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Cancer Patterns in Nasopharyngeal Carcinoma Multiplex Families in Taiwan

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Abstract

Genetic and environmental factors have been implicated in the etiology of nasopharyngeal carcinoma (NPC), a tumor known to be closely associated with Epstein-Barr virus (EBV) infection. Studies have reported familial aggregation of NPC and have suggested the possible aggregation of NPC and other cancers. We evaluated familial aggregation of cancer in 358 high-risk families with two or more NPC cases enrolled in a NPC genetics study in Taiwan. Participants were linked to the Taiwan National Cancer Registry to identify incident cancers diagnosed after study enrollment (started in 1996) and before December 31, 2005 or death. In total, 2,870 individuals from the NPC Multiplex Family Study contributed 15,151 person-years over an average of 5.3 years of follow-up. 110 incident cancers were identified. Multiple-Primary Standardized Incidence Ratios (MP-SIRs) were computed to evaluate cancer risk overall, associated with infectious agents, and with other tumors. The overall MP-SIR was 1.3 (95% CI: 1.1–1.6), which was largely explained by an excess in NPC (MP-SIR=15; 95% CI: 10–23). Exclusion of incident NPC diagnoses led to an overall MP-SIR of 1.0 (95% CI: 0.83–1.3). Similarly, the observed excess risk of cancers associated with infectious agents (MP-SIR=2.0; 95% CI: 1.5–2.6) was driven by the excess in NPC; exclusion of NPC cases led to a reduced MP-SIR that did not differ from 1.0. Analysis of the largest NPC multiplex family study to date confirms the presence of co-aggregation of NPC within families in Taiwan, but does not provide evidence for a broader familial syndrome involving NPC and other tumors.

Keywords

Epstein-Barr virus; nasopharyngeal carcinoma; epidemiology; genetics

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INTRODUCTION

It was estimated that 17% of newly diagnosed cancers worldwide were attributable to infection in 2005 (1). Epstein-Barr virus (EBV) has been implicated in approximately 1% of all cancers worldwide including nasopharyngeal carcinoma (NPC), Burkitt's lymphoma, other lymphomas, and gastric cancer (2). Interestingly, while EBV infection is ubiquitous worldwide, the distribution of malignancies associated with EBV varies dramatically by geography and ethnicity (3). NPC is relatively common in areas of Southeastern Asia and among individuals of Chinese descent but rare in Europe/North America and among individuals of Caucasian descent. Studies to date suggest that both environmental and host susceptibility factors are likely to explain this distinct geographic and ethnic distribution (4–[10]).

Family history of NPC and host susceptibility factors such as human leukocyte antigen, cytochrome p450 2E1, and DNA repair gene (XRCC1 and hOGG1) polymorphisms have been associated with disease risk (4–[6]). Furthermore, genetic susceptibility loci linked to NPC development have recently been identified on chromosomes 3 and 4 (7–[8]). Co-aggregration of other malignancies within NPC families has also been reported (9–[10]). In a recent record linkage study from Greenland, Denmark, increased risk for infectious agent related cancers including salivary, cervical, and gastric cancers was observed among families with a history of NPC (10). For each of the associated cancers, the risk was greater for first-degree relatives compared to second-degree relatives and greater for individuals from NPC multiplex families compared to families with only one member affected with NPC.

Given this evidence, we sought to evaluate familial aggregation of cancer in 358 families with two or more NPC cases enrolled in a study of NPC genetics in Taiwan and to specifically evaluate whether family members from these NPC multiplex families had elevated risk of other cancers associated with infectious agents.

MATERIALS AND METHODS

Participants in a NPC Multiplex Family Study conducted in Taiwan form the basis of our evaluation. Details of the study have been described elsewhere (11–[12]). Briefly, 20,450 NPC cases diagnosed between 1980 and 2003 were identified through the National Cancer Registry, ten tertiary care hospitals, and select outpatient clinics that treat NPC. We successfully screened 10,178 (49.8%) cases for a family history of NPC. Ultimately, 358 NPC multiplex families were identified and recruited into our study. From these families, a total of 3,216 individuals (659 NPC cases and 2557 unaffected family members) were enrolled into our study including NPC cases, their parents, up to 5 siblings, and for deceased NPC cases, their spouse and up to 3 children. When it was necessary to link affected individuals in our families, additional relatives were recruited. For the present evaluation, all live individuals enrolled into the study were included, regardless of NPC affection status resulting in 2,870 individuals for the present evaluation.

Families were administered a questionnaire to obtain complete family history information with instructions by a trained nurse interviewer followed by self-administration by participants or proxies for deceased individuals. Information on age, gender, date of birth, name, and national identification number were also obtained. Informed consent was obtained from participants. Institutional Review Boards at both the National Institutes of Health and National Taiwan University approved the study protocol and informed consent.

