in Table 1. Yet, these data are not

Table 1 SIRs, familial proportions (% of affected offspring with affected parent), and PAFs for offspring with parental history

Cancer site	ICD-7/histology	SIR	95% CI		O[a]	Proportion (%)	PAF (%)
Oral	140–1, 143–8, 161	**1.52**[b]	1.02	2.11	35	1.52	0.52
Esophagus	150	**3.82**	1.38	7.50	7	1.51	1.12
Stomach	151	**1.51**	1.11	1.98	60	4.15	1.41
Small intestinal carcinoids	152/086	8.86	0.84	25.40	2	0.85	0.76
Colorectal adenocarcinoma	153–4/096	**2.04**	1.87	2.22	653	10.11	5.15
Anus	1/541	**12.69**	1.20	36.36	2	0.81	0.74
Liver	155–6	1.53	0.98	2.21	29	2.25	0.78
Pancreas	157	1.52	0.98	2.17	34	2.71	0.93
Lung	162–3	**1.90**	1.67	2.15	280	6.19	2.93
Breast	170	**1.80**	1.72	1.88	1973	8.26	3.67 (7.34)[c]
Cervix	171	**1.95**	1.55	2.40	92	1.91	0.93 (1.86)
Endometrium	172	**2.74**	2.16	3.39	91	3.07	1.95 (3.90)
Ovary	175	**2.91**	2.38	3.49	119	2.87	1.88 (3.77)
Other female genital	176	3.03	0.29	8.67	2	0.50	0.34 (0.67)
Prostate	177	**2.42**	2.21	2.65	507	15.34	9.01 (18.02)
Testis	178	**4.58**	2.56	7.19	15	0.41	0.32 (0.64)
Kidney	180	**1.67**	1.28	2.10	65	2.26	0.90
Bladder	181	**1.73**	1.44	2.04	126	3.81	1.61
Melanoma	190	**2.54**	2.22	2.88	231	2.36	1.43
Skin	191	**2.39**	1.85	3.01	69	3.62	2.11
Nervous system	193	**1.63**	1.38	1.90	155	1.64	0.63
Thyroid	194	**7.13**	5.43	9.07	55	2.00	1.72
Endocrine	195	**2.23**	1.68	2.85	57	1.47	0.81
Connective tissue	197	1.46	0.46	3.03	5	0.33	0.10
Non-Hodgkin's lymphoma	200, 202	**1.76**	1.40	2.16	83	1.83	0.79
Hodgkin's disease	201	**3.02**	1.55	4.97	12	0.50	0.34
Multiple myeloma	203	**2.33**	1.27	3.72	14	1.72	0.98
Leukemia	204–9	**1.53**	1.17	1.95	59	1.18	0.41

[a] O, observed cases with affected parent.
[b] Bold type: 95% CI does not include 1.00.
[c] In parentheses, we show the doubling of PAF for gender-specific cancers.

comparable because all offspring were ≤66 years old, whereas their parents could be at any age. Because of the age limitations, familial proportions in Table 2 were smaller for most sites than those in Table 1. Testicular tumors with relatively young age of onset were the exception; the proportion was 2.30%, higher than their proportion in Table 1. PAFs ranged from 0.03% for oral cancer to 2.85% for breast cancer; even testis cancer with a PAF of 2.07% was high in this group.

Table 3 shows the same parameters for the parent and sibling family history for the limited number of sites in which such clusters were scored. Some of the SIRs were remarkably high, 5198 for small intestinal carcinoids and 244 for thyroid, 53 for endocrine, 25 for endometrial, and 27 for ovarian tumors. In contrast, the SIR breast cancer was not higher than 2.82. The familial proportions were small, and the resulting PAF equally so. The highest PAF was for prostate cancer, shown as 0.99%.

The data shown in Tables 1 to 3 by mutually exclusive proband status are additive on familial proportion and PAF. The sum figures are shown in Table 4. The proportions have increased to 18.58% for prostate, 14.56% for breast, and 12.51% for colorectal cancers. The sum PAFs for these sites have increased to 11.55, 6.94, and 6.87%, respectively. Considering gender-specific cancers and the possibility that both parental lineages contribute equally to the familial risk, results in an increase in PAFs as shown in the parentheses. PAF for breast cancer was increased to 10.61% and that of prostate cancer to 20.55%.

