Cancer Susceptibility in Nasopharyngeal Carcinoma Families—A Population-Based Cohort Study

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Abstract

Undifferentiated nasopharyngeal carcinoma is a result of environmental factors, in particular EBV infection, affecting genetically susceptible individuals. The familial risk of nasopharyngeal carcinoma is among the highest of any malignancy. Whether this susceptibility is restricted to nasopharyngeal carcinoma is unknown as information on the risk of other cancers in relatives is limited. We did a population-based study of the cancer incidence in nasopharyngeal carcinoma families in Greenland, a nasopharyngeal carcinoma–endemic area. Using population-based registers, a cohort of all persons born in Greenland was followed from 1973 to 2002. In this cohort, 134 individuals developed nasopharyngeal carcinoma and their relatives were identified through registers and interviews. Subsequently, the occurrence of cancer was determined by linkage to the population-based cancer register and the risk of cancer in nasopharyngeal carcinoma relatives and nonrelatives compared by relative risks. Among 766 first-degree relatives, the relative risk of nasopharyngeal carcinoma following the family index case was 8.0 [95% confidence interval (95% CI), 4.1-14.0]. Sex and age of the relative or the index case had no modifying effect on the familial risk of nasopharyngeal carcinoma. The relative risks of carcinoma of the salivary glands, 8.4 (95% CI, 2.7-19.5), and uterine cervix, 2.2 (95% CI, 1.1-3.9), were also significantly increased. In families with multiple cases of nasopharyngeal carcinoma, the risk of other cancers than nasopharyngeal carcinoma was further increased. These results indicate that the increased risk of cancer in nasopharyngeal carcinoma families is not restricted to nasopharyngeal carcinoma, but extends to the virally associated cancers of the salivary glands and cervical uteri. (Cancer Res 2005; 65(18): 8567-72)

Introduction

Nasopharyngeal carcinoma is a rare cancer throughout the world, with the exception of populations in areas of Southeast Asia, North Africa, and among Inuit in the Arctic where the undifferentiated type of nasopharyngeal carcinoma is common (1–3). Nasopharyngeal carcinoma is associated with EBV and viral genomes are detected in the vast majority of tumors from high-incidence areas, including Greenland (4–6). The involvement of a genetic factor in the development of the disease is widely accepted and the familial risk of nasopharyngeal carcinoma is among the highest of any malignancy (4, 7, 8). However, the question as to whether this increased risk of disease is limited to nasopharyngeal carcinoma or also includes other, e.g., virally associated cancers, is unknown.

Available studies addressing this question are limited. In Taiwan, a nonsignificant increased proportion of virally associated tumors was observed among first-degree relatives of familial cases of nasopharyngeal carcinoma compared with relatives of sporadic cases (7). Markedly decreased risks of breast, esophagus, and lung cancers among first-degree relatives to nasopharyngeal carcinoma patients were recently observed in a Chinese study (9); however, this study design had considerable methodologic limitations (10).

However, case-control studies on familial risks of disease are subjected to both selection and recall bias. We obviated such problems by establishing a cohort study of the entire population in Greenland, where nasopharyngeal carcinoma is endemic, and determined cancer incidence in relatives of nasopharyngeal carcinoma patients and nonrelatives using high-quality registry information.

As the familial risk of nasopharyngeal carcinoma among Inuits has never been estimated, an additional objective of our study was to estimate the familial risk of nasopharyngeal carcinoma in this population.

Patients and Methods

The risk of cancer among relatives of nasopharyngeal carcinoma patients was analyzed in a cohort design. The cohort consisted of all persons born in Greenland alive by 1973 or later. The cohort was followed from 1973 to 2002, and the risk of cancer in individuals with nasopharyngeal carcinoma–affected relatives was compared with the risk in individuals without affected relatives.

Study population. All individuals in Greenland and Denmark are registered in the Civil Registration System. This system was established in Greenland on May 1, 1972, and all persons alive and resident on that date or later have been registered and given a unique personal identification number. The Civil Registration System includes information on date of birth, place of birth and residence, sex, and continuously updated information on vital status and emigration. For individuals born since the beginning of the 1930s, the updated information on familial relations allows identification of offspring, and for individuals born since the beginning of the 1950s also a person's parents and siblings (11). The personal identification number is used as key identification in national registries, which facilitates high-quality linkages between the different registries.

