



# Familial cancer risk in family members and spouses of patients with early-onset head and neck cancer

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## Abstract

**Background:** Reported patterns of familial aggregation of head and neck cancer (HNC) vary greatly, with many studies hampered by the limited number of subjects.

**Methods:** Altogether 923 early-onset ( $\leq 40$  years old) HNC probands, their first-degree relatives, spouses, and siblings' offspring were ascertained. Cumulative risk and standardized incidence ratios (SIRs) were estimated.

**Results:** Of all early-onset HNC families, only 21 (2.3%) had familial HNC cancers at any age and less than five familial early onset HNC cancers among first-degree relatives. The cumulative risk of HNC for siblings by age 60 (0.52%) was at population level (0.33%). No increased familial risk of early-onset HNC could be discerned in family members (SIR 2.68, 95% CI 0.32–9.68 for first-degree relatives).

**Conclusions:** Our study indicates that the cumulative and relative familial risk of early-onset HNC is modest in the Finnish population and, at most, only a minor proportion of early-onset HNCs are due solely to inherited genetic mutations.

## KEYWORDS

early-onset cancer, familial cancer, head and neck cancer, proband

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## 1 | INTRODUCTION

Head and neck cancers (HNC) comprise a heterogeneous group of malignancies occurring in the lip, oral cavity, salivary glands, nasal cavity, paranasal sinuses, pharynx, and larynx. Epidemiologically, HNCs represent the seventh most common cancer and account approximately for 5% of all malignancies globally.<sup>1</sup> While HNCs cover only 1% to 4% of all cancers in Western countries, they constitute one of the most common malignancies in several developing countries.<sup>1-3</sup> Moreover, over the past three decades, increasing numbers of young patients ( $\leq 40$  or  $\leq 45$  years old depending on the study) worldwide have been diagnosed with HNC.<sup>4</sup> Tobacco and alcohol use are the most common reported etiological factors, but infection with human papillomaviruses (HPV), particularly type 16, has also been linked to the pathogenesis of HNCs arising especially from the oropharynx.<sup>5,6</sup> The average latency period for HPV-positive oropharyngeal cancer has been estimated to be of approximately 10 to 30 years.<sup>7</sup>

The term familial cancer is applied to designate a cancer occurring in families more often than would be expected by chance.<sup>8</sup> In contrast to sporadic cancers, these cancers often develop at an early age, due to inherited germline mutations, but may also be a sign of early shared environmental or lifestyle factors that result in genetic aberrations.<sup>9</sup> The concept of familial cancer was first described in breast cancer literature by James Paget in England and Paul Broca in France, as early as in the 1800s.<sup>10,11</sup> The degree to which site-specific cancers run in families has been investigated in several studies. The overall heritability of cancer has been reported to be 33% (95% CI 30%-37%) based on a large twin cohort.<sup>12</sup> By discerning familial patterns of cancer incidence, a variety of familial cancers have been defined, most notably familial breast and colorectal cancers, which are estimated to account for approximately 10% to 30% and 30% of all breast and colorectal cancers, respectively.<sup>13,14</sup>

Although the majority of HNCs are sporadic, that is, the consequence of somatic mutations, many of which are related to smoking or alcohol consumption,<sup>5</sup> earlier reports of familial clusters of HNC, also in young individuals, provided the first suggestion that at least a hereditary but rare form of HNC might exist.<sup>15-17</sup> The occurrence of familial clustering of cancer in young family members is commonly thought to favor the existence of predisposing genetic factors.<sup>18</sup> Reported patterns of familial aggregation of HNC vary greatly, with many studies hampered by the restricted number of subjects and the comprehensible difficulty to distinguish between inherited and environmental risk factors.<sup>19-21</sup> Moreover, the incidence of early-onset HNC is low, covering less than 5% of all HNC cases,<sup>4</sup> and few centers have had the

opportunity to address the question of familial cancer risk in this patient group separately, with conflicting results.<sup>17,22</sup> This dearth of data has resulted in only minimal inroads to elucidate the familial risk of HNC. Recently, a 43% increased risk of HNC was reported for relatives of HNC patients ( $\leq 60$  years old), when compared with family members of healthy controls.<sup>23</sup>

In this study, our primary goal is to characterize the familial relative and cumulative risks of HNC and other malignancies, including cancers of both the digestive and respiratory organs, for family members and spouses of patients previously diagnosed with early-onset HNC ( $\leq 40$  years old). By investigating familial clustering of HNC, we aim to assess the etiological impact of genetic and shared environmental factors on the disease.

