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Cancer risk in the relatives of patients with nasopharyngeal carcinoma—a register-based cohort study in Sweden

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Background: Little is known about cancer susceptibility among relatives of nasopharyngeal carcinoma (NPC) patients in non-endemic areas. We conducted a register-based cohort study to assess the relative risks (RRs) of cancer in families of NPC probands in Sweden.

Methods: By linking 11 602 616 Swedish-born individuals (defined as 'general population') identified from national censuses to the Swedish Cancer Register and Multi-Generation Register, we identified 9157 relatives (3645 first-degree and 5512 second-degree) of 1211 NPC probands. Cancer incidence during 1961–2009 was ascertained through the Cancer Register. Relative risks of cancer in the relatives of NPC probands, compared with the rest of the general population, were calculated from Poisson regression models.

Results: First-degree relatives had higher risks of NPC ($N=2$, RR = 4.29, 95% confidence interval (CI) = 1.07 to 17.17) and cancers of the larynx ($N=5$, RR = 2.53, 95% CI = 1.05 to 6.09), prostate ($N=76$, RR = 1.35, 95% CI = 1.07 to 1.68), and thyroid ($N=10$, RR = 2.44, 95% CI = 1.31 to 4.53) than the rest of the general population. In addition, a raised risk of cancer of the salivary glands was observed among first-degree relatives of probands with undifferentiated NPC ($N=2$, RR = 6.64, 95% CI = 1.66 to 26.57). In contrast, a decreased risk of colorectal cancer was observed in first- and second-degree relatives ($N=43$, RR = 0.71, 95% CI = 0.53 to 0.96).

Conclusion: The increased risk of NPC and certain other cancers among first-degree relatives may be explained by shared genetic and environmental risk factors, the latter including Epstein–Barr virus infection and smoking or by increased diagnostic intensity.

Familial aggregation of nasopharyngeal carcinoma (NPC) in high-incidence areas is well documented (Friborg *et al*, 2005a; Chang and Adami, 2006; Yu *et al*, 2009). The involvement of genetic factors in the development of NPC is widely accepted, and the familial risk of NPC is among the highest of any malignancy (Goldgar *et al*, 1994; Ung *et al*, 1999; Friborg *et al*, 2005a). Two studies from high-incidence areas, one in Taiwan and one in southern China, have demonstrated that the increased risk of cancer in NPC families is restricted to NPC (Jia *et al*, 2004; Yu *et al*, 2009). By contrast, another study conducted in Greenland, an intermediate-incidence area, showed that relatives of NPC patients were also at increased risks of cancers of the salivary glands and cervix uteri (Friborg *et al*, 2005a). All of these studies focused on the relatives of probands with undifferentiated NPC, that is, the histopathological subtype that comprises the vast majority of NPC in endemic areas, but the minority in non-endemic areas (Malker *et al*, 1990; Vaughan *et al*, 1996; Liu, 1999). Studies of cancer patterns in NPC families in high-incidence areas, however, have been limited by the lack of high-quality register data (Friborg *et al*, 2005b).

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Outside of high- and intermediate-incidence regions, familial patterns of NPC risk are not well documented. In low-incidence areas, distinct aetiologic factors appear to be involved in the pathogenesis of different histopathological types of NPC (Pathmanathan *et al*, 1995; Polesel *et al*, 2011), and aggregation of cancers within NPC families may not be restricted to NPC itself. Understanding the cancer risk among relatives of NPC patients in low-incidence areas can lend insight into the potential shared genetic or environmental risk factors between NPC and other malignancies.

To the best of our knowledge, no previous study has assessed whether cancer risk is increased among relatives of NPC probands in a non-endemic area. The availability of Swedish nation-wide registers, including the Swedish Cancer Register, the Causes of Death Register, and the Multi-Generation Register, provides a unique opportunity to study this research question using high-quality population data.

MATERIAL AND METHODS

Study population. We used data from the Swedish censuses in 1960 (the first national census), 1970, 1980, and 1990 and Swedish Multi-Generation Register to identify the eligible study population. Details about the Swedish Multi-Generation Register have been published (Statistics Sweden, 2009; Ekbom, 2011). In brief, the register includes information on individuals born in 1932 and onward in Sweden, together with their biological or adoptive parents. Familial information is available for nearly all individuals alive in 1991 or deceased before 1968, and for 60% of the individuals who died between 1968 and 1990. From an initial pool of 13 598 327 individuals, we excluded those who were not born in Sweden ($N=1\,963\,784$), had a prevalent cancer ($N=27\,477$), died ($N=3932$), or migrated out of Sweden ($N=518$) before 1961, leaving a total of 11 602 616 eligible individuals in the study, defined as the general population.