We used name, national identification number, sex, and date of birth to link participants in our study to the National Cancer Registry. Linkage was performed for each participant to identify incident cancers diagnosed after enrollment into our study (which started in 1996) and before December 31, 2005 or death. Additional linkage to the National Chronic Disease and National

Death Registries in Taiwan was performed to confirm that all cancer diagnoses were identified via linkage to the tumor registry. Of the 110 incident cases identified through this linkage effort, 93.1% were identified through the National Cancer Registry, supporting the completeness of the registry system in Taiwan during the time period of interest. Annual age- and gender-specific population-based rates for individual cancers were obtained from the National Tumor Registry from 1996 (start of the study) to 2005, and applied to our study participants to estimate the number of expected incident cancer diagnoses by site and overall. Multiple Primary-Standardized Incidence Ratios (MP-SIRs) from SEER*Stat 6.3.6 was used to calculate MP-SIRs and 95% confidence intervals (CIs) (13). Since the population-based rates for individual cancers from the National Tumor Registry include all cancers (i.e., the rates include first and subsequent primary cancers), we too allowed for multiple primaries in our analysis. We evaluated all cancers, all cancers excluding NPC, all cancers associated with an infectious agent (oral, salivary glands, NPC, esophagus, gastric, hepatic, cervical, vulva/vagina, Hodgkin's lymphoma, and Non-Hodgkin's lymphoma), and individual cancers or organ system groups for which ≥5 events were either observed or expected. We restricted our analysis to incident cancers diagnosed after study recruitment for two reasons. First, although the Taiwan Registry system has been in existence since 1979, reporting was <85% complete before 1986 and achieved >99% completeness by 1995. Second, we wished to avoid survival biases that may result from estimating expected cases prior to recruitment based on study participants only. Nonetheless, we understand that there may be treatment effects for second primaries; therefore, we calculated the MP-SIRs restricted to first primaries and observed similar patterns compared to the analysis which included all primaries. Finally, there is the potential bias of differential participation of individuals based on cancers already in the family.

RESULTS

In total, the 2,870 individuals from the NPC Multiplex Family Study contributed 15,151 person-years (male: 7,417 person-years and female: 7,734 person-years) over an average of 5.3 years of follow-up. 110 cancers were linked in this population; of these incident cancers, 84 cancers arose from relatives of NPC cases at study enrollment (i.e., 26 second primary cancers from NPC cases). The overall MP-SIR was 1.3 (95% CI: 1.1–1.6) with MP-SIRs of 1.2 (95% CI: 0.91–1.6) in males and 1.4 (95% CI: 1.1–1.9) in females (Table 1). This observed increase was largely explained by an excess in NPC (MP-SIR=15; 95% CI: 10–23). Exclusion of incident NPC diagnoses led to an overall MP-SIR of 1.0 (95% CI: 0.83–1.3). When we restricted our analysis to relatives of NPC affected individuals from our multiplex families, we observed similar findings. The overall MP-SIR was 1.2 (95% CI: 0.95–1.5) and the observed excess was again largely explained by an excess in NPC among these relatives (MP-SIR=11; 95% CI: 5.8–18). Exclusion of the incident NPC diagnoses led to an overall MP-SIR of 1.0 (95% CI: 0.79–1.3).

We compared observed and expected rates of tumors that have been associated with infectious agents (Table 1). We observed an increased risk for infectious agent related cancers overall (MP-SIR=2.0; 95% CI: 1.5–2.6), an effect that was evident for both males and females. The elevation was driven by the excess in risk observed for NPC. Exclusion of NPC led to an overall MP-SIR for infectious agent related cancers of 1.2 (95% CI: 0.84–1.7).

We compared observed and expected rates of individual and grouped tumors for which an infectious association has not been reported and for which 5 or more events were either observed or expected (Table 1). No significant elevations or reductions in risk were observed.

Finally, we examined the distribution of the 26 second primary cancers from NPC cases observed in our study. 42.3% (n=11) of the second primaries were a second NPC diagnosis, while the remaining cases included tongue (N=2), colorectal (N=2), liver (N=2), trachea (N=2),

breast (N=2), salivary gland (N=1), hypopharynx (N=1), cervical (N=1), prostate (N=1), and urinary bladder (N=1).

DISCUSSION

We sought to evaluate patterns of co-aggregation of incident cancers among individuals from multiplex NPC families in our study of 358 such families in Taiwan. Our results confirm that individuals from multiplex families have an excess risk of prospectively identified NPC. In contrast to the study by Friborg and colleagues from Denmark, however, and despite a comparable number of overall tumors identified (110 in our study; 133 in the Friborg study), we did not observe evidence that individuals from NPC multiplex families are at increased risk of developing a broader constellation of tumors (10). Possible reasons for the difference between these two studies include the length of follow-up time and the distinct geographical and ethnic populations evaluated.

We had originally hypothesized that individuals from families at high risk of NPC development would also have elevated rates of detection of other cancers associated with infectious agents. This hypothesis was not confirmed by our data (MP-SIR = 1.2; 95% CI: 0.84–1.7). Our finding is consistent with those by Wang *et al.* (15) and Scelo *et al.* (14), who both reported a lack of association between EBV infection and second primary cancers after NPC.