## 2 | PATIENTS AND METHODS

ICD-O-3 topographical codes were used to identify an epidemiological series of patients diagnosed with primary early-onset HNC ( $\leq 40$  years old) in Finland from 1970 to 2012 from the Finnish Cancer Registry (FCR). In this study, HNCs were defined as malignancies occurring in the lip (ICD-O-3: C00.0-C00.9), oral cavity (C01.9-C06.9), salivary glands (C07.9-C08.9), pharynx (C09.0-C14.8), nasal cavity and middle ear (C30.0, C30.1), paranasal sinuses (C31.0-C31.9), and larynx and epiglottis (C32.0-C32.9).

The FCR includes all new primary cancers diagnosed in Finland since 1953 with complete follow-up data until death or emigration. Quality assessment studies have shown high coverage (94.8% of HNCs) and accuracy of diagnosis.<sup>24</sup> The Population Information System is a registry of all permanent Finnish residents and records information on family linkages, dates of birth and death, and permits reliable identification of family members and spouses. Links to siblings are available for individuals born after 1955 and alive in 1967.

We define as proband the first member of a family diagnosed with HNC at or under the age of 40 years between January 1, 1970 and December 31, 2012, in Finland.<sup>25</sup> We define as family member any blood relative. Proband with no family members or spouses were excluded from the study. Using the Population Information System, family members (parents, offspring, siblings, and siblings' offspring) and spouses were linked to the probands. The follow-up for all family members and spouses of the probands begins either at the date of birth or January 1, 1953 and ends either at the date of the cancer diagnosis, date of death or emigration, or December 31, 2016. To account for immortal time bias, family members and spouses of the probands were not considered to be at risk of cancer between January 1, 1970 and the date of diagnosis of the proband.

As a measure of familial aggregation of HNC, we used standardized incidence ratios (SIRs), which were estimated using all follow-up outside the immortal periods in order to quantify the risk of cancer in family members and spouses with a proband diagnosed with early-onset HNC, relative to general population incidence of HNC in Finland.<sup>26</sup> The SIR estimates the risk of a cancer developing in a family member or spouse of the proband relative to the first occurrence of cancer among the general population. SIR is thus a ratio of observed cancers to expected cancers, in which the expected number of cancers was calculated for the general population. SIRs were estimated for all first-degree relatives (parents, offspring, and siblings) of the proband combined and for family members (first-degree relatives and siblings' offspring) and spouses distinctly by kinship to the proband, separately for early-onset ( $\leq 40$  years) and late-onset ( $\geq 41$  years) cancers. SIRs were computed for HNC, digestive organs' and respiratory organs' cancers. Cumulative risks and expected cumulative risks from 0 to 60 years of age were estimated for probands' siblings. In the estimation of cumulative risks, we considered only follow-up after the diagnosis date of the proband.

Statistical analyses were performed using the R software (The R Project for Statistical Computing) version 3.6.0 with Epi package version 2.38 and popEpi package version 0.4.7. *P*-values and confidence intervals for SIRs were computed using normal approximation for Poisson-model coefficient. The probands were excluded from the analyses to account for the ascertainment bias due to nonrandomly selected families. *P*-values were two-sided and unadjusted for multiple testing. For data privacy reasons, we do not report observed values, if less than five cases were reported. Research permission for the study design was granted by the National Institute for Health and Welfare in Finland (Dnro THL/264/5.05.00/2015).

