Familial and Attributable Risks in Cutaneous Melanoma: Effects of Proband and Age

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We studied familial risks in invasive and *in situ* cutaneous melanoma by comparing the occurrence of melanoma, or discordant cancer, between parents and offspring, and between siblings, based on the Swedish Family Cancer Database of over 10 million individuals. Offspring were 0–66 y of age. Cancers were obtained from the Swedish Cancer Registry from 1961 to 1998. The study was based on 24,818 invasive and 5510 *in situ* cases of melanoma. Standardized incidence ratios were calculated for familial risk. The standardized incidence ratios for offspring was 2.40 (95% confidence intervals: 2.10–2.72) when only the parent had melanoma and it was 2.98 (95% confidence intervals: 2.54–3.47) when only a sibling was affected; when both a parent and a sibling were affected the standardized incidence ratios was 8.92 (95% confidence intervals: 4.25–15.31). The respective population attributable risks were 1.38, 1.20, and 0.10%. The familial risk showed a clear age dependence and somewhat higher risk in *in situ* melanoma than in the invasive counterpart. The highest standardized incidence ratio of 61.78 (5.82–227.19) was noted for offspring whose parent had multiple melanomas. Superficially spreading melanoma showed the highest familial risk both among invasive and *in situ* tumors. Melanoma associated with breast, nervous system, and skin cancers, and *in situ* melanoma possibly also with connective tissue and thyroid tumors and multiple myeloma. ***Key words: heredity/in situ melanoma/invasive melanoma/parent–offspring risks/sibling risks. J Invest Dermatol 120:217–223, 2003***

Sunburn and overexposure to sun are the main environmental risk factors of melanoma (English *et al*, 1997). Familial risks in population-based studies have been over 2.00 between first-degree relatives (Goldgar *et al*, 1994; Hemminki *et al*, 2001c). Inherited traits such as density of nevi, skin type, and pigmentation, and color of hair and eyes appear to explain a part of the familial risk by modulating the response to solar ultraviolet (UV) radiation or by other mechanisms (English *et al*, 1997; Ang *et al*, 1998; Greene, 1998; Zhu *et al*, 1999; Landi *et al*, 2001; Wachsmuth *et al*, 2001; Landi *et al*, 2002). Associations with low-penetrance genes have been sought in case-control studies of polymorphic candidate genes, such as *melanocortin-1 receptor*, and many DNA repair genes (Berwick and Vineis, 2000; Rees, 2000; Kennedy *et al*, 2001; Schaffer and Bolognia, 2001). Direct measurements of DNA repair rates for UV damage, however, have shown no difference between melanoma patients and controls (Xu *et al*, 2000; Zhao *et al*, 2002). Several segregation analyses of melanoma have been carried out with contradictory results. Evidence has been found on genetic heterogeneity and complex patterns of inheritance (Aitken *et al*, 1998).

Susceptibility to melanoma, particularly in families with many affected individuals is linked to mutations in the cell cycle regulator *CDKN2A (p16)* gene, and less frequently to the *CDK4* gene (Fearon, 1997; Harland *et al*, 1997; Aitken *et al*, 1999; Greene, 1999; Zhu *et al*, 1999). Mutations are rare in kindreds with a fewer number of affected individuals, however, e.g., only 7.8% of the Swedish melanoma and dysplastic nevus syndrome families show *CDKN2A* mutations; in many of these families only two individuals were affected (Platz *et al*, 1997); the percentage has been 20% in the tested families from different countries (Bishop *et al*, 2002). The *CDKN2A* gene also harbors polymorphisms, which may modify risk for and survival in melanoma (Kumar *et al*, 2001; Staume *et al*, 2002). Evidence has been provided on the interactions of the *CDKN2A* and *melanocortin-1 receptor* (van der Velden *et al*, 2001). Even if fragments of the genetic basis of melanoma are understood, however, their contribution to the total burden of familial melanoma remains unknown.

The largest dataset ever used for family studies was utilized, i.e., the Swedish Family Cancer Database with 1 million medically verified tumors and over 10 million individuals organized in 3 million families. We analyzed familial risks in invasive and *in situ* cutaneous melanoma by using parental and sibling probands and by considering multiple melanomas in the same individual. Familial risks by histogenetic types were also determined. Association of melanoma with other neoplasms in families was determined. We also calculated population attributable fractions (PAFS) for familial melanoma depending on the proband status. PAF is an indicator of the population impact of a disease, i.e., the proportion of melanoma that would disappear if the familial disease could be prevented (dos Santos Silva, 1999). These data should provide guidance for clinical counseling and promote the mechanistic understanding on melanoma.