Discussion

Most of the cancer sites studied showed a significant familial effect, which is largely in agreement with the abundant literature on some of the main sites. The familial risk of all site-specific cancer in the Swedish Cancer Registry has been reported to be 1.80 (22). The main question is of course what proportion of the familial risk can be ascribed to heritable and environmental components. Because of interactions, this question cannot be precisely answered and it may even seem tautological. However, it is the question that the twin model, comparison of monozygotic and dizygotic twins, has been traditionally used to answer for all diseases, including cancer. Maximal concordance between twin pairs for a trait or disease is 100%, and this can be apportioned to heritable and environmental variance components. According to the twin data, random environmental variance is the main component of cancer, in agreement with epidemiological studies (23–25). In twin studies, shared environmental component would indicate the environmental component of familial risk. Among 11 site studies, it was not statistically significant for any site; however, in sites where the heritable component was significant, including colorectum, breast, and prostate, it represented 12, 18, and 10% of the sum of heritable and shared environmental effect, respectively (24). Comparison of cancer risks between spouses from the Family-Cancer Database indicated significant shared effects only for stomach and lung cancer, which together with the twin data suggest that the main component of familial clustering is heritable, for cancers that lack strong environmental risk factors (26, 27).

Familial Risks. We have no possibility to discuss the present findings in terms of the global literature on familial risks. Instead, we refer to the earlier site-specific publications from this Database and to summaries of all main sites covered from the earlier versions of the Database (4, 14, 15). The data

Table 2 SIRs, familial proportions (% of affected cases with affected sibling), and PAFs for sibling history

Cancer site	ICD-7/histology	SIR	95% CI		O[a]	Proportion (%)	PAF (%)
Oral	140–1, 143–8, 161	1.17	0.31	2.60	4	0.22	0.03
Stomach	151	1.19	0.11	3.40	4	0.34	0.05
Colorectal adenocarcinoma	153–4/096	**3.01**[b]	2.40	3.69	91	1.85	1.23
Pancreas	157	1.69	0.16	4.85	2	0.21	0.09
Lung	162–3	**2.55**	1.83	3.37	46	1.31	0.79
Breast[c]	170	**2.02**	1.87	2.17	727	5.65	2.85
Cervix[c]	171	**2.15**	1.43	3.02	30	1.07	0.57
Endometrium[c]	172	**3.30**	2.11	4.75	22	1.47	1.03
Ovary[c]	175	**2.82**	1.87	3.95	30	1.35	0.87
Prostate[d]	177	**3.72**	2.60	5.03	34	2.12	1.55
Testis[d]	178	**10.02**	7.38	13.05	48	2.30	2.07
Kidney	180	**5.25**	3.43	7.47	28	1.20	0.97
Bladder	181	**1.84**	1.05	2.85	16	0.62	0.28
Melanoma	190	**3.03**	2.54	3.56	141	1.78	1.19
Skin	191	2.49	0.89	4.87	6	0.40	0.24
Nervous system	193	**2.10**	1.63	2.64	66	0.81	0.43
Thyroid	194	**7.65**	5.16	10.64	32	1.37	1.19
Endocrine	195	**3.84**	2.62	5.28	32	1.01	0.74
Non-Hodgkin's lymphoma	200, 202	**2.61**	1.73	3.67	28	0.75	0.46
Hodgkin's disease	201	**7.13**	3.88	11.35	14	0.68	0.59
Leukemia	204–9	**3.53**	2.30	5.01	26	0.60	0.43

[a] O, observed cases with affected sibling.
[b] Bold type: 95% CI does not include 1.00.
[c] Families with ≥2 daughters.
[d] Families with ≥2 sons.