Established in 1958, the nation-wide Swedish Cancer Register is >98% complete (Barlow *et al*, 2009). Using the Cancer Register, we identified 1811 NPC patients who had not previously been diagnosed with other cancers between 1958 and 2009 and were born in Sweden. Among them, 1213 (67% of 1811) had retrievable information on at least one first- or second-degree relative born in Sweden in the Multi-Generation Register, and 1211 NPC probands were the first NPC case in their families. Histopathological types of NPC were identified based on WHO/HS/CANC/24.1 (PAD) codes 146 for squamous cell carcinoma and 196 for undifferentiated carcinoma.

First-degree relatives were defined as biological parents, siblings, and children; second-degree relatives were defined as grandparents, grandchildren, uncles, aunts, nieces, nephews, and half-siblings. A total of 9158 relatives for the 1211 NPC probands were identified through the Multi-Generation Register. We excluded 1 relative who had been diagnosed with cancer before 1961, leaving 9157 relatives (3645 first-degree relatives and 5512 second-degree relatives) for the analysis.

All subjects (relatives and the rest of the general population) were followed through record-linkages with the Cancer Register, the Causes of Death Register, and the Emigration Register, by using each individual's unique national personal identification number (Ludvigsson *et al*, 2009). The number of person-years at risk for each subject was calculated from the date of birth or January 1, 1961, whichever occurred later, until the date of cancer diagnosis, death, emigration, or December 31, 2009, whichever occurred first. This study was approved by the Regional Ethics Review Vetting Board in Stockholm.

Statistical analyses. We used log-linear Poisson regression models to calculate RRs and 95% confidence intervals (CIs) for overall and site-specific cancer, as the ratio of cancer incidence rates among relatives of NPC probands compared with the rest of the general population. We adjusted for attained age at follow-up (in 5-year intervals), sex, and calendar year at follow-up in all statistical models, and used log-transformed person-years as the offset. We further conducted stratified analyses by the degree of relatedness (first or second) and by histopathological type of NPC (undifferentiated or squamous cell). Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA). All statistical tests were two-sided, and *P*-values of <0.05 were considered to be statistically significant.

RESULTS

First- and second-degree relatives of NPC probands were followed for a median of 49.0 years and 33.2 years, respectively (Table 1). A bimodal pattern in age at study entry was observed among the first-degree relatives of NPC probands, with a first peak at ages 0–4 years and a second peak at ages 10–29 years. The vast majority of second-degree relatives were ages 0–4 years at study entry. Before the end of 2009, 680 relatives died and 272 emigrated out of Sweden.

In NPC families, 453 cancers were diagnosed among first-degree relatives and 192 cancers among second-degree relatives of probands (Table 2). Overall cancer incidence was not significantly increased among NPC families compared with the rest of the general population (relative risk (RR) = 1.03, 95% CI = 0.95 to 1.11, $P=0.50$). The RR of NPC in first-degree relatives of NPC probands *vs* the rest of the general population was 4.29 (95% CI = 1.07 to 17.17), based on the two cases observed. No NPC cases occurred among second-degree relatives of NPC probands.

Risk of buccal cavity cancers other than NPC was marginally significantly increased among first- and second-degree relatives of NPC probands compared with the rest of the general population (RR = 1.53, 95% CI = 0.95 to 2.46, $P=0.080$; Table 2). This association was especially pronounced for cancer of the salivary glands in first-degree relatives of NPC probands ($N=3$, RR = 2.84, 95% CI = 0.92 to 8.82), particularly for probands with undifferentiated NPC ($N=2$, RR = 6.64, 95% CI = 1.66 to 26.57). First-degree relatives were at higher risk of cancers of the larynx ($N=5$, RR = 2.53, 95% CI = 1.05 to 6.09), prostate ($N=76$, RR = 1.35, 95% CI = 1.07 to 1.68), and thyroid ($N=10$, RR = 2.44, 95% CI = 1.31 to 4.53) than the rest of the general population. These associations were stronger among first-degree relatives of probands with differentiated NPC, with RRs of 3.16 (95% CI = 1.02 to 9.80), 1.50 (95% = 1.10 to 2.04), and 2.94 (95% CI = 1.32 to 6.56) for cancers of the larynx, prostate, and thyroid, respectively.

