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# A population-based study on the familial aggregation of cutaneous malignant melanoma in Iceland

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ABSTRACT

The aim of this study was to characterize the familial nature of cutaneous malignant melanoma (CMM) in Iceland. Risk ratio was used to estimate the risk among relatives of all CMM index cases diagnosed in Iceland over a 45-year period (1955–1999), using data from the National Cancer Registry and a genealogy database that covers the whole of Iceland's population. First-, second-, and third-degree relatives of CMM patients did not have an increased risk of the disease, and no added risk of other types of cancer among relatives was observed, except for thyroid cancer in first-degree male relatives. Seven individuals were diagnosed with two or more primary CMM in this period; none of these individuals had a first or second-degree relative with CMM. Altogether, 2.4% of cases were familial, as defined by commonly used criteria. In conclusion, high-penetrance susceptibility genes do not contribute much to CMM in the Icelandic population. The great majority of CMM cases in Iceland are most likely caused by the interplay between environmental causes and low-risk genes.



## 1. Introduction

Although the development of cutaneous malignant melanoma (CMM) is strongly associated with environmental factors, genetic factors also contribute to CMM predisposition. About 8–14% of melanoma patients have a family history of the disease, defined as at least one first-degree relative with melanoma.[1] Population-based studies in Utah and Sweden have reported approximately 2- and 3-fold increased risk of melanoma, respectively, in first-degree relatives of melanoma probands.[2–4] Melanoma has also been associated with cancers of the nervous system, breast and other skin cancers.[2,5]

Linkage analysis of families with multiple cases of melanoma have identified inherited mutations in two genes, the cell-cycle regulator *CDKN2A*,[6] and the cyclin-dependent kinase-4 (*CDK4*).[7] The frequency of *CDKN2A* mutations was estimated at approximately 20% when multiple studies of familial melanoma kindreds from North America, Europe and Australasia were analyzed.[8] In contrast, a recent study by Begg and colleagues found only 65 mutation carriers among 3550 incident case patients (1.8%) from nine different geographic regions.[9] This study also estimated the risk of mutation carriers to be 14% by age 50 years and 28% by age 80 years.[9] The penetrance of *CDKN2A* mutations varies with

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CMM population incidence rates, suggesting that other factors that affect population incidence of melanoma may also affect *CDKN2A* penetrance.[10] Studies in several populations have found an increased incidence of *CDKN2A* mutations in patients with more than one primary melanoma but no family history of the disease.[11–14] Some families with a mutation in *CDKN2A* also have an increased risk of pancreatic cancer but other risk factors are likely to play a role as well.[8] Recently, a susceptibility locus for melanoma on chromosome 1p22 was identified in 49 Australian pedigrees.[15,16]

Epidemiological studies have shown that a high density of dysplastic nevi, light skin, hair and eye colour are also risk factors for CMM.[17] Polymorphisms in the Melanocortin-1 receptor (*MC1R*) have been associated with hair colour and skin type and seem to affect the risk of radiation sensitivity and CMM.[18] *MC1R* variants also influence the penetrance of *CDKN2A* mutations.[19]

Similar to other northern-European populations, CMM incidence has increased rapidly in Iceland in the last decades.[20] During the period 1998–2002, the age-standardized incidence was 9/100,000 for males and 18.5/100,000 for females and had tripled from the incidence observed around 1980 (Annual report of the Icelandic Cancer Registry).[21] Currently, melanoma is the 11th most common malignancy in Iceland. Limited information exists about the genetics of melanoma in Iceland. Several families have been observed that have more than one case of melanoma or one case of melanoma and one case of pancreatic cancer or glioma. A study of 12 of these families failed to identify any germ-line *CDKN2A* mutations.[22] Finally, a population-based study of the familial nature of all cancers in Iceland included data that suggested significant familial aggregation of CMM.[23]

The aim of the present study was to use the population-based Cancer Registry in Iceland to estimate the cancer risk of family members of CMM patients and determine if families with high risk of melanoma are found in the population that might be useful in the search for new genes that predispose to melanoma.

## 2. Patients and methods

All individuals in Iceland diagnosed with CMM (ICD7 190) during a 45-year interval (1955–1999) were included in the study. The Genetical Committee of the University of Iceland traced the families of the probands up to third-degree relatives (first-degree relatives include parents, siblings, and offspring). The committee's data was based on the National Population Registry (NPR), which has been in operation since 1952, and provides every permanent resident of Iceland with a unique identification number. Until the establishment of NPR, birth, death, church and marriage records formed the basis of the Genetical Committee's data, which traces pedigrees of individuals as far back as 1840.