Of the 110 incident cancers identified via linkage to the registry in Taiwan, 26 were second primaries. Although the small number of second primaries in our study cohort prevented a more formal evaluation of these tumors, the types of second primaries (excluding second NPC diagnosis) were similar to those previously published study (14).

Strengths of our study include its population-based design and the large number of multiplex families included. Limitations include the relatively short follow-up (5.3 years, on average), which reduced the power to identify modest elevations that could be present in our population. Given the mean age of our relatives at enrollment (mean age=46 years), it is possible that not enough time has elapsed for these individuals to be at major risk for most cancers. Nonetheless, if there were some broader spectrum of increased risk for other malignancies in this population, it is not unreasonable to expect a hint from this analysis given that most cancer spectrums with a genetic component occur earlier in life. Another limitation of our study was our inability to evaluate tumors diagnosed prior to the date of recruitment of participants into our study. These tumors were not evaluated to avoid biases related to survival (i.e., individuals who died from cancers other than NPC prior to our study would not have been recruited) and due to incomplete reporting to the National Tumor Registry in its earlier years. In addition, NPC cases and their family members were enrolled based on a very specific recruitment scheme designed to allow for genetic linkage studies. To the extent that family members who participated in our study differed from those who did not with respect to their cancer risk, we may be limited in our ability to generalize our results to all high-risk families in Taiwan. Finally, a limitation of all family study designs, we are unable to disentangle the genetic and environmental contributions to the familial aggregation of NPC.

In summary, analysis of the largest NPC multiplex family study to date confirms the presence of co-aggregation of NPC within families in Taiwan, but does not provide evidence for a broader familial syndrome involving NPC and other tumors.

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Table 1

Multiple primary - standardized incidence ratios (MP-SIRs) of cancers in a high-risk Taiwan population.

Cancer Site	*ICD-FT-O*	*Study enrollment-2005 with multiple primaries*									
		Males (7417 per-yrs)			**Females (7734 per-yrs)**			**Total (15151 per-yrs)**			
		O**	**SIR**	**95% CI**	**O****	**SIR**	**95% CI**	**O****	**E****	**SIR**	**95% CI**
All		52	1.2	0.91–1.6	58	**1.4**	**1.1–1.9**	110	83	**1.3**	**1.1–1.6**
All except NPC	Exclude 147	36	0.87	0.61–1.2	49	1.2	0.91–1.6	85	81	1.0	0.83–1.3
Cancers associated with infectious agents											
Oral	140–149 (except 142, 147)	4	0.97	0.26–2.5	1	2.0	0.03–11	5	4.7	1.1	0.35–2.5
Salivary glands	142	1	8.3	0.11–46	0	0	0–45	1	0.2	5.0	0.07–28
Nasopharyngeal	147	16	**13**	**7.6–22**	9	**21**	**9.6–40**	25	1.6	**15**	**10–23**
Esophagus	150	1	0.70	0.01–3.9	1	6.3	0.08–35	2	1.6	1.3	0.14–4.6
Gastric	151	1	0.35	0–2.0	2	1.1	0.12–4.0	3	4.7	0.64	0.13–1.9
Liver & intrahepatic bile ducts	155	9	1.1	0.51–2.1	4	1.0	0.28–2.6	13	12	1.1	0.58–1.9
Cervix uteri	180	--	--	--	12	1.7	0.89–3.0	12	7	1.7	0.89–3.0
Vulva/vagina	184	--	--	--	1	4.0	0.05–22	1	0.25	4.0	0.05–22
Hodgkin's lymphoma	201	0	0	0–77	1	36	0.46–198	1	0.08	13	0.17–74
Non-Hodgkin's lymphoma	200, 202	0	0	0–3.9	1	1.2	0.03–6.8	1	1.8	0.57	0.01–3.2
Infectious + NPC		32	**1.71**	**1.2–2.4**	32	**2.1**	**1.5–3.0**	64	34	**1.9**	**1.5–2.4**
Infectious − NPC		16	0.91	0.52–1.5	23	**1.6**	**1.0–2.4**	39	32	1.2	0.87–1.7
Cancers not associated with infectious agents *											
Colorectal	153–154	3	0.54	0.11–1.6	2	0.39	0.04–1.4	5	11	0.47	0.15–1.1
Respiratory system	160–165	3	0.44	0.09–1.3	4	1.1	0.29–2.8	7	11	0.66	0.27–1.4
Trachea, bronchus and lung	162	3	0.50	0.10–1.5	4	1.2	0.31–3.0	7	9.4	0.74	0.30–1.5
Breast	174–175	0	0	0–97	8	1.2	0.52–2.4	8	6.7	1.2	0.51–2.4
Urinary bladder	188–189	5	1.9	0.60–4.4	4	2.1	0.56–5.3	9	4.6	2.0	0.89–3.7

Restricted to individual cancers or grouped cancers with > 5 observed or expected events

** O=observed and E=expected