Table 3 SIRs, familial proportions (% of affected offspring with affected parent and sibling), and PAFs for parent and sibling history

Cancer site	ICD-7/histology	SIR	95% CI		O[a]	Proportion (%)	PAF (%)
Small intestinal carcinoids	152/086	**5,197.51**[b]	489.97	14,896.73	2	1.08	1.08
Colorectal adenocarcinoma	153–4/096	**7.74**	5.09	10.93	27	0.55	0.48
Lung	162–3	**4.04**	1.05	8.97	4	0.11	0.09
Breast[c]	170	**2.82**	2.25	3.45	84	0.65	0.42
Endometrium[c]	172	**24.61**	8.86	48.25	6	0.40	0.39
Ovary[c]	175	**27.31**	9.83	53.53	6	0.27	0.26
Prostate[d]	177	**8.74**	5.17	13.25	18	1.12	0.99
Bladder	181	**12.50**	3.25	27.75	4	0.16	0.14
Melanoma	190	**10.21**	4.86	17.51	10	0.13	0.11
Nervous system	193	**14.93**	6.37	27.06	8	0.10	0.09
Thyroid	194	**243.51**	135.87	382.34	15	0.64	0.64
Endocrine	195	**52.60**	18.93	103.12	6	0.19	0.19

[a] O, observed cases with affected parent and sibling.
[b] Bold type: 95% CI does not include 1.00.
[c] Families with ≥2 daughters.
[d] Families with ≥2 sons.

presented in Tables 1 to 3 were controlled for a number of variables and because of the size and coverage of the Database, they should give the reference values for familial risks for a 0–66-year-old population.

To our knowledge, no other groups have used the definition of mutually exclusive proband categories that we use in our tables. The specific proband status is not only clinically useful, but it may have genetic connotations. The parent history could be because of dominant heritable effects, sibling history (without an affected parent) attributable to recessive or X-chromosome linked effects, and parent and sibling history attributable to high penetrant dominant effects. An alternative interpretation may be that the first two histories show low penetrant dominant effects. Sibling risk can also be because of shared childhood environmental effects such as infections. A direct comparison of SIRs between Tables 1 and 2 is not justified because of the age truncation in Table 2. However, we have truncated the parental ages to 66 years in some earlier publications, and the result has been only a modest increase in SIRs for offspring (28, 29). Thus, the large differences between sibling risk in Table 2 and offspring risks in Table 1 for *e.g.*, testicular and renal cancers and Hodgkin's disease, are not because of age truncation, and they call for other explanations.

We would like to point out some sites for which familial data are not available or they are limited. For oral cancer, previous data have covered only the lip (30). Anal cancer showed a high risk from the parents but only two cases were identified. The anus is a site for human papilloma virus-related cancers, and an infectious etiology may be considered similar to cervical cancer (31). Familial aggregation of lymphohematopoietic malignancies has been previously described, but many studies are small patient series (30, 32–36). The higher risk among siblings than offspring-parents may suggest childhood infections as etiological factors.

Table 4 SIRs, familial proportions (% of affected cases with affected family member), and total PAFs

Cancer site	ICD-7/histology	O[a]	Proportion (%)	Total PAF (%)
Oral	140–1, 143–8, 161	39	1.74	0.55
Esophagus	150	7	1.51	1.12
Stomach	151	64	4.49	1.46
Small intestinal carcinoids	152/086	4	1.93	1.83
Colorectal adenocarcinoma	153–4/096	771	12.51	6.87
Anus	1/541	2	0.81	0.74
Liver	155–6	29	2.25	0.78
Pancreas	157	36	2.92	1.01
Lung	162–3	330	7.61	3.81
Breast	170	2784	14.56	6.94 (10.61)[b]
Cervix	171	122	2.97	1.50 (2.43)
Endometrium	172	119	4.94	3.36 (5.31)
Ovary	175	155	4.50	3.02 (4.90)
Other female genital	176	2	0.50	0.34 (0.67)
Prostate	177	559	18.58	11.55 (20.55)
Testis	178	63	2.71	2.39 (2.71)
Kidney	180	93	3.46	1.87
Bladder	181	146	4.59	2.03
Melanoma	190	382	4.27	2.74
Skin	191	75	4.02	2.35
Nervous system	193	229	2.55	1.15
Thyroid	194	102	4.02	3.56
Endocrine	195	95	2.67	1.74
Connective tissue	197	5	0.33	0.10
Non-Hodgkin's lymphoma	200, 202	111	2.58	1.25
Hodgkin's disease	201	26	1.18	0.92
Multiple myeloma	203	14	1.72	0.98
Leukemia	204–9	85	1.78	0.84

[a] O, observed cases with affected family member.
[b] In parentheses, we show the doubling of PAF for parental history in gender-specific cancers.