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SUBJECTS AND METHODS

The Swedish Family Cancer Database, updated in 2000, includes persons born in Sweden after 1931 with their biologic parents, totaling over 10.2 million individuals and organized in 3.2 million families (Hemminki and Vaittinen, 1998b; Hemminki *et al*, 1998). Cancers, including *in situ* tumors, were retrieved from the nation-wide Swedish Cancer Registry from years 1961 to 1998. The completeness of cancer registration in the 1970s has been estimated to be over 95%, and is now considered to be close to 100%. The percentage of cytologically or histologically verified cases of melanoma has been 100% in recent years (Center for Epidemiology, 2000).

A four-digit diagnostic code according to the seventh revision of the ICD-7 has been used since 1958, together with a code for histologic type (WHO/HS/CANC/24.1 Histology Code). From year 1993 onwards ICD-O-2/ICD with histopathologic data according to the Systematized Nomenclature of Medicine (SNOMED, http://snomed.org) was used; we refer to this classification as "histopathology" or "histogenetic type". Only the first invasive or *in situ* melanoma was considered, if not stated otherwise. All notified cases of melanoma in the Swedish Cancer Registry have been histologically verified in the hospital of diagnosis. In a recent study an experienced pathologist review notified 5289 cases of invasive and *in situ* melanoma and agreed in 98.4% of the cases (Mansson-Brahme *et al*, 2002). The results were not given separately for invasive and *in situ* melanoma, however, and we have no further data on the distinction of, for example, lentigo maligna melanoma and lentigo maligna *in situ*. Lentigo maligna melanoma was rare, however, and it was not discussed in this paper because there were no familial cases. The following ICD-7 codes were pooled: "oral" cancer codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands) and "leukemia" codes 204–207 (leukemias), 208 (polycythemia vera), and 209 (myelofibrosis). Rectal cancer, ICD-7 code 154 was separated for anus (squamous cell carcinoma, 154.1) and mucosal rectum (154.0). Among the skin cancers, only squamous cell carcinoma is registered at the Cancer Registry.

Standardized incidence ratios (SIR) were used to measure the cancer risks for offspring according to occurrence of cancers in their family (parents or siblings were probands). SIR were calculated as the ratio of observed (O) to expected (E) number of cases. The expected numbers of cancers were obtained by assuming that these persons experienced the same cancer incidence as prevailed in the corresponding general population in the Database. Offspring were diagnosed for their first primary cancer at ages 0–66 y, whereas the age of parents at their diagnosis was not limited. Tumor site, sex, 5 y age, period (10 y bands), socio-economic status (six groups), and residential area (two groups) specific standard incidence rates were applied to the appropriate person-years at risk (Esteve *et al*, 1994). Person-years at risk were accumulated for each offspring beginning with the date of birth or January 1, 1961 and ending with the date of diagnosis of a first primary cancer, date of death, date of emigration, or December 31, 1998. Confidence intervals (95% CI) were calculated assuming that the numbers of cancer cases among offspring follow a Poisson distribution (Esteve *et al*, 1994). Sibling risks were calculated using the cohort method as described (Hemminki *et al*, 2001d). In the cohort method one defines a cohort of individuals with at least one affected sibling, and computes the incidence rates in this cohort. The SIR were calculated only in families of two or more siblings.

The PAF of cases with a family history of invasive melanoma was estimated as follows: proportion of cases with a family history × (familial SIR-1)/familial SIR, as defined by Miettinen (1974) and cited in a textbook as formula 16–21 (Rothman and Greenland, 1998). In calculating PAF, we define probands in three ways: only affected parent or sibling, or affected parent and sibling.

RESULTS

The study was based on 24818 cases of invasive cutaneous melanoma and 5510 cases of *in situ* melanoma. The number of offspring (the offspring cohort from whom the expected number of cases are calculated for the parent–offspring analysis) was 9771 in invasive melanoma and 2446 in *in situ* melanoma. The corresponding numbers in the analysis of sibling risk were 8062 and 2027, as only families with at least two offspring were selected. The incidence rates for invasive and *in situ* melanoma in Sweden for the period 1961–98 (standardized according to European standard population) are shown in **Fig 1**. There has been an increase for male and female rates throughout the period; in the case of *in situ* melanoma particularly after 1985. The rates were equally high between the genders in invasive melanoma, whereas in *in situ* melanoma female rates were somewhat higher.