### 3 | RESULTS

Between the January 1, 1970 and the September 30, 2012, 24 601 occurrences of HNC were registered in the Finnish Cancer Registry, with a total of 1061 early-onset HNC patients (approximately 4% of HNCs were diagnosed under the age of 40 years), of whom 923 had at least one family member or spouse. Number of

**TABLE 1** Numbers of probands according to HNC site

| Site               | ICD-10             | Number | Median age       | % of males |
|--------------------|--------------------|--------|------------------|------------|
| Lip                | C00.0-C00.9        | 63     | 36.6 [32.4-39.0] | 85.7       |
| Mouth, other       | C01.9, C03.0-C06.9 | 119    | 33.8 [28.9-38.0] | 49.6       |
| Tongue             | C02.0-C02.9        | 193    | 33.2 [29.2-37.6] | 58.5       |
| Salivary glands    | C07.9-C08.9        | 239    | 31.7 [26.5-36.8] | 45.6       |
| Pharynx            | C09.0-C14.8        | 153    | 34.0 [25.4-38.2] | 63.4       |
| Nose, sinuses      | C30.0-C31.9        | 88     | 33.3 [25.9-38.1] | 61.4       |
| Larynx, epiglottis | C32.0-C32.9        | 68     | 37.8 [35.3-39.8] | 83.8       |
| Total              |                    | 923    | 33.9 [28.0-38.2] | 58.8       |

Note: Median age at diagnosis with interquartile range (IQR) and proportion of males are shown. Proband with no family members or spouses were excluded.

**TABLE 2** Numbers of cancer cases among 923 families consisting of 6714 family members and 1834 spouses at any age

| Primary site in family members and spouses | ICD-10  | Number of families                               |     |     |    |   |   |     | Familial cancers |                   |
|--|---------|--|-----|-----|----|---|---|-----|------------------|-------------------|
|  |         | Number of cases among family members and spouses |     |     |    |   |   |     | Total            | Number of cancers |
| 0  | 1       | 2  | 3   | 4   | >4 |   |   |     |                  |                   |
| Head and neck                              | C00-C32 | 902  | 21  | 0   | 0  | 0 | 0 | 923 | 21               | 21 (2.3%)         |
| Digestive organs                           | C15-C26 | 800  | 114 | 9   | 0  | 0 | 0 | 923 | 132              | 123 (13.3%)       |
| Lung or trachea                            | C33-34  | 855  | 66  | 1   | 1  | 0 | 0 | 923 | 71               | 68 (7.4%)         |
| Any cancer                                 |         | 472  | 321 | 101 | 21 | 5 | 3 | 923 | 622              | 451 (48.9%)       |

Note: The proband was diagnosed with HNC at age 40 years or less. Proband with no family members or spouses were excluded.

probands included in the study by HNC-subsite are presented in Table 1. The median age of probands was 33.9 years (interquartile range 28.0-38.2) and 58.8% of probands were men. The salivary glands and the tongue were the most common sites of early-onset HNC among

probands, accounting for 25.9% (n = 239) and 20.9% (n = 193) of all cases, respectively.

Probands' family members consisted of first-degree relatives (n = 4371, 50.6% of all family members) and siblings' offspring (n = 2433, 28.2%). Altogether probands'

**TABLE 3** Observed cancers and standardized incidence ratios (SIRs) with 95% confidence intervals (CI) for family members and spouses at age  $\leq 40$  years with a proband diagnosed with early-onset HNC ( $\leq 40$  years old)

