Establishing a Familial Basis for Papillary Thyroid Carcinoma Using the Utah Population Database

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In contrast with most other cancers worldwide, the incidence of thyroid cancer has been increasing over the last several decades.1-4 The most common endocrine malignancy, thyroid cancer demonstrated a 2.4-fold increase from 1973 to 2002.3 This is attributed almost entirely to an increase in incidence of the most common histologic subtype, papillary thyroid carcinoma (PTC), which makes up approximately 80% of all thyroid cancers.1,3-7 Mortality rates have remained stable, and therefore there is some debate as to whether this increase in incidence is simply due to earlier detection of subclinical disease or an actual increase kept at bay with improved treatment methods.1-3,8 Risk factors known to be associated with the development of thyroid cancer include radiation exposure, iodine deficiency or excess, and benign thyroid disease, such as multinodular goiter or Hashimoto thyroiditis. Thyroid cancer occurs in women at a 2- to 4-fold higher rate than in men,2,7 suggesting a likely hormonal effect as well.

Although most cases of PTC are believed to be sporadic, there appears to be a familial component underlying this disease process. The thyroid gland demonstrates the highest estimate of familial relative risk for primary cancer, between 5- and 10.4-fold, compared with all other organs, indicating a significant heritable component to cancer at this site.4 Another strong argument for the heritability of this disease lies in the fact that if PTC occurred only sporadically, the chance of just 2 members of a family being afflicted with the disease would be between 1 in 10 million and 1 in 40 million.9 When certain syndromes with which thyroid cancer is associated are excluded, such as Gardner and Cowden syndromes, this familial pattern is termed familial nonmedullary thyroid cancer.
and consists of patients with 2 first-degree relatives also diagnosed as having nonmedullary thyroid cancer. These cases account for 5% of thyroid cancer and oftentimes display a more aggressive behavior than sporadic cases with higher rates of extrathyroid extension, lymph node metastases, larger tumor size in younger patients, increased tumor multifocality and bilaterality, earlier age of diagnosis in parent-child relationships, and worse outcomes.4,5,10 This illustrates the importance of recognizing cases of familial nonmedullary thyroid cancer for risk stratification and management decisions. Papillary thyroid carcinoma makes up a large part of this group, and that is the specific thyroid cancer histologic subtype we analyze in this study. Our objective was to define the familial risk of PTC using a unique population research database.

### Methods

This research was approved by the institutional review board at University of Utah. The Utah Population Database (UPDB) is a dynamic, shared resource located at the University of Utah and consists of computerized data records for 6.5 million individuals. Most families living in Utah are represented in the UPDB.11 For example, when considering all individuals born in Utah in 1950, 79% have grandparent information available in the UPDB, and 67% have 5 or more previous generations documented in the resource. The UPDB includes statewide vital records and hospital inpatient data that are linked to individuals in existing multigenerational pedigrees or used to create new pedigrees. Comprehensive cancer records from the Utah Cancer Registry (UCR) are linked to the UPDB. The UCR is a Surveillance Epidemiology and End Results (SEER) registry of statewide cancer records, beginning in 1966. For over 30 years, researchers have used the UPDB and linked UCR information to identify and study individuals and their family members who have higher than expected incidence of cancer. Given an ongoing and accurate assessment of family history of cancer that does not depend on self-report, the UPDB provides a valuable resource for a thorough analysis of the familial nature of PTC.

Using a software suite developed specifically for the UPDB,12 we determined the risk of PTC to relatives and spouses of individuals with PTC diagnosed in Utah between 1966 and 2011. Papillary thyroid carcinoma was defined as International Classification of Diseases for Oncology site code C73.9, morphology codes 8050, 8260, 8340-8344, 8350, and 8450 to 8460. The risk of PTC in first-through fifth-degree relatives of PTC cases was compared with matched, population-based controls within the following categories of relationship: first degree, including parents, children, and siblings; second degree, including grandparents, grandchildren, aunts/uncles, and nieces/nephews; third degree (first cousins); fourth degree (first cousins once removed); and fifth degree (second cousins). We also examined the risk of PTC in spouses of probands to determine evidence of shared environment in disease etiology.