Table 1. Characteristics of first- and second-degree relatives of 1211 NPC probands in Sweden, 1961–2009

Characteristics	First-degree relatives ($N=3645$)	Second-degree relatives ($N=5512$)
Mean age at study entry, years (s.d.)	15.1 (15.3)	3.1 (10.2)
Age group at entry, no. (%)		
0–4	1220 (33.5)	4910 (89.1)
5–9	380 (10.4)	104 (1.9)
10–29	1538 (42.2)	266 (4.8)
30–49	342 (9.4)	160 (2.9)
50+	165 (4.5)	72 (1.3)
Median duration of follow-up, years	49.0	33.2
Total no. of person-years at risk	150 902	176 724
No. of cancer cases	453	192
Mean age at end of follow-up, years (s.d.)	56.5 (17.0)	35.2 (16.5)

Abbreviations: No. = number; NPC = nasopharyngeal carcinoma.

Table 2. Relative risks and 95% CIs for cancer occurrence in the relatives of NPC probands in Sweden, 1961–2009

	Overall		First-degree relatives		Second-degree relatives	
Cancer site or type (ICD-7 code)	Cases in NPC relatives	RR (95% CI)	Cases in NPC relatives	RR (95% CI)	Cases in NPC relatives	RR (95% CI)
All cancers (140–209)	645	1.03 (0.95, 1.11)	453	1.07 (0.97, 1.17)	192	0.94 (0.82, 1.08)
NPC (146)	2	2.79 (0.70, 11.18)	2	**4.29 (1.07, 17.17)** (*P* value = 0.040)	0	NA
Buccal cavity, excluding NPC (140–145, 147–148)	17	1.53 (0.95, 2.46)	11	1.46 (0.81, 2.64)	6	1.66 (0.75, 3.70)
Salivary glands (142)	4	2.45 (0.92, 6.52)	3	2.84 (0.92, 8.82)	1	1.72 (0.24, 12.22)
Esophagus (150)	4	0.88 (0.33, 2.35)	3	0.94 (0.30, 2.91)	1	0.74 (0.10, 5.28)
Stomach (151)	13	0.80 (0.46, 1.37)	13	1.13 (0.66, 1.95)	0	NA
Colon and rectum (153, 154.0)	43	**0.71 (0.53, 0.96)** (*P* value = 0.026)	30	0.71 (0.50, 1.02)	13	0.72 (0.42, 1.24)
Liver cancer (155)	11	0.97 (0.54, 1.75)	7	0.88 (0.42, 1.84)	4	1.18 (0.44, 3.16)
Pancreas (157)	20	1.51 (0.97, 2.34)	13	1.40 (0.81, 2.42)	7	1.76 (0.84, 3.70)
Larynx (161)	6	2.07 (0.93, 4.62)	5	**2.53 (1.05, 6.09)** (*P* value = 0.038)	1	1.08 (0.15, 7.69)
Lung (162)	50	1.27 (0.96, 1.67)	35	1.29 (0.93, 1.80)	15	1.22 (0.73, 2.02)
Breast (170)	90	0.93 (0.76, 1.15)	70	1.15 (0.91, 1.45)	20	**0.57 (0.37, 0.88)** (*P* value = 0.011)
Cervix (171)	16	1.12 (0.69, 1.84)	11	1.31 (0.72, 2.36)	5	0.86 (0.36, 2.06)
Endometrium (172)	13	0.71 (0.41, 1.22)	10	0.83 (0.45, 1.55)	3	0.48 (0.15, 1.47)
Prostate (177)	101	**1.30 (1.07, 1.58)** (*P* value = 0.008)	76	**1.35 (1.07, 1.68)** (*P* value = 0.010)	25	1.18 (0.80, 1.75)
Kidney (180)	13	0.78 (0.45, 1.35)	8	0.71 (0.36, 1.43)	5	0.93 (0.39, 2.24)
Bladder (181.0)	25	1.06 (0.72, 1.57)	15	0.91 (0.55, 1.50)	10	1.43 (0.77, 2.66)
Skin cancer, melanoma (190)	27	0.86 (0.59, 1.26)	18	0.98 (0.62, 1.55)	9	0.70 (0.36, 1.34)
Skin cancer, non-melanoma (191)	23	1.20 (0.80, 1.81)	18	1.30 (0.82, 2.06)	5	0.95 (0.39, 2.27)
Brain (193)	25	0.84 (0.57, 1.25)	14	0.83 (0.49, 1.40)	11	0.87 (0.48, 1.57)
Thyroid (194)	14	**2.04 (1.21, 3.44)** (*P* value = 0.008)	10	**2.44 (1.31, 4.53)** (*P* value = 0.005)	4	1.44 (0.54, 3.84)
Lymphoma (200–202)	26	0.88 (0.59, 1.32)	19	0.98 (0.61, 1.57)	7	0.72 (0.34, 1.50)
Hodgkin lymphoma (201)	3	0.51 (0.17, 1.59)	0	NA	3	1.16 (0.37, 3.59)
Non-Hodgkin lymphoma (200, 202)	21	1.04 (0.68, 1.60)	17	1.28 (0.79, 2.05)	4	0.58 (0.22, 1.56)
Multiple myeloma (203)	10	1.39 (0.75, 2.58)	8	1.59 (0.79, 3.18)	2	0.92 (0.23, 3.67)
Leukaemia (204–207)	22	1.19 (0.78, 1.81)	10	0.85 (0.46, 1.59)	12	**1.78 (1.01, 3.13)** (*P* value = 0.046)

