Familial Nasopharyngeal Carcinoma in a Cohort of 200 Patients

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Objectives: To describe the characteristics of familial nasopharyngeal carcinoma (NPC) in a high-risk population and to determine the role of screening first-degree relations.

Design: An analysis on a cohort of 200 patients newly diagnosed as having NPC.

Setting: A tertiary-level institution.

Patients: The patients were divided into 2 groups. Patients in group 1 had a first-degree relative with NPC, and those in group 2 did not. For patients in group 1, the relationship and the time interval between affected relatives were noted. The clinical and pathological factors of the 2 groups were obtained and statistically analyzed.

Results: There were 15.5% of NPC patients who had an affected first-degree relative. Of the affected relatives, 71% were siblings and 29% were parents. The mean interval between affected siblings was 5.3 years, while that between an affected parent and a child was 24.5 years. No differences were noted in the clinical factors between familial and nonfamilial NPC patients. Most patients in both groups were diagnosed as having stage III or IV NPC.

Conclusions: The rate of familial NPC in our study is 15.5%. Siblings are more commonly affected, and the interval between 2 affected siblings is relatively short. No distinct clinical pattern exists in familial NPC. We recommend that siblings of NPC patients be screened as soon as possible once the index case is diagnosed.

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Nasopharyngeal carcinoma (NPC) is the fifth most common cancer in Singapore. It commonly affects patients in the economically active age groups, with 50% of the patients aged 31 to 50 years.1 Most patients with NPC present with either stage III or IV disease.2-4 Despite improvements in radiation techniques and increasing trends toward combination chemotherapy and radiation, the key to higher disease-free survival rates lies in early diagnosis. Good correlation has been shown between the stage of the disease and 5-year survival rates.25 The implication is that the overall 5-year survival rates will be expected to improve if more patients were diagnosed as having disease at an earlier stage. Screening is a method that aims to diagnose NPC at an early stage. However, one of the controversies in the screening for NPC is the population that should be targeted. The obvious targets would be those with a high risk. In our practice, some patients with NPC have similarly affected first-degree relatives. This led to the hypothesis that first-degree relatives of NPC patients are a suitable target group for screening. This study was performed to characterize our NPC patients who have affected first-degree relatives and to compare their clinical and pathological factors with those of patients with nonfamilial NPC. In doing so, we aim to determine the suitability of first-degree relatives as a target group for screening for NPC.

Methods

This prospective study involved 200 consecutive patients diagnosed as having NPC from May 1, 1998, to December 31, 2003. Only patients newly diagnosed as having undifferentiated carcinoma (World Health Organization type 2b) were included in the study. All patients who were unable to provide information about the existence of malignancy in their first-degree relatives were excluded. The information provided on the first-degree relatives was confirmed with the Singapore Cancer Registry. The patients were divided into 2 groups. Group 1 consisted of patients with familial NPC. Group 2 was composed of the remaining patients (those with nonfamilial NPC). Familial NPC is de-
fined as NPC occurring in 2 or more first-degree relatives within the same family. Hence, the patients in group 1 had at least 1 first-degree relative with NPC. First-degree relatives refer to parents, siblings, or children. The index NPC patient refers to the affected NPC patient in our study. The relationship between affected relatives and the time from the diagnosis of the affected relative to the diagnosis of the index NPC patient was noted. Because our study defined familial NPC as being limited to first-degree relations, patients with relatives such as uncles and cousins with NPC were included in group 2. The demographic data and clinical and pathological variables were recorded and compared between the 2 groups of patients. Staging was performed using the 1997 American Joint Committee on Cancer and International Union Against Cancer classification. Stage I and II disease was classified as early NPC, while stage III and IV disease was classified as advanced NPC. Statistical analysis of the variables between the 2 groups was performed.

RESULTS

Of the 200 patients with NPC, 35 (17.5%) had a relative with NPC; 31 were first-degree relatives, and 4 were second-degree relatives. The rate of familial NPC in this series was 15.5% (31 of 200 patients). All of these 31 patients with familial NPC had only a single affected first-degree relative. The 4 patients with second-degree relatives were included in group 2.