The magnitude of familial risk was estimated by calculating odds ratios using conditional logistic regression, adjusting for number of biological relatives, their degree of relatedness, and their person-years at risk as described elsewhere.13,14 Randomly selected controls with a follow-up year in Utah equal to or greater than the case year of diagnosis were matched 5:1 to cases by sex, year of birth, and place of birth (in Utah or outside of Utah). To appropriately match exposure periods, a control had to have been followed up (known to reside in Utah) for at least as long as the date of diagnosis for their respective case as previously described.14 All relatives of PTC probands and matched controls with adequate follow-up in Utah, who were linked to a UPDB pedigree comprising at least 2 generations, were included in the calculations even if that relative had been counted previously. For example, in sibships that contain multiple patients with PTC, each case was included as a separate proband and risk among all siblings of each case calculated separately. This approach has been shown to lead the unbiased estimates of familial risk.15 Because observations within families are nonindependent, a robust variance estimator for clustered data similar to a generalized estimating equations approach was incorporated.16

### Results

There were 4426 PTC probands in Utah with family information identified through the UCR from 1966 through 2009. An additional 34 cases were identified through the University of Utah Health Care’s system of hospitals and clinics in 2010 and 2011 for a total of 4460 PTC cases available for study (Table 1). Cases and matched controls were predominantly female (78%) and the mean age at diagnosis was 44 years. The mean number of relatives per case or control subject was similar.

Family members who were first-degree relatives had a 5.4-fold increased risk (95% CI, 4.4-6.5; P < 10^-15) of being diagnosed as having PTC compared with population-based matched controls (Table 2). Siblings of probands were at highest risk within this group at 6.8-fold (95% CI, 5.2-9.0; P < 10^-15). Second-degree relatives of PTC probands, who are less likely than first-degree relatives to be raised in the same household, exhibited a 2.2-fold increased risk (95% CI, 1.8-2.8; P < 10^-15). This significantly increased relative risk extended to third-degree relatives of probands (first cousins), who displayed a 1.8-fold increased risk (95% CI, 1.5-2.1; P < 10^-15). There was no significant increased risk observed in relatives beyond the third degree of relatedness or in spouses of probands. Familial risk of PTC detailed by degree of relatedness and relationship to the proband is given in Table 2.

### Table 1. Descriptive Characteristics of Papillary Thyroid Carcinoma Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 4460)</th>
<th>Controls (5:1) (n = 22 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No. (%)</td>
<td>984 (22)</td>
<td>4990 (22)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>3476 (78)</td>
<td>17 310 (78)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD) (range), y</td>
<td>44 (15.9) (8-90)</td>
<td>44 (15.9) (8-90)</td>
</tr>
<tr>
<td>First-degree relatives, No.</td>
<td>5.1</td>
<td>4.5</td>
</tr>
<tr>
<td>Second-degree relatives, No.</td>
<td>10.7</td>
<td>9.4</td>
</tr>
</tbody>
</table>

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Discussion

This Utah population-based study assessed the risk of developing PTC in relatives of PTC probands over more than a 40-year period. Multiple prior studies have demonstrated an increased familial risk of thyroid cancer but are limited by inclusion of multiple histopathologic groups, or even cancer diagnoses, in their risk analysis. The familial risk for first-degree relatives of thyroid cancer probands of being diagnosed as having cancer of the same site has been shown in prior studies to range from 7.1- to 8.6-fold. Because these numbers include all thyroid cancer histopathologic subtypes, they are likely skewed by the influence of medullary thyroid carcinoma and its well-established inheritance risk, such as that seen in multiple endocrine neoplasia. When the included histopathologic subtype is limited to nonmedullary thyroid carcinoma, meaning papillary and follicular thyroid carcinoma, first-degree familial risk was shown to range from a 2.8- to 7.8-fold increased risk with studies by Galanti et al,19 Hemminki and Dong,20 and Frich et al,21 of which the latter 2 demonstrated a standardized incidence ratio of 4.23. We evaluated the risk to children of PTC probands and found offspring to be at a 4.86-fold increased risk (Table 2).