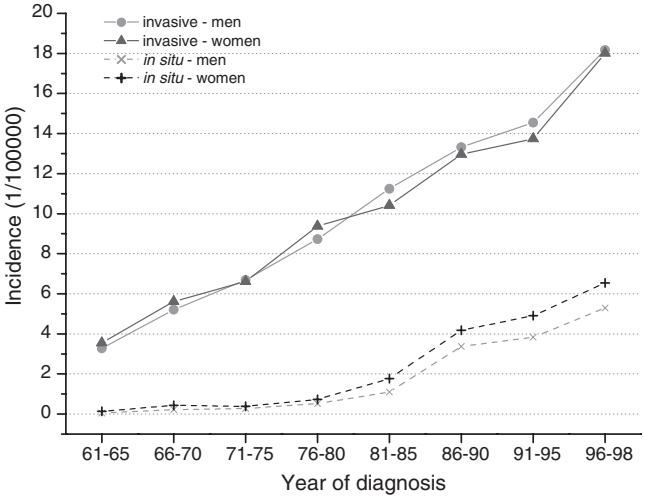

Figure 1. Age-standardized incidence rate of invasive and *in situ* melanoma in years 1961–98.

Familial risks in offspring In this section we show results on melanoma risk in offspring when parents were diagnosed with melanoma, irrespective of whether siblings were also affected. Familial risks for invasive melanoma were 2.41 and 3.15 when a parent presented with one invasive or *in situ* disease, respectively (**Table I**). The corresponding SIR for *in situ* melanoma were 4.03 and 2.92. We considered also familial risks in offspring by multiple melanomas in parents. When a parent presented with two invasive melanomas, the offspring SIRs were 8.02 and 11.71 for invasive and *in situ* melanoma, respectively. If the parent additionally had an *in situ* melanoma, the SIRs were 23.18 and 61.78. When parental invasive melanoma risks were analyzed, the same trend was observed; SIRs in parents were 1.91 (n = 219; 95% CI: 1.67–2.19) and 17.50 (n = 4; 95% CI: 4.55–45.26) when offspring had one invasive, or two invasive and one *in situ* melanoma, respectively (data not shown).

Table II shows familial risks by histogenetic type; however, these codes were only available from year 1993 and thus the numbers of cases were decreased. SIRs in **Table II** were calculated by considering only the person-years of life after 1993 in the offspring, whereas parental cancers were diagnosed at any time. Among invasive types, superficially spreading melanoma showed the highest risk of 2.61, compared with 2.15 (0.92–4.26) for nodular melanoma. For *in situ* types, superficially spreading melanoma showed a high risk of 5.40, whereas the SIR for lentigo type was not significantly increased. χ^2 heterogeneity test showed no significant differences between subtypes of invasive or *in situ* melanoma.

Offspring melanoma was analyzed in terms of any invasive cancer in parents (**Table III**). In addition to melanoma, associations were noted between both forms of melanoma and nervous system cancer. Invasive melanoma associated with breast and skin (squamous cell) cancer. *In situ* melanoma associated with thyroid and connective tissue cancers and multiple myeloma. There was no evidence on the association of melanoma and non-Hodgkin's lymphoma in families. When the associations were studied reversed way, as risk for cancer in offspring by parental melanoma, skin and nervous system cancers remained increased with SIR of 1.56 (n = 27; 95% CI: 1.03–2.20) and 1.25 (n = 105; 95% CI: 1.03–1.51), respectively.