The relationship between the index NPC patients and their affected first-degree relatives is shown in Figure 1. Of the 31 patients with familial NPC, 9 (29%) of the affected first-degree relatives were parents (5 fathers and 4 mothers). In the remaining 22 (71%) of the familial NPC patients, the affected first-degree relatives were siblings. Of these siblings, 17 were brothers and 5 were sisters.

The mean (SD) interval between an affected first-degree relative and the index NPC patient was 12.1 (12.0) years (range, 5 months–43 years). The mean (SD) interval between an affected parent and the index NPC patient was 24.5 (12.1) years (range, 8–43 years). Between 2 affected siblings, the mean (SD) interval was 5.3 (3.3) years (range, 5 months–16 years).

The clinical variables of the patients with familial NPC were similar to those of the group with nonfamilial NPC.

### Table. Clinical Factors for Patients With Familial and Nonfamilial NPC*

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Familial NPC (n = 31)</th>
<th>Nonfamilial NPC (n = 169)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-female ratio</td>
<td>5.2:1</td>
<td>2.8:1</td>
<td>.17</td>
</tr>
<tr>
<td>Age, y†</td>
<td>48.0 (9.2)</td>
<td>49.7 (12.6)</td>
<td>.46</td>
</tr>
<tr>
<td>Chinese race</td>
<td>93.5</td>
<td>91.7</td>
<td>.46</td>
</tr>
<tr>
<td>Symptom duration, mo†</td>
<td>2.3 (1.4)</td>
<td>3.4 (4.6)</td>
<td>.22</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck lumps</td>
<td>46.7</td>
<td>56.4</td>
<td>.51</td>
</tr>
<tr>
<td>Blood-stained sputum</td>
<td>43.3</td>
<td>34.8</td>
<td>.37</td>
</tr>
<tr>
<td>Unilateral deafness</td>
<td>23.3</td>
<td>29.2</td>
<td>.87</td>
</tr>
<tr>
<td>IgA/VCA level, ≤40</td>
<td>41.2</td>
<td>22.7</td>
<td>.13</td>
</tr>
<tr>
<td>IgA/EA level, ≥10</td>
<td>23.5</td>
<td>34.7</td>
<td>.57</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12.9</td>
<td>11.8</td>
<td>.49</td>
</tr>
<tr>
<td>II</td>
<td>38.7</td>
<td>26.0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22.6</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>25.8</td>
<td>30.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EA, early antigen; NPC, nasopharyngeal carcinoma; VCA, viral capsid antigen.

*Data are given as percentage of each group unless otherwise indicated. †Data are given as mean (SD).

Undifferentiated NPC is a common cancer in Singapore, and its incidence has remained largely stable during the past 10 years. The associated causative factors include infection with Epstein-Barr virus and an underlying genetic predisposition. This study clearly shows the existence of familial NPC, defined as NPC occurring in at least 1 first-degree relative within the same family.
2 first-degree relatives. The specific genetic factors that are responsible for the association with NPC remain unanswered. First-degree relatives represent the closest genetic association to an affected NPC patient. If genetic factors do play a role in NPC, then it would be prudent to maintain surveillance of first-degree relatives of affected patients. First-degree relatives of NPC patients are at a higher risk of developing the disease. Several researchers have reported the relative risk of first-degree relatives of NPC patients in developing the disease to vary from 6.3 to 21.3 when compared with the relatives of healthy control subjects. The rate of familial NPC in our study is 15.5%. Applying our definition of familial NPC to other studies, the rates vary from 5.8% to 19% in endemic regions. Familial cancers have also been reported for other malignancies, most notably the breast. Pharoah and colleagues reported a familial rate of 13.8% for breast cancer. Our reported rate of 15.5% would be considered high. This and the higher risk of developing the disease in first-degree relatives would support our view that this group forms an important target for screening. This study did not set out to identify any correlation in genetic factors between the affected relatives. Indeed, shared environmental risk factors may be just as important as genetic factors in the group of patients we defined as having familial NPC. In our study, familial NPC does not imply an exclusive genetic cause or shared environmental risk factors. Our premise was that we first had to determine if the rate of familial NPC was high enough to warrant targeting first-degree relatives of NPC patients for screening.

