Re: High Frequency of Multiple Melanomas and Breast and Pancreas Carcinomas in CDKN2A Mutation-Positive Melanoma Families

Susceptibility to cutaneous malignant melanoma has been associated with inherited mutations in the CDKN2A tumor suppressor gene, which encodes the p16 protein *(1).* The recent report by Borg et al. *(2)* showing an increased risk of breast cancer in CDKN2A mutation carriers suggests that melanoma and breast cancer share a susceptibility gene. Using the nationwide Swedish Family-Cancer Database *(3),* we have previously suggested such an interaction of breast cancer and melanoma genotypes. This database has been recently updated, providing the opportunity to increase the power of our statistical analysis. The present database includes persons born in Sweden after 1934 ("offspring") and their biological parents, totaling more than 9.6 million individuals *(4).* Cancer cases, taken from the nationwide Swedish Cancer Registry, totaled about 88 000 cases in the offspring (including 17 528 cases of breast cancer and 8075 cases of melanoma), as compared with 21 220 cancer cases in the offspring from the previous version of the database *(3).* Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases. The expected numbers were calculated from age- and sex-standardized rates *(5),* considering offspring of the cancer-free parents as the reference group (SIR = 1.00), and 95% confidence intervals (CIs) were calculated on the basis of the Poisson distribution *(5).*

Cancer risk in the offspring was analyzed according to parental breast cancer and melanoma status (Table 1). When both parents had breast cancer, the SIRs of all cancers and of breast cancer in the offspring were 5.65 (95% CI = 2.24 to 10.60) and 18.63 (95% CI = 5.88 to 38.53), respectively. When both parents had melanoma, the SIR of melanoma in the offspring was 13.25 (95% CI = 1.25 to 37.97). When the mother had breast cancer and the father had melanoma, the SIR of all cancers in the offspring was 2.19 (95% CI = 1.53 to 2.98), and the SIRs of breast cancer and melanoma were much higher: 4.74 (95% CI = 2.64 to 7.44) and 5.70 (95% CI = 2.59 to 10.04), respectively.

Our data thus provide a strong indication of possible interactions among parental susceptibility genes in the offspring, because the SIRs were much lower when only one parent had breast cancer or melanoma. This result is in line with our previous finding that the breast cancer risk in daughters is increased if both parents have breast cancer *(6).* The data also are suggestive of an interaction among breast cancer and melanoma susceptibility genes because breast cancer in the mother and melanoma in the father increased the risk of breast cancer and melanoma in the offspring. In addition, an interaction between breast cancer and melanoma susceptibility genes was shown by the analysis of breast cancer in daughters (younger than 50 years) when the mother had a double primary first breast cancer and a second melanoma (SIR = 5.21; 95% CI = 1.64 to 10.78).

Our results, therefore, suggest that both parents contribute susceptibility genes to pathways partially shared in breast cancer and melanoma. This hypothesis could explain the only moderate familial cancer risks between discordant sites for breast cancer and melanoma in offspring when the cancer status of the parents is analyzed separately *(7).* The recent identification of CDKN2A as a breast cancer susceptibility gene *(2)* strengthens this hypothesis because CDKN2A has already been implicated as the major melanoma susceptibility gene.

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Table 1. Standardized incidence ratio (SIR) of cancer in offspring by parental breast cancer and melanoma*

	SIR of cancers in offspring (observed No.; 95% confidence interval)		
Parental cancer status	Breast cancer in father	Melanoma in father	No cancer in father
Breast cancer in mother			
All cancer in offspring	**5.65** (7; 2.24 to 10.60)	**2.19** (35; 1.53 to 2.98)	**1.25** (3534; 1.21 to 1.3)
Breast cancer in offspring	**18.63** (5; 5.88 to 38.53)	**4.74** (15; 2.64 to 7.44)	**1.97** (1129; 1.85 to 2.08)
Melanoma in offspring	No cases	**5.70** (9; 2.59 to 10.04)	**1.14** (3.08; 1.02 to 1.27)
Melanoma in mother			
All cancer in offspring	No cases	1.97 (3; 0.37 to 4.84)	**1.35** (394; 1.22 to 1.49)
Breast cancer in offspring	No cases	No cases	1.12 (62; 0.86 to 1.42)
Melanoma in offspring	No cases	**13.25** (2; 1.25 to 37.97)	**3.06** (84; 2.44 to 3.75)
No cancer in mother			
All cancer in offspring	1.03 (19; 0.62 to 1.55)	**1.25** (358; 1.12 to 1.38)	1.00 (55 586; 0.99 to 1.01)
Breast cancer in offspring	1.01 (4; 0.26 to 2.25)	1.00 (52; 0.74 to 1.29)	1.00 (9811; 0.98 to 1.02)
Melanoma in offspring	1.13 (2; 0.11 to 3.24)	**2.39** (66; 1.95 to 3.00)	1.00 (4994; 0.97 to 1.03)

*Offspring whose parents are cancer free are the referents (SIR = 1.00; bottom right corner of table); **values shown in bold** are those for which the 95% confidence interval does not include 1.00.