| Primary site in family members and spouses at age $\leq 40$ | Number | Observed | Expected | PYR    | SIR [95% CI]     | P-value |
|---|--------|----------|----------|--------|------------------|---------|
| <i>Head and neck</i>  |        |          |          |        |                  |         |
| First degree relatives                                      | 4281   | <5       | <5       | 78 027 | 2.68 [0.32-9.68] | .383    |
| Siblings' offspring   | 2433   | <5       | <5       | 48 943 | 3.00 [0.08-16.7] | .772    |
| Spouse  | 1834   | 0        | 0.31     | 33 077 | 0.00 [0.00-11.9] | .731    |
| <i>Digestive organs</i>                                     |        |          |          |        |                  |         |
| First degree relatives                                      | 4281   | <5       | <5       | 78 079 | 0.78 [0.09-2.80] | .96     |
| Siblings' offspring   | 2433   | <5       | <5       | 48 931 | 1.70 [0.21-6.13] | .767    |
| Spouse  | 1834   | <5       | <5       | 33 073 | 1.68 [0.20-6.07] | .776    |
| <i>Lung or trachea</i>                                      |        |          |          |        |                  |         |
| First degree relatives                                      | 4281   | <5       | <5       | 77 996 | 2.31 [0.06-12.9] | .919    |
| Siblings' offspring   | 2433   | 0        | 0.12     | 48 948 | 0.00 [0.00-29.9] | .284    |
| Spouse  | 1834   | 0        | 0.2      | 33 077 | 0.00 [0.00-18.7] | .496    |
| <i>Any cancer</i>   |        |          |          |        |                  |         |
| First degree relatives                                      | 4281   | 25       | 28.2     | 78 510 | 0.89 [0.57-1.31] | .609    |
| Siblings' offspring   | 2433   | 20       | 16.4     | 48 765 | 1.22 [0.75-1.89] | .441    |
| Spouse  | 1834   | 9        | 13.7     | 33 056 | 0.66 [0.30-1.25] | .255    |

**TABLE 4** Observed cancers and standardized incidence ratios (SIRs) with 95% confidence intervals (CI) for family members and spouses at any age with a proband diagnosed with early-onset HNC ( $\leq 40$  years old)

| Primary site in family members and spouses at any age | Number | Observed | Expected | PYR     | SIR [95% CI]     | P-value |
|---|--------|----------|----------|---------|------------------|---------|
| <i>Head and neck</i>                                  |        |          |          |         |                  |         |
| First degree relatives                                | 4371   | 19       | 15.2     | 144 595 | 1.25 [0.75-1.95] | .398    |
| Siblings' offspring                                   | 2433   | <5       | <5       | 49 964  | 2.46 [0.06-13.7] | .883    |
| Spouse  | 1834   | <5       | <5       | 60 791  | 0.21 [0.01-1.17] | .136    |
| <i>Digestive organs</i>                               |        |          |          |         |                  |         |
| First degree relatives                                | 4371   | 104      | 101      | 144 489 | 1.03 [0.84-1.25] | .813    |
| Siblings' offspring                                   | 2433   | <5       | <5       | 49 954  | 1.38 [0.17-4.98] | .967    |
| Spouse  | 1834   | 26       | 26.2     | 60 659  | 0.99 [0.65-1.46] | .946    |
| <i>Lung or trachea</i>                                |        |          |          |         |                  |         |
| First degree relatives                                | 4371   | 55       | 54.4     | 144 599 | 1.01 [0.76-1.32] | .984    |
| Siblings' offspring                                   | 2433   | 0        | 0.19     | 49 970  | 0.00 [0.00-19.8] | .467    |
| Spouse  | 1834   | 16       | 12       | 60 775  | 1.33 [0.76-2.17] | .313    |
| <i>Any cancer</i>                                     |        |          |          |         |                  |         |
| First degree relatives                                | 4371   | 469      | 472      | 142 440 | 0.99 [0.91-1.09] | .898    |
| Siblings' offspring                                   | 2433   | 25       | 18.4     | 49 759  | 1.36 [0.88-2.01] | .155    |
| Spouse  | 1834   | 128      | 155      | 60 052  | 0.83 [0.69-0.98] | .035    |

family members ( $n = 6804$ , 78.8%) and spouses ( $n = 1834$ , 21.2%) contributed 252 251 to 255 350 person-years (PYR) of follow-up (depending on family members' or spouses' primary site of cancer). The study comprised 4281 first-degree relatives of age  $\leq 40$ .