Our data also showed that the stage of disease between familial and nonfamilial NPC is similar. In an unscreened population of NPC patients, most would have stage III or IV disease. It, therefore, follows that in an unscreened population of first-degree relatives of NPC patients, those who will eventually develop NPC will also do so with greater likelihood of having stage III or IV disease. However, if these relatives were screened, the potential will be that the disease may be diagnosed at an earlier stage. This could have important consequences in improving survival rates.

Although the entity of familial NPC exists, it does not possess distinct clinical characteristics. Our clinical data between the 2 groups of patients did not reveal any significant differences. Sex, age, and race were similar in familial and nonfamilial NPC. There were no differences in symptoms between the 2 groups. Therefore, there is no potential in using specific clinical or pathological factors to differentiate between familial and nonfamilial NPC. Our study confirmed the findings in a recent study by Ung et al, which had indicated that familial NPC as a clinical entity does not exist. It then follows that using clinical or pathological variables is unlikely to help us identify which first-degree relatives of index NPC patients will develop the disease. The implication of this fact is that while first-degree relatives should be screened, the optimal method of screening needs to be clarified.

There are certain characteristics in our series of patients with familial NPC that would help us plan a screening program. The affected first-degree relatives were most commonly siblings of index NPC patients. Indeed, of the 31 affected relatives, only siblings and parents were involved. The male preponderance in familial NPC is not surprising, given the fact that NPC occurs more commonly in men. These characteristics of familial NPC allow further refinement of the target population for a screening program. It is clear that only siblings and children of affected NPC patients need to be screened, because it is unlikely that the parents of an affected NPC patient will develop the disease. The mean interval between affected siblings is 5.3 years (range, 5 months–16 years), while that between an affected parent and a child is 24.5 years (range, 8–43 years). Data from the Singapore Cancer Registry show that the incidence of NPC in men starts to increase from the age group of 25 to 30 years at 2.5 per 100 000 and peaks at the age group of 45 to 50 years at 55.7 per 100 000. It remains high even at the age group of older than 80 years, with the incidence rate being 19.7 per 100 000. The information from our study and from the Singapore Cancer Registry provides evidence-based planning for the age group at which first-degree relatives of NPC patients should be screened. Once an NPC patient is diagnosed as having the disease, we recommend that all the siblings should be screened. Based on our data, the longest duration between 2 affected siblings was 16 years. The inference would be that if a sibling of an NPC patient was screened for at least 16 years without developing the disease, this sibling's chances of being diagnosed as having NPC will be low. Therefore, the evidence would suggest a reasonable screening period of 20 years for all siblings. Beyond 20 years, siblings who had been screened and did not develop NPC are not likely to be diagnosed as having the disease. While we recommend that children of NPC patients be screened, the exact age of the children to be screened is debatable. We suggest that children should be screened from the age of 25 years. The rationale for such a recommendation is based on the fact that the mean interval between affected parent and child in our series was 24 years, and that the incidence in our population only increases significantly from the age of 25 years. While it is clear that siblings are a reasonable high-risk target group for screening NPC, the ability to diagnose these siblings at an early stage of disease remains to be proved. Toward this end, we have embarked on a prospective program to screen the siblings of all our patients newly diagnosed as having NPC. In addition to a detailed medical history, the siblings will have an examination of the nasopharynx. Measurements of IgA viral capsid antigen and IgA early antigen and plasma Epstein-Barr virus DNA will be performed. We will assess the role of plasma Epstein-Barr virus DNA in detecting early NPC. In the coming years, we will expect to have an answer with regard to the efficacy of such a screening program. Our present study supports the feasibility of screening first-degree relatives of NPC patients. However, as in any screening program, many challenges need to be overcome, not the least of which is to be able to ensure that all the targeted population is reached. This screening program can only be considered a success if the survival rates are improved.

In conclusion, the rate of familial NPC in our study is 15.5%. While all first-degree relatives should be screened for NPC, siblings of the index NPC patients should be screened as soon as possible. A prospective
program is necessary to determine the efficacy of screening siblings.

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REFERENCES