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RESPONSE

We fully agree with Drs. Plna and Hemminki that genes from both the maternal and paternal sides might contribute to the overall incidence of cancer in offspring, even in the setting of hereditary cancer syndromes. For example, such genes might increase disease penetrance or modify tumor phenotype. This phenomenon may at least partly explain why some families with CDKN2A mutations also develop breast or pancreatic cancer. Unpublished data from our group (Olsson H, Johannsson O, Loman N) suggest that, in families with hereditary cancer syndromes with a high disease penetrance, cancer incidence is also increased above expected levels in family members who do not carry the cancer-predisposing mutation.

In addition, we have evidence of a geographic heterogeneity in Sweden of the familial incidence of malignant melanoma and breast cancer. We have previously used the same database as Hemminki and co-workers for Sweden as a whole in publications on colorectal cancer and breast cancer *(1,2);* here, we consider the geographic distribution of familial breast cancer and malignant melanoma risk in relation to the site of residence of the mother at time of diagnosis (Table 1). The highest risk for melanoma when the mother had melanoma diagnosed before age 50 years is seen in the southeastern, Stockholm–Gotland, and southern regions of Sweden, corresponding to the geographic distribution of families carrying the known CDKN2A founder mutation that is thought to have originated in the southeastern region of Sweden about 107 generations ago *(3,4).*

Table 1. Breast cancer and malignant melanoma incidence in women born to mothers with breast cancer or malignant melanoma*

Region of diagnosis of the mother	OBS	EXP†	SMR	95% CI
Breast cancer in women born to all mothers with breast cancer				
Northern	65	41.33	1.57	1.21 to 2.00
Uppsala–Örebro	183	83.51	2.19	1.89 to 2.53
Stockholm–Gotland	145	73.21	1.98	1.67 to 2.33
Southeastern	101	51.37	1.97	1.60 to 2.39
Western	143	72.01	1.99	1.67 to 2.34
Southern	168	78.83	2.13	1.82 to 2.48
Breast cancer in women born to mothers with breast cancer before the age of 50 years				
Northern	8	5.36	1.49	0.64 to 2.94
Uppsala–Örebro	33	12.37	2.68	1.84 to 3.75
Stockholm–Gotland	29	11.64	2.49	1.67 to 3.58
Southeastern	21	6.89	3.05	1.89 to 4.66
Western	37	11.00	3.36	2.37 to 4.64
Southern	28	11.00	2.55	1.69 to 3.68
Breast cancer in women born to mothers with breast cancer at 50 years of age or older				
Northern	57	35.97	1.58	1.20 to 2.05
Uppsala–Örebro	150	71.14	2.11	1.78 to 2.47
Stockholm–Gotland	116	61.57	1.88	1.56 to 2.26
Southeastern	80	44.48	1.80	1.43 to 2.24
Western	106	61.01	1.74	1.42 to 2.10
Southern	140	67.83	2.06	1.74 to 2.44
Malignant melanoma in children born to mothers with malignant melanoma				
Northern	2	0.79	2.53	0.31 to 9.14
Uppsala–Örebro	8	3.31	2.42	1.04 to 4.76
Stockholm–Gotland	12	4.05	2.96	1.53 to 5.18
Southeastern	14	3.06	4.58	2.50 to 7.68
Western	8	4.38	1.83	0.79 to 3.60
Southern	18	6.40	2.81	1.67 to 4.44
Malignant melanoma in children born to mothers with breast cancer before the age of 50 years				
Northern	3	3.90	0.77	0.16 to 2.25
Uppsala–Örebro	10	8.57	1.17	0.56 to 2.15
Stockholm–Gotland	6	7.42	0.81	0.30 to 1.76
Southeastern	5	4.55	1.10	0.36 to 2.57
Western	10	6.73	1.49	0.71 to 2.73
Southern	8	7.53	1.06	0.46 to 2.09
Malignant melanoma in children born to mothers with breast cancer at 50 years of age or older				
Northern	16	17.88	0.89	0.51 to 1.45
Uppsala–Örebro	35	35.89	0.98	0.68 to 1.36
Stockholm–Gotland	43	28.26	1.52	1.10 to 2.05
Southeastern	27	20.42	1.32	0.87 to 1.92
Western	44	27.23	1.62	1.17 to 2.17
Southern	46	32.64	1.41	1.03 to 1.88

*OBS = observed cases; EXP = expected cases; SMR = standardized mortality rate; CI = confidence interval.

†Calculated by regional reference incidences.

If we look at breast cancer in a similar way, the northern region of Sweden has a statistically significantly lower incidence of breast cancer in the female offspring than the rest of the country ($P = .04$). (Table 1). This difference is more pronounced if the mother is young. The offspring of young mothers with breast cancer do not show a statistically significantly increased melanoma incidence; however, the offspring of older women with breast cancer in the western, Stockholm-Gotland, and southern regions of Sweden (i.e., regions that do not fully correspond with the origin of the CDKN2A founder mutation) have a statistically significantly higher risk of malignant melanoma. The data thus suggest another breast cancer–melanoma relationship in older patients with breast cancer than the one associated with the CDKN2 founder mutation. The overall lower familial incidence of breast cancer

in northern Sweden could perhaps be attributable to the influence of genes from people of Finnish and Laplandic origins in this part of Sweden. These results thus suggest that targeting searches for cancer-predisposing genes to families of a specific geographic origin in Sweden might be especially worthwhile.

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