In addition to a nonspecific histologic subtype grouping, some other common limitations seen in prior studies include reliance on self-reporting of personal or family cancer history and limited case numbers. The strengths of our study include a unique genealogical and medical database linked to a comprehensive statewide cancer registry since 1966 (the UCR received SEER designation in 1973). Thus, selection bias is minimized from near-complete ascertainment of cancer records in Utah. Family relationships have been determined from genealogies and dynamically updated from vital records without reliance on self-reported data. Hemminki et al 17,20,22 use the Swedish Family-Cancer Database in their studies of thyroid cancer, which has similar access to extensive medical and pedigree data. However, our study is novel in this field in that we analyze data for strictly the PTC histologic subtype, making this the largest population study to date.

To our knowledge, there is no other study in the PTC literature that evaluates familial risk beyond first-degree relatives. We have shown that a significant risk extends through third-degree relatives of probands, indicating a shared genetic basis for familial risk. This finding suggests patients may benefit from simply the collection of a more extensive family history during a medical visit if a family history of thyroid cancer is observed. Although the incidence of thyroid cancer in the Utah population is relatively uncommon (15.1 per 100,000 population per year, age-adjusted),23 an estimated 1.08% of individuals (1 in 92) born today in the United States will be diagnosed during their lifetime.24 Our observation of an estimated 5.35-fold increased relative risk of PTC (based on the odds ratio) in first-degree relatives of probands compared with first-degree relatives of controls, while small in terms of an absolute increased risk or risk difference (0.8%, as derived from Table 2), could result in a nontrivial lifetime risk of approximately 5%.25 Knowledge of increased cancer risk due to a positive family history could lead to increased surveillance and potentially earlier detection of cancer, which in turn could mean decreased treatment morbidity and a better overall prognosis. We also observed in this study that elevated risk in the spouses of patients with PTC, who share a common environment, was not statistically significant; however, power may have been limited to detect an association. Overall, our study supports a shared genetic rather than environmental basis to the familial risk of PTC in relatives of patients with this cancer and that environmental factors may influence this risk.

We acknowledge that the cases and controls linked to UPDB genealogies to assess cancer risk in relatives may differ from subjects without pedigree information in the UPDB; individuals linked to the genealogies are more likely to be born in Utah and to relocate outside of Utah less often. Despite this potential bias, we presented unadjusted P values for specific study...
hypotheses and performed only a limited number of analyses in PTC subgroups. Our observations of increased risk in categories of first- through third-degree relatives were significant below the 10^{-8} level and unlikely to represent chance findings. This relatively geographically stable population leads to more accurate and extensive data on subjects and their various relatives than could be collected otherwise. In addition, Utah has the highest fertility rate in the nation. This increased number of replicates for analysis can better reveal a genetic predisposition when one exists. Another limitation of this study is that we were not able to exclude from our data familial syndromes in which PTC is prevalent, such as Gardner and Cowden syndromes. These known syndromes could skew our results toward a higher familial relative risk than would be seen otherwise.

Although a specific etiology to this familial predisposition to PTC has yet to be identified, these study results support a genetic rather than strictly environmental inheritance pattern. We plan to identify high-risk families with clustering of PTC above expected levels for gene identification. These findings also indicate that family members of known PTC probands will likely benefit from closer clinical attention, including collecting and maintaining a 3-generation family history. Translational studies are needed to better define the genetic predisposition to familial PTC and development and implementation of optimal screening approaches.

REFERENCES