The high SIRs noted for parent and sibling history indicate heritable effects through high penetrant genes. Some susceptibility genes have been identified for colorectal adenocarcinoma and endometrial cancer, for breast and ovarian cancer, for melanoma, and for nervous system, thyroid, and endocrine tumors (37, 38). Although the identified genes explain only a small proportion of familial clustering of cancer, they may explain a large proportion of the high penetrant families of Table 3. However, it is remarkable that for small intestinal carcinoids, lung, prostate, and bladder cancer and leukemia, no susceptibility genes have yet been unambiguously identified, although for prostate cancer, candidate genes have been put forward (10, 39–42).

The significance of familial risk is often underestimated from SIRs that are derived for the whole population, because the population SIR is usually the sum effect from families of marginally increased familial risk to those rare families with a very high risk. For example, hereditary nonpolyposis colorectal cancer, the most prevalent cancer syndrome known, only causes a familial risk of 1.5 for colorectal cancer in the Finnish population, despite predisposing the mutations carriers to a 70-fold risk of colorectal cancer (43–46). Carriers of rare mutations of even very high risk may contribute only negligibly to the population risk of a common cancer (47).

Population Risks. PAFs have been commonly calculated for environmental exposures, but for familial cancer, limited data are available (48, 49). Even the concept of PAF for family history is less concrete than that for an environmental exposure such as smoking or asbestos. Genes are inherited from parents, and thus the mechanistically interpreted PAF for heritable effects should only consider the parent-offspring relationship. However, because of low penetrance, this single family relationship would underestimate the magnitude of heritable effects.

The PAF values give an estimate on the heritable effects for cancer when only nuclear families can be studied for single locus or additive effects (48, 49). The independence of the contributing risks from different proband categories is a prerequisite to make the PAFs additive. In the literature, no uniform way of presenting familial PAF has been agreed upon, and consequently, the cited values show a large variation such as from 2.5 to 19% for breast cancer (50–53). The terms first-degree or second-degree relative appear imprecise in this context because of difficulties in defining the ages and numbers of the relatives (54). Even the PAF for siblings depends on the average family size. Another problem in a gender-limited cancer is that the effects to *e.g.*, daughters' breast cancer could be transmitted by the paternal grandmother, on whom information is lacking (55). Technically, this issue could be handled by considering in the PAF calculation that both the maternal and paternal lineage can contribute equally to the risk in daughters and, hence, the multiplication of the derived parental PAF with 2.

The highest PAF, 20.55%, was noted for prostate cancer. However, PAF is a function of age, and for prostate cancer, the age range, 0–66 years, covered in the present study is a young age, and the population would be enriched in familial cases. In a fully aged population, the PAF for prostate cancer would be expected to be lower. PAF for breast cancer was 10.61%, for colorectal adenocarcinoma 6.87%, for lung cancer 3.81%, and for thyroid cancer 3.56%. Even for cancer of very high familial risk, testicular cancer, the PAFs were no higher than 2.71%. An interesting question is the correspondence of PAFs to the her-

itability estimates derived from twin studies or family relationships modeled from this database. The heritability estimates from the twin study for colorectal, breast, and prostate cancer were 35, 27, and 42%, respectively, thus 2–5 times higher than the present estimates. Using the modeling that has been developed for twin studies but applying it to the family data set gave heritability estimates of 13% for colon and rectal cancer and 25% for breast cancer, whereas prostate cancer was not analyzed (38). One reason for the difference between the present and the twin estimates is the inability of this study to fully cover low penetrant and polygenic effects. Low penetrant gene effects will make familial patterns difficult to observe but they affect monozygotic twins. In conclusion, the data suggest that apart from prostate, breast, and colorectal cancer, familial risks observable in nuclear families contribute a small etiological proportion. However, in the families affected with high penetrant gene mutations, the risks may be very high and preventable to a certain degree.