In 21 families (2.28% of all families), two individuals (proband and one family member or proband and spouse) were affected by HNC (Table 2). There were no families with more than two individuals (including proband) affected with HNC. Of the 21 HNCs observed among family members or spouses of probands, 10 cases were observed in the pharynx (C01, C09-14) and less than five cases in each of the other anatomic locations.

Of the family members affected with HNC, less than five were younger than 40 (less than 0.50% of all families affected or less than 0.07% of all family members). Similarly, less than five cases of cancer of the digestive organs and less than five cases of cancer of the respiratory organs, were diagnosed in family members of age  $\leq 40$ . Most of the observed cancer cases in probands' family members occurred after the age of 40.

Familial relative risks (SIRs) for family members and spouses are outlined in Table 3 (age  $\leq 40$ ) and Table 4 (any age). No statistically significant elevated familial relative risk of cancer could be discerned in probands' first-degree relatives or siblings' offspring, neither at age  $\leq 40$  nor at  $>40$ . For probands' spouses at any age, the SIRs for HNC

(SIR 0.21, 95% CI 0.01-1.17,  $P = .136$ ) and for any cancer (SIR 0.83, 95% CI 0.69-0.98,  $P = .035$ ) were lower than for the general population. The SIR for any cancer was also lower for spouses at age  $> 40$  (SIR 0.84, 95% CI 0.70-1.01,  $P = .069$ ), when compared to the general population.

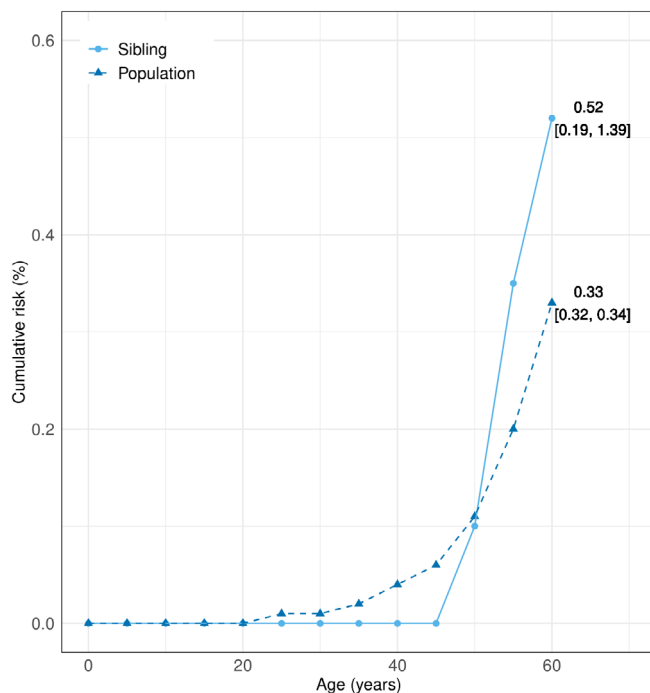
Among the 4371 first-degree relatives, HNC had been diagnosed in less than 0.10% at age  $\leq 40$  and in 0.43% at any age. Correspondingly, digestive and respiratory organ cancers were diagnosed in 2.38% and 1.26% of the probands' first-degree relatives at any age, respectively. It could be observed that the cumulative risk for probands' siblings by age 60 (0.52%, 95% CI 0.19-1.39) did not markedly differ from the general population's risk (0.33%, 95% CI 0.32-0.34), as shown in Figure 1. There were no cases of early-onset HNC (age  $\leq 40$ ) among siblings.

## 4 | DISCUSSION

The majority of HNC cases are sporadic, representing more than 97% of cases in this familial cohort. No increased relative risk of HNC or other malignancies could be discerned in first- or second-degree relatives of a patient diagnosed with early-onset HNC ( $\leq 40$  years old), when compared to the risk in the general population. Among the first-degree relatives of probands diagnosed with early-onset HNC, less than 0.10% were diagnosed with HNC at age  $\leq 40$  and 0.43% at any age.