Based on the Civil Registration System, we formed a study cohort consisting of all Greenlanders alive on January 1, 1973, or later, in total 73,222 individuals. A Greenlander was defined as a person born in Greenland. No exact definition of a Greenlander exists, but the vast majority of individuals born in Greenland are Inuits.

Identification of nasopharyngeal carcinoma patients. Information on nasopharyngeal carcinoma patients was retrieved from the Danish Cancer Registry (12). Reporting of cancer cases to the Danish Cancer Registry is mandatory in both Greenland and Denmark, and the main source of information in the registry has been notifications from physicians diagnosing and treating cancer patients, supplemented by information from pathology reports and death certificates. At the initiation of the study,

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when nasopharyngeal carcinoma cases were identified before the family identification process, cancer data up to February 1998 were available, and a total of 116 cases of nasopharyngeal carcinoma were diagnosed in the cohort. These included 5 cases diagnosed before 1973 and 111 cases of nasopharyngeal carcinoma diagnosed from 1973 to February 1998. The 116 nasopharyngeal carcinoma cases comprised 60 males (mean age, 51.9 years) and 56 females (mean age, 53.9 years).

After the family identification process was completed, cancer data up to 2002 became available (including an additional 18 nasopharyngeal carcinoma cases diagnosed in 1998-2002), resulting in a total of 134 nasopharyngeal carcinoma cases in the cohort.

Identification of relatives. Using the personal identification number, children of the 116 nasopharyngeal carcinoma patients were identified in the Civil Registration System. Children born before the 1950s and children who died before the Civil Registration System was established were identified via contact to the local municipalities or by manual searches in church books and census papers in Greenland. If the nasopharyngeal carcinoma patient was childless, the closest living relative was identified using the same sources.

To ensure complete information on familial relations, we also approached the two closest relatives from each case and asked them to draw their family tree. After returning the questionnaire, the relative finally underwent a structured telephone interview to ensure that the obtained information on familial relations was as complete and correct as possible. Based on this information, parents and siblings of the nasopharyngeal carcinoma patient were then identified in the Civil Registration System, and using the family data in the Civil Registration System, a pedigree with all descendants was constructed for each family.

A total of 5,127 relatives in the cohort were identified (Table 1). In 4 of the 116 cases of nasopharyngeal carcinoma, relatives could not be identified. First-degree relatives were defined as parents, siblings, or children; second-degree relatives as grandchildren or nieces/nephews; and the remaining relatives (great-grandchildren, great-great-grandchildren, grandnieces/nephews, great-grandnieces/nephews) were defined as other relatives. Siblings to the nasopharyngeal carcinoma patient's parents were not identified.

Identification of cancer in relatives. The study cohort, including information on family links to nasopharyngeal carcinoma cases, was subsequently linked to the Danish Cancer Registry using the personal identification number, and all cases of cancer in the cohort were retrieved. Cases diagnosed before 1978 were coded according to the slightly expanded International Classification of Diseases (ICD)-7 code used by the Danish Cancer Registry (12), and cases diagnosed after 1978 according to both the ICD-O code and the modified ICD-7 code. Cancers in Greenlanders living in Denmark at the time of diagnosis were included in the study. The analysis is based on the ICD-7 code, except for carcinoma of the salivary gland in which case the ICD-O classification was used.

Statistical analysis. The risk of nasopharyngeal carcinoma among first-degree relatives and second-degree relatives following the first case of nasopharyngeal carcinoma in the family (index case) was compared with individuals without affected relatives using log-linear Poisson regression with adjustment for sex, age (5 years), and calendar period (5 years). The cohort members were followed from date of birth or January 1, 1973, whichever came last, until date of possible cancer diagnosis, death, emigration, or December 31, 2002, whichever came first. The observational period for relatives began at date of birth, January 1, 1973, or date of diagnosis of the first case of nasopharyngeal carcinoma in the family (index case), whichever came last.

The risk of a given non–nasopharyngeal carcinoma in first-degree and second-degree relatives of nasopharyngeal carcinoma patients was analyzed in the same manner with the exception that the observational period for relatives also began at date of birth or January 1, 1973, whichever came last. We investigated whether restricting the observation period for relatives to begin at date of diagnosis of the first case of nasopharyngeal carcinoma in the family (index case) changed the overall estimates of non–nasopharyngeal carcinoma risk among relatives. However, there were no differences in risk estimates, and we decided to let the observation period begin as described.