References

1. Potter, J. At the interfaces of epidemiology, genetics and genomics. Nat. Rev. Genet., *2:* 142–147, 2001.

2. dos Santos Silva, I. Cancer epidemiology: principles and methods. Lyon: IARC, 1999.

3. Hemminki, K., Vaittinen, P., Dong, C., and Easton, D. Sibling risks in cancer: clues to recessive or X-linked genes? Br. J. Cancer, *84:* 388–391, 2001.

4. Dong, C., and Hemminki, K. Modification of cancer risks in offspring by sibling and parental cancers from 2,112,616 nuclear families. Int. J. Cancer, *91:* 144–150, 2001.

5. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet, *358:* 1389–1399, 2001.

6. Narod, S. Genetic epidemiology of prostate cancer. Biochim. Biophys. Acta, *1423:* F1–F13, 1999.

7. Hemminki, K., and Dong, C. Familial prostate cancer from the family-cancer database. Eur. J. Cancer, *36:* 229–234, 2000.

8. Matikainen, M., Pukkala, E., Schleutker, J., Tammela, T., Koivisto, P., Sankila, R., and Kallioniemi, O-P. Relatives of prostate cancer patients have an increased risk of prostate and stomach cancers: a population-based, cancer registry study in Finland. Cancer Causes Control, *12:* 223–230, 2001.

9. Glanz, K., Grove, J., Le Marchand, L., and Gotay, C. Underreporting of family history of colon cancer: correlates and implications. Cancer Epidemiol. Biomark. Prev., *8:* 635–639, 1999.

10. Gibbs, M., Stanford, J., McIndoe, R., Jarvik, G., Kolb, S., Goode, E., Chakrabari, L., Schuster, E., Buckley, V., Miller, E., Brandzel, S., Li, S., Hood, L., and Ostrander, E. Evidence for a rare prostate cancer-susceptibility locus at chromosome 1p36. Am. J. Hum. Genet., *64:* 776–787, 1999.

11. Goldgar, D., and Easton, D. Optimal strategies for mapping complex diseases in the presence of multiple loci. Am. J. Hum. Genet., *60:* 1222–1232, 1997.

12. Peto, J., Easton, D., Matthews, F., Ford, D., and Swerdlow, A. Cancer mortality in relatives of women with breast cancer: the OPCS study. Int. J. Cancer, *65:* 275–283, 1996.

13. Carstensen, B., Soll-Johanning, H., Villadsen, E., Söndergaard, J., and Lynge, E. Familial aggregation of colorectal cancer in the general population. Int. J. Cancer, *68:* 428–435, 1996.

14. Hemminki, K., Vaittinen, P., and Kyyrönen, P. Age-specific familial risks in common cancers of the offspring. Int. J. Cancer, *78:* 172–175, 1998.

15. Hemminki, K., and Vaittinen, P. Familial cancers in a nation-wide family-cancer database: age distribution and prevalence. Eur. J. Cancer, *35:* 1109–1111, 1999.

16. Hemminki, K. Genetic epidemiology: science and ethics on familial cancers. Acta Oncol., *40:* 439–444, 2001.

17. Hemminki, K., Li, X., Plna, K., Granström, C., and Vaittinen, P. The nation-wide Swedish Family-Cancer Database: updated structure and familial rates. Acta Oncol., *40:* 772–777, 2001.

18. Centre for Epidemiology. Cancer incidence in Sweden 1998. Stockholm, 2000.

19. Esteve, J., Benhamou, E., and Raymond, L. Statistical methods in cancer research. IARC Scientific Publication. Lyon: IARC, 1994.

20. Miettinen, O. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am. J. Epidemiol., *99:* 325–332, 1974.

21. Rothman, K., and Greenland, S. Modern epidemiology. Philadelphia: Lippincott-Raven, 1998.

22. Lindelof, B., and Eklund, G. Analysis of hereditary component of cancer by use of a familial index by site. Lancet, *358:* 1696–1698, 2001.