This study utilizes a large population-based database from the Finnish Cancer Registry (FCR), first, to determine the fraction of HNC cases that can be considered to exhibit familial clustering, and secondly, to define the relative risk of HNC for family members and spouses of patients previously diagnosed with early-onset HNC. This work highlights the fact that at most, only a trivial proportion of HNCs is primarily and solely due to inherited genetic mutations. Although a family cancer history cannot be altered, findings could provide the basis for the development of improved clinical management of HNC cancer families and adequate cancer screening guidelines for this patient population.

Family history of cancer can be used as a proxy to detect not only genetic predisposition to disease, but also shared environmental and lifestyle factors that can contribute to multiple cancers in the same family.<sup>27</sup> In contrast to other studies, focusing on families with early-onset HNC permits to disentangle potential inherited factors of HNC, as high-penetrance genetic mutations are commonly assumed to manifest at an early age.<sup>18</sup> Moreover, by including extended family members (proband's siblings' offspring) and spouses, the data are likely to hold more statistical power than studies restricted to specific genetic relationships, such as those focusing on twins or



**FIGURE 1** Cumulative risk of head and neck cancer (HNC) in probands' siblings. Five siblings were diagnosed with HNC during follow-up [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

parents. The strength of our study also lies in the accuracy of cancer information contained in the FCR and the information on probands' family members and spouses. Risk of HNC in family members and spouses was estimated with SIRs, which mitigates the confounding effects of ascertainment and immortal biases, and the used Poisson excess risk model adjusts not only for censoring in time-to-event outcomes, but also for alterations in population cancer risk by calendar time, age and sex.

Several case-control studies in different countries have reported an elevated risk of HNC in subjects with a family history of HNC. Foulkes et al reported in two independent studies an adjusted relative risk of 3.79 (95% CI 1.11-13.0) and 3.65 (95% CI 1.97-6.76) in Canada and Brazil, respectively. The adjusted relative risk for HNC was 7.89 (95% 1.50-41.6) in first-degree relatives of patients with multiple primary head and neck tumors.<sup>16,28</sup> Risks in these two studies were adjusted for age, sex, city, and tobacco and alcohol consumption. In the study of Garavello et al, conducted in Switzerland and Italy, the odds ratios (OR) were 3.1 (95% CI 2.0-4.8) for oropharyngeal and laryngeal cancers combined and 7.1 (95% CI 1.3-37.2) for subjects with two or more first-degree relatives affected.<sup>29</sup> A French study similarly described an elevated risk for HNC among first-degree relatives of HNC probands (OR = 1.9, 95% CI 1.2-2.8), which increased with the number of first-degree relatives affected.<sup>30</sup> A pooled international study, comprising 12 case-control studies (8967 patients and 13 627 controls), also established that a family history of HNC in first-degree relatives increased the risk of HNC (OR 1.7, 95% CI 1.2-2.3). Noteworthy, this risk was limited to subjects with a history of tobacco smoking or alcohol consumption.<sup>31</sup> A second pooled international study, consisting of 25 case-control studies, concluded that young adults ( $\leq 45$  years old) with a family history of early-onset HNC had an increased risk of HNC (OR 2.27, 95% CI 1.26-4.10), which was not detectable in their older counterparts. Risk estimates were adjusted for sex, race, age, education level, and tobacco and alcohol consumption.<sup>22</sup> In compliance with the previous findings, a study conducted in Utah (USA), by means of population-based genealogy and state cancer registry databases, reported a relative risk for first-degree relatives of 5.31 (95% CI 1.45-13.59,  $P = .0074$ ). For second-degree relatives, no statistically significant elevated risk could be noted.<sup>21</sup> Renkonen et al, in a comparably designed study conducted in Sweden, established a 1.43-fold increased risk (95% CI 1.28-1.61) for developing HNC in first-degree relatives of HNC patients when compared to relatives of healthy controls.<sup>23</sup> Risk estimates were, however, not adjusted for confounding factors, such as tobacco and alcohol consumption, in these two studies.