The Icelandic Cancer Registry (ICR) provided information on cancer in relatives. The ICR has been in operation since 1954,[24] covers the entire population of Iceland and determines incidence of cancer by site. The registry receives information from all pathology and cytology laboratories in Iceland, in addition to hematology laboratories, hospital wards, private medical practitioners and other individual health care workers.[25] Approximately 94.5% of diagnoses in the ICR have histological confirmation.[25] The population-based cancer registration and the follow-up of individuals, is made possible by the NPR. In the period 1961–2000, immigration ranged between 0.07% and 1.05% per annual population, emigration ranged between 0.17% and 1.33%, and the net change ranged between 0.02% and 0.67%.[26–28] When calculating person-years at risk, individuals were considered at risk from birth or from the year 1955, which ever came later, until diagnosis of the cancer in question, death, or the end of the year 1999, which ever came first. Immigration/emigration was not controlled for. However, given the small percentage of immigration/emigration during the research period, the effects can be considered negligible.

Calendar year from 1955 up to and including 1999 and patient age were used as stratification variables when calculating person-years. Both variables were defined by 5-year strata. The risk of cancer was estimated as the ratio between the observed and expected number of cases (standardized incidence ratio, SIR). The SIR compares the observed number of cases in a cohort with an expected number obtained by applying calendar- and age-specific standard rates to the cohort age structure.[29] The SIRs were estimated separately for males and females.

Two-sided confidence intervals (CI) were calculated assuming a Poisson distribution.[29] Since the confidence intervals were always 95%, one interval out of 20 is expected to exclude 1.00 by chance. Since the data obtained was centralized and population-based, complete ascertainment of cases was accounted for. All CMM cases were counted as both probands and relatives. However, each individual was counted only once when counting observed number of cases, thus avoiding inflating the estimates of the SIRs. The confidence intervals were calculated based on the assumption of independence. Since some individuals came from the same families, the assumption of independence leads to narrower confidence intervals. All data analysis was done using the statistical system R.[30]

## 3. Results

A total of 497 (166 males and 331 females) individuals were diagnosed with CMM in Iceland during 1955–1999. The mean age at diagnosis was 57.5 for males and 51.7 for females (Table 1). Seven probands had more than one diagnosis of primary CMM; their mean age at first diagnosis was 44.3 (95%CI 30.23–58.34, range 31–62). None of the probands with more than one diagnosis of CMM had either a first or second-degree relative with the disease. Examination of the families of these probands revealed no significant history of cancer except in two families; in one family there were several cases of cutaneous melanoma in situ on the same side of the family and the other family had two family members with kidney cancer. Eight probands had a first-degree relative with CMM, divided into four families. These individuals did not have a second or a third-degree relative with the disease. The mean age at diagnosis of melanoma among the eight probands who had a first-degree relative with the disease was 59 years (95%CI 42.97–75.03, range 26–86 years). Twenty-two probands had a second-degree relative with melanoma, the mean age at diagnosis was 50.5 (95%CI 42.92–62.03, range 15–83). Finally, four

**Table 1 – Distribution of age at first diagnosis (years) of cutaneous malignant melanoma (CMM) in 497 probands diagnosed in Iceland 1955–1999**

| | N | Mean | SEM | Range | Fractiles | | |
|---|---|---|---|---|---|---|---|
| | | | | | 25% | 50% | 75% |
| Total CMM | 497 | 53.6 | 0.87 | 0–93 | 38 | 53 | 70 |
| Male | 166 | 57.5 | 1.42 | 13–92 | 44 | 57 | 73 |
| Female | 331 | 51.7 | 1.08 | 0–93 | 35 | 51 | 67 |
| Sporadic CMM | 485 | 53.5 | 0.88 | 0–93 | 38 | 52 | 69 |
| Familial CMM | 12 | 59.5 | 4.78 | 26–86 | 50 | 62 | 73 |
| Multiple primary CMM | 7 | 44.3 | 5.74 | 31–62 | 32 | 43 | 58 |

Fractiles refer to the proportion of individuals diagnosed at or younger than the given age. "Familial" refers to probands with a first-degree relative or two or more relatives up to third-degree with melanoma.
N, number of individuals; SEM, standard error of the mean.

probands were identified that had three relatives with CMM up to third-degree, the mean age at diagnosis for these probands was 60.5 (95%CI 41.30–79.70, range 44–73).