23. Doll, R. Epidemiological evidence of the effects of behaviour and the environment on the risk of human cancer. Recent Results Cancer Res., *154:* 3–21, 1998.

24. Lichtenstein, P., Holm, N., Verkasalo, P., Illiado, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., and Hemminki, K. Environmental and heritable factors in the causation of cancer. N. Engl. J. Med., *343:* 78–85, 2000.

25. Peto, J. Cancer epidemiology in the last century and the next decade. Nature (Lond.), *411:* 390–395, 2001.

26. Hemminki, K., Dong, C., and Vaittinen, P. Cancer risks to spouses and offspring in the Family-Cancer Database. Genet. Epidemiol., *20:* 247–257, 2001.

27. Hemminki, K., and Jiang, Y. Cancer risks among long-standing spouses. Br. J. Cancer, *86:* 1737–1740, 2002.

28. Plna, K., and Hemminki, K. Familial bladder cancer in the national Swedish family cancer database. J. Urol., *166:* 2129–2133, 2001.

29. Hemminki, K., and Granström, C. Familial breast cancer risks by morphology: a nation-wide epidemiologic study from Sweden. Cancer (Phila.), *94:* 3063–3070, 2002.

30. Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A., and Skolnick, M. H. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J. Natl. Cancer Inst. (Bethesda), *86:* 1600–1607, 1994.

31. Hemminki, K., Dong, C., and Vaittinen, P. Familial risks in cervix cancer: is there a hereditary component? Int. J. Cancer, *82:* 775–781, 1999.

32. Yuille, M., Houlston, R., and Catovsky, D. Anticipation in familial chronic lymphocytic leukemia. Leukemia (Baltimore), *12:* 1696–1698, 1998.

33. Brown, L. M., Linet, M. S., Greenberg, R. S., Silverman, D. T., Hayes, R. B., Swanson, G. M., Schwartz, A. G., Schoenberg, J. B., Pottern, L. M., and Fraumeni, J. F., Jr. Multiple myeloma and family history of cancer among blacks and whites in the U. S. Cancer (Phila.), *85:* 2385–2390, 1999.

34. Grosbois, B., Jego, P., Attal, M., Payen, C., Rapp, M. J., Fuzibet, J. G., Maigre, M., and Bataille, R. Familial multiple myeloma: report of fifteen families. Br. J. Haematol., *105:* 768–770, 1999.

35. Lynch, H., Sanger, W., Pirruccello, S., Quinn-Laquer, B., and Weisenburger, D. Familial multiple myeloma: a family study and review of the literature. J. Natl. Cancer Inst. (Bethesda), *93:* 1479–1483, 2001.

36. Hemminki, K., and Jiang, Y. Risks among siblings and twins for childhood acute lymphoid leukemia: results from the Swedish Family-Cancer Database. Leukemia (Baltimore), *16:* 297–298, 2002.

37. Vogelstein, B., and Kinzler, K. W. (eds.). The genetic basis of human cancer. New York: McGraw-Hill, 1998.

38. Czene, K., Lichtenstein, P., and Hemminki, K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. Int. J. Cancer, *99:* 260–266, 2002.

39. Xu, J., Meyers, D., Freije, D., Isaacs, S., Wiley, K., Nusskern, D., Ewing, C., Wilkens, E., Bujnovszky P., Bova, O. S. *et al.* Evidence for a prostate cancer susceptibility locus on the X chromosome. Nat. Genet., *20:* 175–179, 1998.

40. Grönberg, H., Smith, J., Emanuelsson, M., Jonsson, B-A., Bergh, A., Carpten, J., Isaacs, W., Xu, J., Meyers, D., Trent, J., and Dambert, J. E. In Swedish families with hereditary prostate cancer, linkage to the HPC1 locus on chromosome 1q24-25 is restricted to families with early-onset prostate cancer. Am. J. Hum. Genet., *65:* 134–140, 1999.