In contrast to the previously quoted studies, Copper et al., in a case-control study (not adjusted for risk factors), conducted in the Netherlands and including 105 cases with 617 first-degree relatives, found no higher rate of HNC in probands' first-degree relatives.<sup>32</sup> Goldstein et al in a similar study consisting of 487 cases and 485 controls and adjusted for tobacco and alcohol consumption, concluded that there is, at most, a weak familial aggregation of oropharyngeal cancers.<sup>19</sup> Huang et al did not observe a strong association between family history of HNC and HNC risk after taking into account lifestyle factors (tobacco smoking, alcohol consumption, and betel quid chewing) in a Chinese population comprising 921 cases.<sup>20</sup> When focusing on early-onset HNC, our results are in line with Mork et al who reported no increased risk of HNC or esophagus and lung cancers for first-degree relatives of patients diagnosed with HNC at age  $\leq 45$ . The study comprised, however, only 127 HNC probands and risk estimates were not adjusted for risk factors.<sup>17</sup>

Interestingly, spouses of probands in our study had a lower relative risk of HNC and other malignancies (SIR = 0.83, 95% CI 0.69-0.98,  $P = .035$ ). The results are in contrast to the study of Renkonen et al, that reported an increased risk for spouses of HNC probands (hazard ratio of 1.25, 95% CI 1.01-1.53).<sup>23</sup> Other studies have similarly reported an increased risk. In the study of Hemminki et al, stomach, lung, and bladder, showed concordant increases of cancer among spouses (minimum 15 years of cohabitation on average) with SIRs ranging from 1.19 to 1.38.<sup>33</sup> Likewise, a modest trend of increased risk in HPV-associated cancers among spouses of patients with HPV-related cancer has been described.<sup>34</sup> The reduced risk in our study could be attributed to low-risk lifestyle behaviors adopted by spouses after diagnosis of the proband's cancer, or it may simply be an artifact due to confounding variables, such as smoking habits and HPV-status, not adjusted for. Also, the definition of spouse in our study did not include any specific time period, which entails the possibility of underestimating the risk.<sup>34</sup>

While the existing literature reveals an increased cancer risk among subjects with a family history of HNC, the amplitude of the risk varies across studies. A few factors relating to the aforementioned studies need to be considered. Certain case-control studies obviously present a limitation of power, as the number of cases was limited. More importantly, methodological difficulties that may bias risk estimations among the different studied populations must be considered. In most of the cited studies, cases of cancer among probands' relatives were not confirmed but were self-reported by the probands themselves by means of questionnaires or interviews,

which could lead to reporting bias. It has been indeed demonstrated that people have a tendency to over-report their medical and cancer screening history, so an over-reporting history of family cancer cannot be completely ruled out.<sup>35,36</sup> However, underreporting for certain cancers has also been described.<sup>37</sup> The studies by Monroe et al and Renkonen et al were the only ones based on cancer registries and genealogy databases, but, as already stated before, did not adjust for confounding factors. It is nevertheless likely that the genetic risk profiles vary across populations, as has been detected for some alternative phenotypes associated with DNA repair enzymes or the metabolism of carcinogens, which could, at least partially, explain the disparities between the different populations.<sup>38-41</sup> Several phenotypes involved in carcinogen metabolism have been linked to HNC risk, though results have not always been in agreement.<sup>42-44</sup> As a consequence, extrapolations of results of individual studies to other populations cannot be made without further evaluation.