Effects of age and proband status on invasive melanoma In this section we cover only invasive melanoma by distinguishing three mutually exclusive proband groups: only parent with melanoma, only sibling with melanoma, and both parent and

Table I. SIR for melanoma in offspring by multiple parental melanoma

	Invasive melanoma in offspring				*In situ* melanoma in offspring			
Parental melanoma history	O	SIR	95%CI		O	SIR	9s5%CI	
1 invasive	214	**2.41**	**2.10**	**2.76**	88	**4.03**	**3.23**	**4.96**
1 *in situ*	53	**3.15**	**2.36**	**4.12**	12	**2.92**	**1.50**	**5.12**
1 invasive and 1 *in situ*	6	**5.44**	**1.96**	**11.92**	0			
2 invasive	14	**8.02**	**4.37**	**13.50**	5	**11.71**	**3.70**	**27.55**
2 *in situ*	1	3.17	0.00	18.18	1	12.71	0.01	72.83
2 invasive and 1 *in situ*	3	**23.18**	**4.37**	**68.63**	2	**61.78**	**5.82**	**227.19**
1 invasive and 2 *in situ*	1	15.84	0.01	90.81	0			
Invasive, any	241	**2.63**	**2.30**	**2.98**	96	**4.24**	**3.44**	**5.18**
In situ, any	64	**3.44**	**2.65**	**4.40**	15	**3.31**	**1.84**	**5.46**

O, Observed cases; CI, confidence interval.
Bold type: 95%CI does not include 1.00.

Table II. SIR for histopathological type of melanoma in offspring by any parental invasive melanom[a]

	Invasive melanoma in offspring[b]					*In situ* melanoma in offspring[c]			
Type	O	SIR	95%CI		Type	0	SIR	95%CI	
Melanoma, non-specified	31	**2.11**	**1.43**	**3.00**	*In situ* , non-specified	25	**3.64**	**2.36**	**5.39**
Superficially spreading	49	**2.61**	**1.93**	**3.45**	Superficially spreading	8	**5.40**	**2.30**	**10.68**
Nodular	8	2.15	0.92	4.26	Lentigo	3	1.89	0.36	5.59
Other	2	1.75	0.17	6.44	Other	1	1.29	0.00	7.41
All melanoma	90	**2.35**	**1.89**	**2.89**	All melanoma	37	**3.46**	**2.43**	**4.77**

[a]Period of follow-up: 1993–1998. O, Observed cases; CI, confidence interval.
Bold type: 95%CI does not include 1.00.
[b]χ^2 test for heterogeneity = 4.6 on 3 d.f.; p = 0.2
[c]χ^2test for heterogeneity = 6.2 on 3 d.f.; p = 0.1

Table III. SIR for melanoma in offspring by parental cancer*

	Melanoma in offspring				*In Situ* Melanoma in offspring			
Parental Invasive	O	SIR	95%CI		O	SIR	95%CI	
Oral	102	1.01	0.80	1.24	19	0.66	0.35	1.06
Esophagus	30	1.03	0.68	1.45	10	1.34	0.61	2.35
Stomach	220	0.97	0.83	1.12	52	0.98	0.70	1.30
Colorectal adenocarcinoma	496	1.05	0.94	1.15	120	1.03	0.84	1.25
Liver	131	0.89	0.72	1.07	28	0.75	0.47	1.11
Pancreas	149	1.11	0.92	1.31	29	0.94	0.61	1.34
Lung	318	1.02	0.90	1.14	76	0.95	0.73	1.20
Breast	538	**1.12**	**1.02**	**1.22**	135	1.15	0.96	1.37
Cervix	74	**0.78**	**0.60**	**0.98**	17	0.84	0.51	1.26
Endometrium	110	1.01	0.82	1.22	26	0.95	0.60	1.37
Ovary	94	0.94	0.75	1.15	28	1.00	0.63	1.45
Other female genitals	14	0.92	0.50	1.46	5	0.50	0.05	1.42
Prostate	589	1.01	0.93	1.10	161	1.12	0.95	1.31
Kidney	144	1.01	0.84	1.18	44	1.18	0.84	1.58
Bladder	210	1.03	0.89	1.18	58	1.10	0.82	1.42
Melanoma	241	**2.63**	**230**	**2.98**	**96**	**4.24**	**3.44**	**5.18**
Skin	191	**1.40**	**1.20**	**1.61**	34	0.96	0.65	1.32
Nervous system	141	**1.20**	**1.01**	**1.41**	43	**1.45**	**1.04**	**1.92**
Thyroid	33	1.01	0.69	1.39	16	**1.97**	**1.13**	**3.06**
Endocrine	82	1.18	0.93	1.45	26	1.50	0.98	2.13
Connective tissue	30	1.16	0.78	1.61	13	**2.00**	**1.06**	**3.24**
Non-Hodgkin's lymphoma	120	1.06	0.88	1.26	32	1.11	0.75	1.53
Multiple myeloma	66	1.03	0.79	1.29	25	**1.58**	**1.02**	**2.27**
Leukemia	124	1.08	0.90	1.28	35	1.23	0.86	1.67
Total	4247	**1.07**	**1.03**	**1.10**	1128	**1.13**	**1.06**	**1.19**

*Cancer sites with less than 5 cases excluded.
O, Observed cases; CI, confidence interval.
Bold type: 95%CI does not include 1.00.