41. Berry, R., Schaid, D. J., Smith, J. R., French, A. J., Schroeder, J. J., McDonnell, S. K., Peterson, B. J., Wang, Z. Y., Carpten, J. D., Roberts, S. G., Tester, D. J., Blute, M. L., Trent, J. M., and Thibodeau, S. N. Linkage analyses at the chromosome 1 loci 1q24-25 (HPC1), 1q42.2-43 (PCAP), and 1p36 (CAPB) in families with hereditary prostate cancer. Am. J. Hum. Genet., *66:* 539–546, 2000.

42. Wang, L., McDonnell, S. K., Elkins, D. A., Slager, S. L., Christensen, E., Marks, A. F., Cunningham, J. M., Peterson, B. J., Jacobsen, S. J., Cerhan, J. R., Blute, M. L., Schaid, D. J., and Thibodeau, S. N. Role of HPC2/ELAC2 in hereditary prostate cancer. Cancer Res., *61:* 6494–6499, 2001.

43. Aaltonen, L., Salovaara, R., Kristo, P., Canzzian, F., Hemminki, A., Peltomäki, P., Chadwick, R., Kääriäinen, H., Eskelinen, M., Järvinen, H., Mecklin, J-P., and de la Chapelle, A. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N. Engl. J. Med., *338:* 14811–14817, 1998.

44. Aarnio, M., Sankila, R., Pukkala, E., Salovaara, R., Aaltonen, L., de la Chapelle, A., Peltomäki, P., Mecklin, J-P., and Järvinen, H. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int. J. Cancer, *81:* 214–218, 1999.

45. Salovaara, R., Loukola, A., Kristo, P., Kaariainen, H., Ahtola, H., Eskelinen, M., Harkonen, N., Julkunen, R., Kangas, E., Ojala, S., Tulikoura, J., Valkamo, E., Jarvinen, H., Mecklin, J., Aaltonen, L., and de la Chapelle, A. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. J. Clin. Oncol., *18:* 2193–2200, 2000.

46. Hemminki, K., and Li, X. Familial colorectal adenocarcinoma and hereditary nonpolyposis colorectal cancer: a nation-wide epidemiological study from Sweden. Br. J. Cancer, *84:* 969–974, 2001.

47. Hopper, J. L., and Carlin, J. B. Familial aggregation of a disease consequent upon correlation between relatives in a risk factor measured on a continuous scale. Am. J. Epidemiol., *136:* 1138–1147, 1992.

48. Risch, N. The genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. Cancer Epidemiol. Biomark. Prev., *10:* 733–741, 2001.

49. Hemminki, K. Correspondence re: Risch, N. Genetic epidemiology of cancer: interpreting family and twin studies and their implications for molecular genetic approaches. Cancer Epidemiol. Biomark. Prev., *11:* 423–426, 2002.

50. Sellers, T. A., Kushi, L. H., Potter, J. D., Kaye, S. A., Nelson, C. L., McGovern, P. G., and Folsom, A. R. Effect of family history, body-fat distribution, and reproductive factors on the risk of postmenopausal breast cancer. N. Engl. J. Med., *326:* 1323–1329, 1992.

51. Slattery, M. L., and Kerber, R. A. A comprehensive evaluation of family history and breast cancer risk. The Utah population database. J. Am. Med. Assoc., *270:* 1563–1568, 1993.

52. Colditz, G. A., Willett, W. C., Hunter, D. J., Stampfer, M. J., Manson, J. E., Hennekens, C. H., and Rosner, B. A. Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. J. Am. Med. Assoc., *270:* 338–343, 1993.

53. Madigan, M. P., Ziegler, R. G., Benichou, J., Byrne, C., and Hoover, R. N. Proportion of breast cancer cases in the United States explained by well-established risk factors. J. Natl. Cancer Inst. (Bethesda), *87:* 1681–1685, 1995.

54. Potter, J. Colorectal cancer: molecules and populations. J. Natl. Cancer Inst. (Bethesda), *91:* 916–932, 1999.

55. Thompson, W. Genetic epidemiology of breast cancer. Cancer (Phila.), *74:* 279–287, 1994.

Attributable Risks of Familial Cancer from the Family-Cancer Database

Kari Hemminki and Kamila Czene

Cancer Epidemiol Biomarkers Prev 2002;11:1638-1644.