No significantly increased risk of melanoma was observed among first-, second-, or third-degree relatives of CMM cases (Table 2). The risk of brain, pancreatic, thyroid or breast (female) cancer was not significantly increased among first-, second-, or third-degree relatives (Table 2), except for the risk of thyroid cancer among first-degree male relatives (SIR 2.61, 95% confidence interval 1.30–4.67). The risk of cancer of the stomach, colon, rectum, kidney, bladder, cervix or ovary was not significantly increased (data not shown). The risk of prostate cancer was not significantly increased among first and second-degree male relatives, but was slightly increased in third-degree relatives (data not shown). Finally, the risk of breast cancer was significantly reduced in first-degree relatives and risk of thyroid cancer was significantly reduced in second-degree female relatives.

**Table 2 – Relative-risk of cancer in first-, second-, and third-degree relatives of melanoma patients**

| Cancer | Relative | Gender | N | O | SIR | CI (95%) |
|---|---|---|---|---|---|---|
| Melanoma | First | Male | 1899 | 3 | 1.09 | [0.22–3.18] |
| | | Female | 1901 | 5 | 0.94 | [0.30–2.19] |
| | Second | Male | 5849 | 5 | 0.77 | [0.25–1.80] |
| | | Female | 5649 | 17 | 1.32 | [0.77–2.11] |
| | Third | Male | 9809 | 15 | 1.46 | [0.82–2.41] |
| | | Female | 9420 | 23 | 1.07 | [0.68–1.61] |
| Brain | First | Male | 1899 | 6 | 1.01 | [0.37–2.20] |
| | | Female | 1901 | 8 | 1.57 | [0.68–3.09] |
| | Second | Male | 5849 | 13 | 0.89 | [0.47–1.52] |
| | | Female | 5649 | 7 | 0.54 | [0.22–1.11] |
| | Third | Male | 9809 | 17 | 0.72 | [0.42–1.15] |
| | | Female | 9420 | 17 | 0.81 | [0.47–1.30] |
| Pancreas | First | Male | 1899 | 9 | 1.10 | [0.50–2.09] |
| | | Female | 1901 | 10 | 1.33 | [0.64–2.45] |
| | Second | Male | 5849 | 22 | 1.17 | [0.73–1.77] |
| | | Female | 5649 | 18 | 1.05 | [0.62–1.66] |
| | Third | Male | 9809 | 21 | 0.92 | [0.57–1.41] |
| | | Female | 9420 | 19 | 0.89 | [0.54–1.39] |
| Thyroid | First | Male | 1899 | 11 | 2.61 | [1.30–4.67] |
| | | Female | 1901 | 11 | 1.08 | [0.54–1.93] |
| | Second | Male | 5849 | 11 | 1.15 | [0.57–2.06] |
| | | Female | 5649 | 12 | 0.51 | [0.26–0.89] |
| | Third | Male | 9809 | 13 | 0.94 | [0.50–1.61] |
| | | Female | 9420 | 44 | 1.26 | [0.92–1.69] |
| Breast | First | Female | 1901 | 40 | 0.68 | [0.49–0.93] |
| | Second | Female | 5649 | 127 | 1.03 | [0.86–1.23] |
| | Third | Female | 9420 | 196 | 1.02 | [0.88–1.17] |

N, number of relatives; O, observed number of cases; SIR, standardized incidence ratio; CI: confidence interval.

## 4. Discussion

Approximately 5–12% of melanoma cases can be classified as familial, i.e., occurring in families with either two first-degree relatives with melanoma, or three (irrespective of degree of relationship) relatives with the disease.[31] In our study of all 497 probands diagnosed with CMM over a period of 45 years (1955–1999) in Iceland, only four families were identified that had a family history of the disease among first-degree relatives. Two families had two siblings each with CMM, and two other families had a parent-offspring pair with CMM. In addition, four probands had two or more relatives (up to third-degree) with CMM on the same side of the family. Therefore, 2.4% (12/497) of CMM cases were familial based on the above definition. It is notable that the mean age at diagnosis in cases with family history is marginally higher than in sporadic cases, further supporting the lack of substantial genetic effect. However, the mean age at first diagnosis of probands that were diagnosed with more than one CMM was lower than that of the sporadic group. Several probands had a family history of other cancers, including brain, pancreas and breast cancer. While these families contribute very little to total CMM in Iceland, they warrant further study.