Abbreviations: CI = confidence interval; ICD = International Classification of Diseases; NA = not available; NPC = nasopharyngeal carcinoma; RR = relative risks.

By contrast, the RRs for first-degree relatives of undifferentiated NPC probands were 1.76 (95% CI = 0.25 to 12.51), 1.02 (95% CI = 0.63 to 1.64), and 1.70 (95% CI = 0.43 to 6.81) for cancers of the larynx, prostate, and thyroid, respectively.

Colorectal cancer risk was significantly decreased among first- and second-degree relatives of NPC probands compared with the rest of the general population ($N = 43$, RR = 0.71, 95% CI = 0.53 to 0.96), with no substantial difference in the RR by degree of relatedness (Table 2).

Risk of other EBV-associated cancers, including Hodgkin lymphoma, non-Hodgkin lymphoma, and possibly gastric cancer, was not significantly different among relatives of NPC probands compared with the rest of general population (Table 2).

DISCUSSION

To the best of our knowledge, this is the first cohort study to evaluate cancer risk among relatives of NPC probands in a low-risk population. The present study shows an increased risk of NPC among first-degree relatives of NPC probands in a non-endemic geographic area. This study also shows an increased risk of salivary gland cancer among first-degree relatives of probands with undifferentiated NPC, a result that is consistent with findings from one study in Greenland (Friborg *et al*, 2005a). However, we did not detect a significantly increased risk of cervical cancer in NPC families, as was observed in the Greenland study. The observed increase in risk of salivary gland cancer among relatives of probands with undifferentiated NPC may be due in part to shared genetic background and/or environmental risk factors, the latter including EBV infection and diet (Saemundsen *et al*, 1982; Leung *et al*, 1995; Shebl *et al*, 2010).

Elevated risks of cancers of the larynx, prostate, and thyroid among relatives of NPC probands, particularly those with differentiated NPC, have not previously been reported. The observed increase in laryngeal cancer risk among first-degree relatives of NPC probands may be due to shared environmental risk factors, such as tobacco smoking and alcohol consumption (Franceschi *et al*, 1990; Gronbaek *et al*, 1998). This explanation is supported by evidence that smoking and alcohol drinking are more

consistently associated with risk of differentiated than undifferentiated NPC (Vaughan *et al*, 1996; Hsu *et al*, 2011; Polesel *et al*, 2011). There is no evidence to date linking prostate cancer and NPC. The cumulative uptake of PSA testing in men aged 55 to 69 years in Sweden increased from 0% in 1997 to 56% in 2007 (Jonsson *et al*, 2011). Therefore, we conducted a secondary analysis stratified by calendar period of follow-up: before 1997 *vs* 1997 and thereafter. Compared with the rest of the general population, the RRs of prostate cancer among first-degree relatives of NPC probands before and after 1997 were 0.77 (95% CI = 0.47 to 1.28) and 1.60 (95% CI = 1.25 to 2.06), respectively. Therefore, the observed increase in prostate cancer risk among first-degree relatives of NPC probands may be due to increased diagnostic intensity (including prostate cancer screening and diagnostic work-up) among relatives of NPC probands. The increased risk of thyroid cancer in NPC families could be due to a shared aetiologic association with EBV infection, as suggested by a small case series of thyroid carcinomas in which EBV was universally expressed (Shimakage *et al*, 2003). Alternatively, increased diagnostic intensity may also partly explain the observed higher risk of thyroid cancer (Welch and Black, 2010). A chance finding cannot be ruled out.