Table IV. Age-specific SIRs for melanoma by parental history of melanoma

Parental age at diagnosis		Offspring's age at diagnosis														
		0–19			20–29			30–39			40–49			50–66		
0–39	O		4			7			6			0			0	
	SIR		**8.71**			**4.03**			**4.52**							
	95% CI	**2.27**		**19.34**	**1.60**		**7.58**	**1.63**		**8.86**						
40–49	O		7			11			12			3			3	
	SIR		**10.02**			**3.22**			**3.13**			1.15			4.09	
	95% CI	**3.97**		**18.82**	**1.60**		**5.40**	**1.61**		**5.14**	0.22		2.83	0.77		10.02
50–59	O		3			10			24			13			3	
	SIR		4.43			**2.27**			**3.51**			**2.23**			1.15	
	95% CI	0.83		10.85	**1.08**		**3.89**	**2.25**		**5.06**	**1.18**		**3.60**	0.22		2.82
60–69	O		1			9			16			23			16	
	SIR		2.07			**2.38**			**1.86**			**2.40**			**3.34**	
	95% CI	0.00		8.13	**1.08**		**4.19**	**1.06**		**2.89**	**1.52**		**3.48**	**1.90**		**5.17**
70 +	O		0			4			15			21			20	
	SIR					1.58			**1.98**			**1.68**			**1.93**	
	95% CI				0.41		3.50	**1.10**		**3.10**	**1.04**		**2.47**	**1.18**		**2.87**

O, Observed cases; CI, confidence interval.
Bold type: 95% CI does not include 1.00.

Table V. Age-specific SIRs for melanoma by sibling's history of melanoma

Sibling's age at diagnosis		Age at diagnosis														
		15–29			30–39				40–49				50–66			
15–29	O		8			3				5				0		
	SIR		**5.85**			1.61				**3.11**						
	95% CI	2.50		10.61	0.30		3.96	0.98			6.43					
30–39	O		3			12				9				8		
	SIR		1.64			**3.20**				2.05				**2.92**		
	95% CI	0.31		4.01	1.65		5.27	0.93			3.60	1.25				5.30
40–49	O		5			10				34				15		
	SIR		2.97			**2.21**				**4.88**				**2.76**		
	95% CI	0.94		6.15	1.05		3.80	3.38			6.66	1.54				4.34
50–66	O		0			8				15				22		
	SIR		0.00			**2.73**				**2.69**				**3.61**		
	95% CI	1.11		1.11	1.17		4.96	1.50			4.22	2.26				5.27

O, Observed cases; CI, confidence interval.
Bold type: 95% CI does not include 1.00.

sibling with melanoma. **Table IV** shows the age-specific risks for offspring invasive melanoma by age at diagnosis when only a parent was affected. The table was constructed for guidance to a clinical counseling situation when an offspring of an affected parent is being advised. Because of different age truncations, the offspring and parental diagnostic ages are not symmetrical. The highest risk was at the youngest diagnostic age groups of offspring, SIR 8.71 and 10.02, when a parent was diagnosed before age 50 y.

Table V gives familial SIR for affected siblings. Young diagnostic age was a risk factor, showing the highest SIR of 5.85 for siblings, both of whom were diagnosed before age 30. No clear age-dependent trend can be discerned at higher ages. We do not show a separate table for the third proband group (both a parent and a sibling affected) because only 10 such triplets were identified and some detailed data are shown below. The SIR for this group was 8.92 (95% CI: 4.25–15.31).

PAF PAF depends on both the familial risk and the proportion of familial cases among all offspring melanomas, and both of these depend on age. In **Table VI** we show offspring SIR in age groups and the related proportions, to enable calculation of PAF. The total SIRs for the three proband groups were 2.40, 2.98, and 8.92. The comparable proportions were 2.36, 1.81, and 0.12%, thus giving a PAF of 1.38, 1.20, and 0.10%. A combined PAF would thus be 2.69%. The total PAF represents an average of the age-specific PAF factors. In **Fig 2** age-specific SIRs from **Table VI** are plotted by parental or sibling family history. **Figure 2** also includes a graph for offspring when the parental age was limited to 66 y, to make it comparable with age of the offspring population. This truncation caused a small elevation in the SIR curve. The SIR for offspring by 0–66 y old parent was 2.82 (n = 153; 95% CI: 2.39–2.28).