In multiplex families (families with at least two nasopharyngeal carcinoma cases), subsequent analyzes were done on individuals who were first- or second-degree relatives to at least one of the nasopharyngeal carcinoma cases.

The possible association of age of the relative and the index case on the familial cancer risk was investigated using an age interval under or equal/above 45 years of age. The limit was chosen to ensure a reasonable number of cases in the younger age group.

Due to the small number of cases among relatives, confidence intervals (CI) for relative risks (RR) were estimated based on a Poisson distribution of number of cases among relatives (analogue to the exact method for standardized mortality ratio; ref. 13). The approach is chosen as relatives only make up a very small proportion of the cases (i.e., determine most of the SE values) and because adjusting had a negligible effect on SE values in the Poisson regression analyses. All statistical tests are two sided.

Results

In total, the cohort consisted of 766 first-degree relatives, 4,361 other relatives, and 68,095 nonrelatives. During the 30-year period of follow-up, 81 cancers were diagnosed among first-degree relatives, 45 cancers among second-degree relatives, and 3,086 cancers among nonrelatives (Table 1).

Familial risk of nasopharyngeal carcinoma. We identified a total of 12 cases of nasopharyngeal carcinoma among first-degree relatives following an index case of nasopharyngeal carcinoma in the family (Table 2). The RR of nasopharyngeal carcinoma among first-degree relatives was 8.0 (95% CI, 4.1-14.0). Gender and age of the relative and the index case did not have any significant

Table 1. Number of persons, years of observation, and number of cancers in relatives and nonrelatives in the cohort of all persons born in Greenland, followed from 1973 to 2002

	No. persons	Years of observation	No. cancers
Relatives			
First-degree relatives (parents, siblings, children)	766	19,304	81
Second-degree relatives* (nephews/nieces, grandchildren)	1,744	42,974	45
Other relatives*,†	2,617	42,815	7
Nonrelatives	68,095	1,525,544	3,086
Total	73,222	1,630,367	3,219

*The relatively low number of cases in second-degree and other relatives is due to young ages.
†Great-grandchildren, great-great-grandchildren, grandnieces/nephews, great-grandnieces/nephews.

Table 2. Number of nasopharyngeal carcinoma cases in nonrelatives and first-degree relatives after first case of nasopharyngeal carcinoma in the family and RR among first-degree relatives according to sex, age, sex of index case, age of index case, and type of relation

	No. cases		RR* (95% CI)	$P^{\dagger}$
	Nonrelatives	Relatives		
All	122	12	8.0 (4.1-14.0)	
Sex ‡				
Male	61	7	10.2 (4.1-21.0)	0.43
Female	61	5	6.3 (2.0-14.7)	
Age (y) ‡				
<45	50	2	4.2 (0.5-15.2)	0.26
≥45	72	10	9.8 (4.7-18.0)	
Sex of index case§				
Male	—	6	7.2 (2.6-15.7)	0.84
Female	—	6	8.1 (3.0-17.7)	
Age of index case (y)§				
<45	—	3	9.3 (1.9-27.2)	0.68
≥45	—	9	7.3 (3.3-13.9)	
Type of relation§				
Affected sibling	—	11	10.9 (5.4-19.5)	0.96
Affected child	—	1	10.3 (0.3-57.4)	

*RR adjusted for sex, age, and calendar period.
†Test for heterogeneity using likelihood-ratio test.
‡Sex and age of persons followed in the cohort.
§Both groups compared with all nonrelatives.

modifying effect on the familial risk of nasopharyngeal carcinoma. No cases of nasopharyngeal carcinoma were observed among second-degree relatives following an index case.

Familial risk of non–nasopharyngeal carcinomas. The RR of non–nasopharyngeal carcinoma in general among first-degree relatives of nasopharyngeal carcinoma patients was increased to 1.2 (95% CI, 1.0-1.5) compared with nonrelatives (Table 3). Among first-degree relatives in multiplex families, the RR of non–nasopharyngeal carcinoma (n = 18) was increased to 1.6 (95% CI, 0.9-2.5). The RR of non–nasopharyngeal carcinoma among second-degree relatives was 0.9 (95% CI, 0.6-1.2) and 1.1 (95% CI, 0.4-2.3) in all families and multiplex families, respectively.