The observed decrease in the risk of colorectal cancer among relatives of NPC probands in our study is consistent with results from the studies in Taiwan and Greenland (Friborg *et al*, 2005a; Yu *et al*, 2009). Notably, the risk of colorectal cancer following primary diagnosis of NPC is also lower than expected (Scelo *et al*, 2007; Chen *et al*, 2008). The underlying reasons for this finding remain to be elucidated, and such knowledge may similarly shed light on the aetiology and prevention of NPC.

Risk of another EBV-associated cancer, Hodgkin lymphoma, which occurs at a relatively high incidence rate in Sweden (Grufferman and Delzell, 1984; Chang *et al*, 2004), tended to be lower in relatives of NPC probands than in the rest of the general population. Although both Hodgkin lymphoma and NPC are aetiologically associated with EBV, the patterns of risk factors diverge between the two malignancies. For example, Hodgkin lymphoma occurs more frequently in Europe and North America and among individuals of Caucasian descent, whereas NPC is relatively common in Southeast Asia and among individuals of southern Chinese descent (Ferlay *et al*, 2013; Forman *et al*, 2013). A history of infectious mononucleosis, which is caused by relatively late primary infection with EBV, is associated with an increased risk of Hodgkin lymphoma, whereas it may be inversely associated with NPC risk (Vaughan *et al*, 1996; Hjalgrim *et al*, 2000, 2007). Different tissues (i.e., epithelium *vs* lymphoid tissue) may be more susceptible to different EBV strains, and may be infected with EBV through different mechanisms. Although the small number of Hodgkin lymphoma cases among relatives of NPC probands observed in our study precludes firm conclusions about whether Hodgkin lymphoma risk is indeed lower than expected in NPC families, such a finding seemed to be consistent with existing knowledge of the epidemiology of the two malignancies.

Human leukocyte antigen (HLA) genes have shown the most consistent evidence for associations with NPC risk, although it is unclear whether these associations are due to a direct causal relation (Hildesheim *et al*, 2002; Bei *et al*, 2010). The development of other malignancies, including thyroid (Knoll *et al*, 1997) and cervical cancers (Madeleine *et al*, 2008), may also be mediated by certain HLA alleles. Thus, HLA-related susceptibility might underlie familial risks of NPC and other cancers, and this area warrants further investigation.

Strengths of our study include its population-based design, the use of high-quality Swedish registers, and the ability to reliably identify first- and second-degree relatives using the Multi-Generation Register. However, there are several limitations of the present study. First, the lack of family information for 598 otherwise eligible NPC cases (33% of 1811) in the Multi-Generation Register may affect the generalisability of the present study. Given that a primary reason for missing data is death, and that cancer is one of the leading causes of death in Sweden, we believe these individuals were at a higher risk of cancer than those with family information available in the Multi-Generation Register. Therefore, it is likely that the excess risk of cancers in relatives of NPC cases was underestimated in the present study. Second, we lacked information on environmental exposures and genetic risk factors, thereby preventing the investigation of potential shared risk factors. Third, the number of cancers observed in relatives was modest for most sites. The limited numbers were due in part to the relatively young age of the relatives, which was restricted to subjects enrolled after 1961 and diagnosed with cancer by 2009. Finally, the observed elevated risk in first-degree relatives of patients with NPC was based on only two cases. Although we determined that the parents of one of these cases were also born in Sweden, we cannot rule out the possibility that one or both of the parents of the other NPC case migrated from a country with high NPC incidence, where familial aggregation of NPC is relatively common. However, after excluding the family of the NPC probands without parents' information, we could still observe an increased risk of NPC among the first-degree relatives (RR = 3.85, 95% CI = 0.54 to 27.38) of NPC probands, compared with the rest of the general population. Interpretation of these findings should be cautious given the small number of cancer cases observed among relatives of NPC probands.

In conclusion, relatives of NPC probands in the low-incidence population of Sweden are at increased risk of not only NPC, but also certain other cancers. This increased risk is especially pronounced among relatives of probands with differentiated NPC, the histopathological type that is most common in non-endemic areas. Shared environmental risk factors such as EBV infection and smoking may explain the observed associations, although shared genetic susceptibility, increased diagnostic intensity, and chance cannot be ruled out.

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