DISCUSSION

Familial risk may be due to heritable or environmental effects, or their interactions. For melanoma, skin type and pigmentation could be a heritable cause and exposure to solar UV an environmental cause; however, according to the previous Swedish studies, shared environment only accounted for 10% of the variance in melanoma risk between all types of family members, compared with 21% for heritable and 69% random environmental effects (Czene *et al*, 2002). Moreover, spouse concordance for melanoma can only be observed for the early onset disease (Hemminki *et al*, 2001a; Hemminki and Jiang, 2002). These data suggest that most familial clustering of melanoma is due to heritable causes.

We have previously used an earlier version of the Swedish Family Cancer Database to assess familial risks in invasive melanoma, but no *in situ* cases were included and the analysis

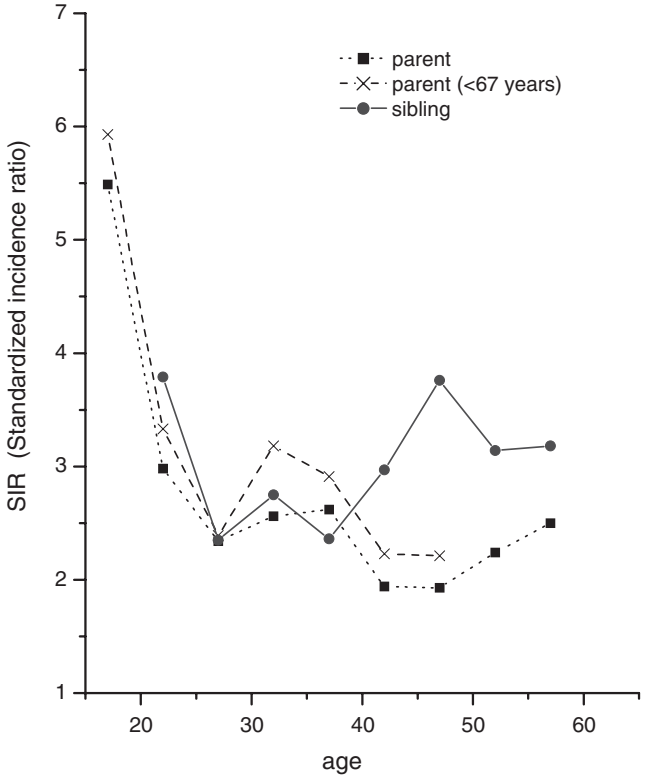

Figure 2. SIR of invasive melanoma in offspring as a function of diagnostic age according to parental or sibling probands. An additional graph shows the SIR for offspring whose parents were limited to age 66 y. Note that numbers of cases, SIR and 95% CI for the offspring and sibling data are shown in **Table VI**.

did not cover histogenetic types, different proband groups or PAF (Hemminki *et al*, 2001c). Melanoma has also been considered among all main cancer sites from a previous version of the Database, and the risk from a parental proband was given as 2.41, identical to the present estimate of 2.40, presently based on the 0–66 y old offspring population (Dong and Hemminki, 2001a). A recent summary estimate for familial melanoma risks between first-degree relatives was 2.5 (95% CI: 2.1–3.0) (Peto and Houlston, 2001). We show additionally here that when only a sibling was affected, the SIR was 2.98; however, when the parental age was limited to 66 y, comparable with the age of offspring, the SIR was 2.82, indicating that the risks from parental and sibling probands were practically identical. Histogenetic types of melanoma were only available from years 1993 to 1998, and the number of familial cases by any parental invasive melanoma was limited. Superficially spreading melanoma, the most common type in Sweden (Mansson-Brahme *et al*, 2002), showed the highest risk of 2.61 among invasive tumors; SIR for nodular melanoma was 2.15 and it did not reach statistical significance. Superficially spreading melanoma showed also the highest risk, 5.40 for *in situ* melanomas. The lentigo maligna *in situ* form was not significant with a SIR of 1.89. Superficially spreading and nodular melanomas are located commonly on the trunk and they are related to intermittent sun exposure (Elwood, 1992; Cox *et al*, 1996; Elwood and Gallagher, 1998; Gillgren *et al*, 1999). Lentigo maligna is common at sun-exposed sites in old people.