A highly increased risk of salivary gland carcinoma was observed among first-degree relatives in all families (RR, 8.4; 95% CI, 2.7-19.5; Table 3) and in multiplex families (RR, 8.5; 95% CI, 0.2-47.3). The RR of salivary gland carcinoma among second-degree relatives was 1.7 (95% CI, 0.1-9.4) in all families, with no affected second-degree relatives in multiplex families. If benign (mixed) forms of salivary gland carcinoma (pleomorphic adenoma and adenolymphoma) were included, the RRs among first-degree relatives were 7.8 (95% CI, 2.5-18.1) and 7.9 (95% CI, 0.2-44.0) in all families and multiplex families, respectively. None of the salivary gland carcinoma patients developed subsequent nasopharyngeal carcinoma in the observation period.

A significantly increased risk of cervical cancer was observed among first-degree relatives from all families (RR, 2.2; 95% CI, 1.1-3.9) and multiplex families (RR, 3.7; 95% CI, 1.0-9.4). The risk of cervical cancer among second-degree relatives was comparable with nonrelatives, both in all families (RR, 0.8; 95% CI, 0.3-1.7) and in multiplex families (RR, 1.8; 95% CI, 0.2-6.5).

Two cases of tonsil cancer were diagnosed in first-degree relatives from multiplex families: in all families (RR, 4.7; 95% CI, 0.6-17.0) and in multiplex families (RR, 31.4; 95% CI, 3.8-113).

Cases of hepatocellular carcinoma or Hodgkin's lymphoma were not observed in relatives.

There was no significant difference in the risk of non–nasopharyngeal carcinoma among male and female relatives, and relatives under or above 45 years of age (Table 4). Gender and age of the nasopharyngeal carcinoma index case had no modifying effect on the overall familial cancer risk among the relatives.

Mean maternal age at first birth and mean number of births at the end of the observation period did not differ between relatives and nonrelatives.

Discussion

The present study is the first on cancer risk in relatives of nasopharyngeal carcinoma patients based on incidence data. It documents a significantly increased risk of cancer of the salivary glands and uterine cervix in first-degree relatives.

As previously observed, we found an increased risk of nasopharyngeal carcinoma in close nasopharyngeal carcinoma relatives, although our RR of 8.0 is in the lower end of those observed by others (95% CI, 4.5-14.2; refs. 14–16). Results from case-control studies on familial cancer risk are especially prone to recall bias, resulting in overestimated risks, a possibility that is minimized in this study. On this basis, we conclude that the familial risk of nasopharyngeal carcinoma among Inuits is comparable with the familial risks reported from Southeast Asia and other high-incidence areas, and hence the influence of the genetic susceptibility in undifferentiated

Table 3. Number of cancers other than nasopharyngeal carcinoma in nonrelatives and first-degree relatives in all nasopharyngeal carcinoma families, and RR among first-degree relatives adjusted for sex, age, and calendar period

	ICD codes*	No. cases		RR (95% CI)
		Nonrelatives	Relatives	
Eye	192	2	1	29.5 (0.7-164)
Salivary gland	142	32	5	8.4 (2.7-19.5)
Tonsil	145	20	2	4.7 (0.6-17.0)
Testis	178	14	1	4.4 (0.1-24.5)
Rectum	154	84	5	2.8 (0.9-6.5)
Corpus uteri	172	17	1	2.7 (0.1-15.0)
Cervix uteri	171	302	12	2.2 (1.1-3.9)
Stomach	151	132	6	2.2 (0.8-4.8)
Mouth	143-144	44	2	2.1 (0.3-7.6)
Metastases	198	78	3	1.8 (0.4-5.3)
Pancreas	157	124	5	1.8 (0.6-4.2)
Other skin	191	67	2	1.5 (0.2-5.4)
Brain	193	74	2	1.4 (0.2-5.0)
Esophagus	150	153	4	1.2 (0.3-3.0)
Ovary	175	83	2	1.2 (0.1-4.3)
Lung	162.0-162.1	643	17	1.2 (0.7-1.9)
Bladder	181	42	1	1.1 (0.0-6.1)
Unspecified	199	133	3	1.0 (0.2-2.9)
Breast	170	285	5	0.8 (0.3-1.9)
Colon	153	208	2	0.4 (0.0-1.4)
All malignant neoplasms	140-205	3,062 †	77 †	1.2 (1.0-1.5)

*Malignancies with no cases in first-degree relatives are not shown.
†The numbers differ from the numbers of cancers in total (Table 1), as only the first cancer in an individual is included.

nasopharyngeal carcinoma seems similar in different nasopharyngeal carcinoma high-incidence areas. The occurrence of a distinct familial form of nasopharyngeal carcinoma with an earlier age at onset is described in some high-incidence areas, although reports are not consistent (17). A similar characteristic familial form of nasopharyngeal carcinoma is not observed among Inuits, as neither age of the relative nor age of the index case had any significant effect on the risk of nasopharyngeal carcinoma among relatives.