Risk of CMM was not increased in close relatives of melanoma probands. Neither was there increased risk of other cancers, except for thyroid cancer in male first-degree relatives. However, this increase was accompanied by a significant reduction in risk of thyroid cancer in first-degree female relatives. These rather surprising results need further study but it should be noted that the incidence of thyroid cancer in Iceland is among the highest in the world.[21] A possible link between mutations in the tumour suppressor *PTEN*, thyroid cancer and melanoma has been suggested.[32] The presence or absence of *PTEN* mutations in the Icelandic population is unknown at present.

The Icelandic population varies from some other populations of Northern European origin where increased risk of melanoma has been found in first-degree relatives of melanoma probands. Goldgar and colleagues reported a significant (2-fold) increased risk of melanoma among first-degree relatives of melanoma patients, based on the Utah Population Database.[2] Dong and Hemminki, using the population-based Swedish Family Cancer Database, also observed significantly increased risk of melanoma (SIR 2.41, 95%CI 2.04–2.83) in offspring if one parent had melanoma, whereas the risk was higher (SIR 3.27, 95%CI 2.68–3.96) when a sibling was affected.[3] The present results from the Icelandic population are in line with the work of Milan and colleagues who, using

the Finnish Twin Cohort, found no added risk of malignant melanoma of the skin among 60 twins diagnosed with melanoma out of 25,882 twins with established zygosity, suggesting that environmental and possibly low-risk hereditary factors are most important in malignant skin cancers in this predominantly white population with low levels of sun exposure.[33] Amundadottir and colleagues reported a significantly increased risk of CMM among first and second-degree relatives of probands diagnosed in Iceland over a 48 year period (1955–2002).[23] There are three possible reasons why the results of the two studies are different. First, Amundadottir and colleagues used a different estimator of the relative risk than we did, and counted multiple times affected relatives of multiple probands. In our approach, each individual was counted only once. Second, the time period covered in the study by Amundadottir and colleagues extended to 2002, three years longer than the period covered in the present study. During these three years, it is possible that families with multiple CMM cases may have been observed, in particular since 121 individuals were diagnosed with CMM in the period 2000–2002. However, Amundadottir and colleagues did not provide information on the number of observed cases, or families, for each degree of relatedness. We cannot, therefore, compare their results directly with ours. Finally, the two studies are based on different genealogy databases which may have resulted in some (hopefully small) discrepancy in family relations. However, such discrepancy has large effects on the estimates of relative-risk based on small number of families in which many family members are affected. During the period 1955–1999 only six families (12 individuals) show aggregation of CMM in Iceland and only four families have 2 (including the proband) first-degree relatives each with the disease. None of the probands with an affected first-degree relative also has a second or a third-degree relative with CMM. In addition, individuals with family history of CMM are not diagnosed at a younger age with CMM than those without family history (Wilcoxon rank sum test, $P = 0.300$). These data clearly suggest very low familial aggregation of CMM in Iceland.

Mutations in the tumour suppressor gene *CDKN2A* are associated with about 18% of familial melanoma.[10] Several of the mutations described so far are founder mutations,[34–37] including the majority of *CDKN2A*-associated melanoma families in Sweden.[11,38] The penetrance of mutations in the *CDKN2A* gene appears to be higher in countries with high melanoma incidence, than in countries with lower incidence of the disease.[10] Gretarsdottir and colleagues screened 27 individuals from 12 Icelandic melanoma kindreds (kindreds with two or more melanoma cases or melanoma, pancreas and/or glioma cases), and found no germline mutations in *CDKN2A*.[22] The Icelandic population is both small (the current population of Iceland is approximately 300,000) and young (established around 1100 years ago) compared to most other European populations. One can, therefore, not expect to find many founder mutations affecting CMM in Iceland, unless they were in relatively high-frequency before settlement. The effect of founder mutations can be quite important in isolated populations like Iceland. For example, a single founder mutation in the *BRCA2* gene, *BRCA2999del5*,[39] has been shown to explain a substantial proportion of the familial breast cancer, and most of the familial prostate and ovarian cancer in families of breast cancer patients.[40] Together with the results of the present study, this suggests strongly that penetrating founder mutations affecting CMM are likely to be rare in Iceland, if they exist at all.

Families with at least two first or second-degree relatives affected and carrying mutations in CDKN2A have been shown to have higher risk of pancreatic and breast cancer.[11,41–44] The apparent paucity of melanoma-prone families precludes a comparable analysis in Iceland.

In summary, 2.4% of CMM cases in Iceland have a family history of the disease. No added risk of other types of cancer (including brain, pancreas, and breast) was observed. High-risk founder mutations affecting melanoma may, therefore, be uncommon or even absent in Iceland.

## Conflict of interest statement

None declared.

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