Whereas the two mutually exclusive proband groups, parents and siblings, could signal dominant and recessive effects, respectively, they could not distinguish low penetrant dominant effects. The equal magnitude of the SIR from parent and sibling may be due to chance, or it may support the operation of low penetrant dominant heritable mechanisms. The third proband group with an affected parent and offspring was likely to identify families with high penetrant susceptibility genes, such as *CDKN2A*. The high SIR of 8.92 (95% CI: 4.25–15.31) for offspring in these families argue for the biologic basis for the clustering rather than chance, which would be very unlikely. Also, multiple melanomas in a patient, which showed high familial risks in this study, were probably due to genetic susceptibility. Accordingly, *CDKN2A* mutations have been reported from patients with multiple melanoma (Burden *et al*, 1999). The penetrance of *CDKN2A* mutations was recently estimated at 76% for the analyzed US families by age 80 y (Bishop *et al*, 2002). In an international comparison, penetrance correlated with the background risk of melanoma.

PAF have been commonly calculated for environmental exposures but for familial cancer limited data are available, and to the best of our knowledge none specifically on melanoma (Risch, 2001; Hemminki, 2002). Even the concept of PAF for family history is less concrete than that for an environmental exposure (Hemminki and Czene, 2002). 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, the parent–offspring relationship would underestimate the magnitude of heritable effects. Here we give an example on a possible compensation for low-penetrant effects by adding PAF up from various probands, which can be done if the proband categories are mutually exclusive, as in this study. The derived PAF were 1.38% from a parent, 1.20% from a sibling, and 0.10% from a parent and a sibling, summing up to 2.69% (**Table VI**). Based on analysis of all main sites of cancer, these PAF values were intermediate (Hemminki and Czene, 2002). Even though the familial risk was relatively high for melanoma, the proportion of offspring with an affected family member was relative small, inflating the PAF. Indeed, 2.36% of the affected offspring had an affected parent, which was far below the cited figures from Australia and the U.S.A., 6–14% (Goldstein and Tucker, 1995; Ang *et al*, 1998). In a Utah cohort study like ours, the proportion with an affected first-degree relative was 3.9% (Goldgar *et al*, 1994). The reasons for the difference could be in the definition or magnitude of familial predisposition, in the environmental modification of the familial risk through exposure to sun, or in technical bias introduced in case-control studies by an inaccurate reporting of malignancies in family members.

To the best of our knowledge, no previous estimates are available on familial risks for *in situ* melanoma, except for our older study on all *in situ* cancers (Hemminki and Vaittinen, 1998a). That study noted for many neoplasms that the *in situ* forms displayed a higher familial risk than the invasive counterparts. The same appeared to be true for *in situ* melanoma in our study. In **Table I**, the highest familial risk was for *in situ* melanoma by parental invasive melanoma, thus indicating that in families both invasive and *in situ* cases occurred, as they did occur in single individuals as multiple tumors (**Table II**). Thus there was no evidence that the two forms were separate entities; however, whether the *in situ* form is a precursor lesion to invasive melanoma does not appear to be settled (see Wassberg *et al*, 1999b). One reason for the apparently higher familial risks for *in situ* tumors is that they may be removed in suspicion of malignancy preferentially in affected families. Although the high level of histologic confirmation of malignancy in cases reported to the Swedish Cancer Registry would guard against false diagnosis, increasing vigilance would result in earlier diagnosis, which would cause a lead-time bias, and an apparent increase in familial risk.