The risk of salivary gland carcinoma among first-degree relatives, which was 8.4 times that of nonrelatives, indicates a causal association.

Although rare, secondary spread of nasopharyngeal carcinoma to the salivary glands has been reported (18). In the present study, secondary spread of nasopharyngeal carcinoma to the salivary glands cannot be completely excluded, but is unlikely as none of the salivary gland cancer patients developed subsequent nasopharyngeal carcinoma during follow-up. Nearly all malignant Inuit salivary gland tumors are anaplastic carcinomas of the lymphoepithelioma type, and histopathologically undifferentiated nasopharyngeal carcinoma resembles the equally EBV-associated salivary gland carcinoma (3, 5, 19). A bias could occur if relatives of nasopharyngeal carcinoma patients were more likely than nonrelatives to be precisely diagnosed with salivary gland carcinoma. This is not likely as a tumor of the salivary glands seldom remains undetected, just as the possibility of a higher tendency to classify tumors malignant in relatives can be excluded because the risk estimates are preserved when benign forms are included.

Salivary gland carcinoma is very rare in most populations, but occurs with the world's highest incidence among Inuits (1, 2). Although the incidence of salivary gland carcinoma in other nasopharyngeal carcinoma–endemic areas is lower, cases of EBV-positive salivary gland carcinoma have been observed. However, no examples of family co-occurrence with nasopharyngeal carcinoma have been reported (1, 20, 21).

Other than EBV, little is known about risk factors for salivary gland carcinoma among Inuits, and case-control studies have not shown any relationship with tobacco use (22). A high content of nitrosamines has been found in dried fish from Greenland (23), and ingestion of this popular food item could be a risk factor for both nasopharyngeal carcinoma and salivary gland carcinoma, equivalent to the association between Cantonese-style salted fish and nasopharyngeal carcinoma in Southeast China (4).

The high risk of salivary gland carcinoma among first-degree relatives in this study is comparable with their risk of nasopharyngeal carcinoma. Given the shared association with EBV, the mechanisms leading to EBV infection and transformation of the epithelium in the nasopharynx and salivary glands are likely to be identical and a common genetic background is possible.

A limitation of the study is the lack of information on environmental risk factors, as this information is not included in the registers. Familial aggregation could be a result of a shared environment, but the very high RR of nasopharyngeal carcinoma and salivary gland carcinomas and the identification of susceptibility loci support the involvement of a genetic factor. The absence of an increased risk of nasopharyngeal carcinoma among second-degree relatives could support the role of shared environment as a contributing factor in the pathogenesis; however, the generally low number of cancer cases among second-degree relatives makes it

difficult to draw conclusions on this basis. The general increased risk of cancer among family members could suggest family patterns for an influential environmental factor, most obviously tobacco use. However, tobacco use cannot explain the generally increased risk, as lung cancer rates in relatives were not increased, neither were rates of other closely tobacco-associated cancers (bladder and esophagus).

Cancer of the cervix, another virally associated cancer, was found to occur in excess in first-degree relatives. The risk was 2-fold increased in nasopharyngeal carcinoma–affected relatives and almost 4-fold increased in multiplex families. Cervical cancer is strongly associated with genital infection of oncogenic types of human papilloma virus (24). However, cases of cervical tumors also display familial aggregation and shared genes have been suggested to account for 27% of the total variation in liability to the disease, with shared environment only responsible for a limited contribution (25, 26). The responsible genes are not identified, but associations between HLA class II alleles and cervix cancer have been reported (27). Thus, specific HLA alleles seem to influence the risk of both cervix cancer and nasopharyngeal carcinoma, but the great variability in results from different regions does not allow a direct comparison. Loss of heterozygosity has been detected in several chromosome regions in cervical cancer (28). Especially progressive deletions at one or more 3p regions, including 3p21, are interesting, as a susceptibility locus at 3p21 linked to familial nasopharyngeal carcinoma recently has been identified (29). Sharing of environmental risk factors cannot readily explain the increased risk of cervical cancer among nasopharyngeal carcinoma relatives. Smoking increases the risk of both cancers, but the risk of lung cancer among female nasopharyngeal carcinoma relatives was not increased in this study. A diagnostic bias is difficult to imagine, as this would require relatives of nasopharyngeal carcinoma patients to be less likely to attend cervical cancer screenings. Both nasopharyngeal carcinoma and cervical cancer is associated with low socioeconomic status, but available proxy measures for socioeconomic status, maternal age at first birth, and number of children did not differ between relatives and nonrelatives.