Familial clustering of cancer may hint to inheritable genetic factors, but may also suggest similar environmental or behavioral risk factors, such as alcohol and tobacco consumption, among family members and spouses. Tobacco use by family members has been reported to increase the risk of tobacco use in an individual and may partially explain the higher rates of tobacco-associated malignancies in subjects with a family history of oropharyngeal cancer.<sup>45,46</sup> Also, the involvement of dietary risk factors, such as consumption of nitrosamine-rich salted fish, as observed in Southeast Asia reporting one of the highest incidences of nasopharyngeal cancer, can explain familial clustering of HNC in certain families.<sup>47</sup> In regards to the pattern of alcohol use, studies have linked genetic mutations in alcohol metabolism genes to an increased risk of HNC.<sup>44</sup> Consequently, it is not unconvivable that the familial risk of HNC results not only from lifestyle factors but from inherited faulty genes along with cumulative carcinogenic exposures, that is, somatic and germline mutations. The interactions between genetic susceptibility and continuous environmental factors, as smoking, alcohol consumption, infection with HPV, and dietary exposure, may have critical implications in carcinogenesis. HNC would be assumed to develop in these circumstances at a later age, which may then explain why the risk of HNC was not elevated when focusing on early-onset HNC, in contrast to other studies with no age cutoff or with a cutoff at a later age than in our study. However, only a few of these genotype-environment interactions have been documented, due comprehensibly to the intricate nature of this complex polygenic interplay.<sup>48,49</sup> Based on the results of a meta-analysis, a polymorphism (Arg194Trp)

associated with the DNA repair gene *XRCC1* was described as having an effect on HNC risk in smokers, even though the involvement was suggested to be minor.<sup>50</sup> Another study concluded that specific polymorphisms of the anti-apoptotic protein survivin, combined with betel quid chewing and/or tobacco consumption, could substantially promote predisposition to oral cancer.<sup>51</sup> Some evidence of increased HNC risk also exists for certain genotypes associated with the genes *ADH1B*, coding the enzyme alcohol dehydrogenase 1B involved in ethanol catabolism, and *HEL308*, coding the enzyme helicase involved in polymerase pathway when associated with tobacco consumption.<sup>52</sup> These findings hint that a familial factor in the pathogenesis of HNC could be attributable to inherited germline mutations predisposing to sensitivity toward tobacco- and alcohol-related carcinogens.

Some inherent weaknesses in our study should be acknowledged. The inability to evaluate the effects of HPV status and smoking or alcohol consumption habits sets restrictions on speculating any underlying mechanisms, especially those supporting interactions between inherited susceptibility and environmental risk factors. Neither was any information available on genetic variations of potential susceptibility genes. The environmental risk factors represent genetic modifying factors that interfere with the ability to elucidate the precise genetic involvement in disease-onset, and our risk estimates could not be adjusted for these factors. Other caveats relate to the short follow-up for late-onset cancers in probands' family members and spouses, which results in less statistical power, especially for late-onset effects. Also, a lower fertility rate among early-onset cancer subjects may lead to observing more cancer-free relatives and thus to an underestimation of the cancer risk in these families.<sup>53</sup> Early-onset HNC is associated with moderate survival (73% survival rate after eight years of follow-up in 15-39 year-old patients) and mortality of early-onset cancer probands before reproduction could also predispose to an underestimation of the familial risk in our study.<sup>54</sup>

The cumulative incidence for HNC for first-degree relatives of a proband diagnosed with early-onset HNC was less than 0.10% by age 40. Evidence linking shared genetic mutations with some early-onset cancers exists.<sup>55,56</sup> However, our study indicates that the contribution of shared familial factors, such as inherited germline components or early HPV-exposure, to early-onset HNC is, at least in the Finnish population, negligible from a clinical point of view and, at most, only a minor proportion of HNCs are due solely to inherited genetic mutations. Instead, environmental factors, such as tobacco and alcohol consumption, yielding somatic mutations or genotype-environment interactions, may

play a more prominent role in disease onset. In order to disentangle the precise contribution of genetic and environmental components to familial HNC risk, larger study populations and longer follow-up periods are warranted.

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## CONFLICT OF INTEREST

The authors state no conflict of interest.

## AUTHOR CONTRIBUTIONS

Rayan Mroueh, Tomas Tanskanen, Aaro Haapaniemi, Tuula Salo, Nea Malila, Antti Mäkitie, and Janne Pitkaniemi conceived and designed the study. Tomas Tanskanen and Janne Pitkaniemi conceived the data. Rayan Mroueh, Tomas Tanskanen, and Janne Pitkaniemi analyzed the data. Rayan Mroueh devised the manuscript. All authors contributed to the revision of the manuscript and had final approval of the submitted and published versions.

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