Socio-economic status may be an intervening factor in the analysis of familial associations across cancer sites. For this reason we adjusted the data for socio-economic status. A limited number of cancers associated with melanoma in families (**Table III**). As one, the aggregation of melanoma and squamous cell carcinoma of the skin was evident but the risk was only to invasive melanoma. Skin was also the only discordant cancer site that associated with sibling risk for invasive melanoma with a SIR of 1.97 (n = 24; 95% CI: 1.26–2.83; data not shown). The aggregation may be due to a shared risk factor, or a shared sensitivity to UV radiation (English *et al*, 1997). These associations have been noted in the second skin cancer after the first melanoma (Swerdlow

TableVI. SIRs, familial proportions and PAFs in offspring with familial history of melanoma

Offspring's age at diagnosis Parent only	O	SIR	95% CI		Proportion (%)	PAF (%)
00–14	3	**7.66**	**1.45**	**22.69**	6.67	5.80
15–19	12	**5.49**	**2.83**	**9.04**	5.29	4.32
20–24	18	**2.98**	**1.76**	**4.52**	3.02	2.00
25–29	23	**2.34**	**1.48**	**3.39**	2.49	1.43
30–34	34	**2.56**	**1.77**	**3.49**	2.78	1.69
35–39	39	**2.62**	**1.86**	**3.51**	2.81	1.74
40–44	31	**1.94**	**1.32**	**2.69**	2.06	1.00
45–49	29	**1.93**	**1.29**	**2.69**	1.90	0.91
50–54	24	**2.24**	**1.43**	**3.22**	1.99	1.10
55–59	14	**2.50**	**1.36**	**3.99**	1.83	1.10
60–67	4	1.81	0.47	4.03	1.10	0.49
All	231	**2.40**	**2.10**	**2.72**	2.36	1.38
Sibling only						
15–19	1	1.90	0.00	7.46	0.48	0.23
20–24	7	**3.79**	**1.50**	**7.12**	1.24	0.91
25–29	8	**2.35**	**1.00**	**4.25**	0.92	0.53
30–34	15	**2.75**	**1.53**	**4.31**	1.35	0.86
35–39	18	**2.36**	**1.40**	**3.58**	1.39	0.80
40–44	26	**2.97**	**1.94**	**4.22**	1.95	1.30
45–49	37	**3.76**	**2.65**	**5.07**	2.74	2.02
50–54	25	**3.14**	**2.03**	**4.49**	2.45	1.67
55–59	16	**3.18**	**1.81**	**4.93**	2.58	1.77
60–67	4	1.91	0.50	4.24	1.54	0.73
All	157	**2.98**	**2.54**	**3.47**	1.81	1.20
Parent & sibling						
15–29	5	**29.78**	**9.40**	**70.05**	0.30	0.29
30–67	5	**5.25**	**1.66**	**12.34**	0.07	0.06
All	10	**8.92**	**4.25**	**15.31**	0.12	0.10

O, Observed cases; CI, confidence interval.
Proportion, proportion of cases with a family history.
Bold type: 95%CI does not include 1.00.

et al, 1995; Wassberg *et al*, 1996, 1999a; Schenk *et al*, 1998) and in the second melanoma after the first skin cancer (Frisch and Melbye, 1995; Levi *et al*, 1997, 1998; Wassberg *et al*, 1999b; Hemminki and Dong, 2000a, b). Invasive melanoma also associated with breast and nervous system cancers, associations of which have been recognized previously (Hemminki *et al*, 2001c). The melanoma-breast cancer association is linked to germline *CDKN2A* (Borg *et al*, 2000; Plna and Hemminki, 2001) and *BRCA2* mutations (The Breast Cancer Linkage Consortium, 1999). The association to nervous system tumors is mainly due to brain astrocytomas (Hemminki *et al*, 2001b). The association of *in situ* melanoma with thyroid cancer may be a chance finding because no excess was observed for invasive melanoma. The same was true for connective tissue neoplasms, but these have been associated earlier with invasive melanoma when parental melanoma risks were analyzed (Hemminki *et al*, 2001c). A study on soft tissue tumors found no association to melanoma (Hemminki and Li, 2001). No association was noted for familial melanoma and non-Hodgkin's lymphoma. In an earlier study from this Database a marginal clustering was observed (Hemminki *et al*, 2001c), and there are some contradictory results on an increased risk of subsequent melanoma after an initial non-Hodgkin's lymphoma (Travis *et al*, 1991, 1993; Adami *et al*, 1995; Levi *et al*, 1996; Brennan *et al*, 2000; Dong and Hemminki, 2001b).

In summary, this large study on familial melanoma showed an equal risk from parents and siblings, clear age dependence in risk, and somewhat higher risk in *in situ* melanoma than in the invasive counterpart. The highest risk was in families were two offspring and a parent were affected, and in those families where a proband had multiple melanomas. Melanoma associated with breast, nervous system, and skin cancers, and *in situ* melanoma possibly also with connective tissue and thyroid tumors.

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