Our additional finding of a significant increased risk of cancer of the tonsils among multiplex families is interesting in this context, as 50% to 60% of tonsil cancers are associated with human papilloma virus (30–32). However, the number of these cases was limited and we did not have any information on human papilloma virus presence in the tumors.

The increased, although nonsignificant, risk of cancer of the stomach is noticeable. A variable proportion (3-12%) of stomach carcinomas is associated with EBV. In the subgroup of stomach cancer with lymphoepithelial-like morphology, EBV seems particularly prevalent and has been detected in 78% to 100% of cases (33, 34). Studies of stomach cancer in nasopharyngeal carcinoma high-incidence and low-incidence areas in China have shown a higher frequency of EBV detection in stomach carcinomas in the nasopharyngeal carcinoma high-incidence area, suggesting overlapping risk factors (35). We were, however, unable to evaluate the association with possible lymphoepitheliomas, as this information was not available.

If nasopharyngeal carcinoma relatives have an increased susceptibility for virally associated cancers, an increased risk of hepatocellular carcinoma would be expected, as chronic hepatitis B virus infection increases the risk of hepatocellular carcinoma considerably (36). However, the risk of hepatocellular carcinoma was not increased among first-degree relatives. A possible association might be obscured, as the incidence of hepatocellular carcinoma in Greenland is low, despite a high prevalence of HBsAg carriers (2, 37, 38), indicating a limited influence of hepatitis B infection on the risk of hepatocellular carcinoma among Greenlanders. Likewise, an increased risk of EBV-associated Hodgkin's lymphoma could have been expected (4), but Hodgkin's lymphoma is a rare malignancy in the Inuit population (2).

Table 4. Number of cancers other than nasopharyngeal carcinoma in nonrelatives and first-degree relatives in all nasopharyngeal carcinoma families, and RR among first-degree relatives, according to sex, age, sex of nasopharyngeal carcinoma index case, and age of nasopharyngeal carcinoma index case

	No. cases*		RR (95% CI)†	P‡
	Nonrelatives	Relatives		
Sex				
Male	1,266	34	1.4 (1.0-1.9)	0.26
Female	1,796	43	1.1 (0.8-1.5)	
Age (y)				
<45	640	14	1.5 (0.8-2.5)	0.37
≥45	2,422	63	1.1 (0.8-1.4)	
Sex of index case§				
Male	—	38	1.2 (0.9-1.6)	0.57
Female	—	39	1.3 (0.9-1.8)	
Age of index case (y)§				
<45	—	14	1.2 (0.7-2.0)	0.88
≥45	—	63	1.2 (0.9-1.6)	

*The numbers differ from the numbers of cancers in total (Table 1) among first-degree relatives as only the first cancer in an individual is included.
†RR adjusted for sex, age, and calendar period.
‡Test for heterogeneity using likelihood-ratio test.
§Both groups compared with all nonrelatives.

The present study made use of a true population-based cohort design, and selection bias is therefore not a problem. Theoretically, individuals could remember cancer-affected relatives better than noncancer relatives; however, this is not believed to be a problem in close relatives. Furthermore, we used information on cancer occurrence from the national cancer registry, which eliminated problems with recall bias of the outcome. Relatives of nasopharyngeal carcinoma cases diagnosed and deceased before 1973 or diagnosed after February 1998 were not identified and would be misclassified as nonrelatives. Relatives were identified through interview and in registers, and the possibility of nonrelatives being classified as relatives is small. However, both types of nondifferential misclassification would tend to reduce the risk estimates.

In conclusion, we found that the increased familial risk of nasopharyngeal carcinoma among Inuits is comparable with other nasopharyngeal carcinoma high-risk areas, and that the increased risk of cancer in nasopharyngeal carcinoma families is not restricted to nasopharyngeal carcinoma, but extend to the virally associated cancers of the salivary glands and cervical uteri. Especially the magnitude of the association with salivary gland carcinoma, which equals the RR of nasopharyngeal carcinoma in these families, indicates a common genetic background for these EBV-associated malignancies.

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