Increased Melanoma Risk in Individuals With Papillary Thyroid Carcinoma

Gretchen M. Oakley, MD; Karen Curtin, PhD; Lester Layfield, MD; Elke Jarboe, MD; Luke O. Buchmann, MD; Jason P. Hunt, MD

IMPORTANCE Determining the associated risk between papillary thyroid carcinoma (PTC) and cutaneous malignant melanoma (CM) and the rate of BRAF v600e mutation could help identify a common genetic component of these 2 cancers.

OBJECTIVES To define the relative risk of PTC in patients with CM, and vice versa, and their first- through fifth-degree relatives and spouses by using a unique population research database; and to assess the rate of BRAF v600e mutation in a group of patients with both diagnoses.

DESIGN, SETTING, AND PARTICIPANTS Retrospective review using the Utah Population Database (which is linked to medical records and the Utah Cancer Registry from 1966 to 2011) and tissue analysis in a tertiary care facility. Included were 4460 patients diagnosed with PTC and 14 569 with CM in Utah between 1966 and 2011 and their first- through fifth-degree relatives and spouses. These were compared at a 5:1 ratio with matched, population-based controls.

MAIN OUTCOMES AND MEASURES Statistically significant increased risk of PTC in patients with CM, and vice versa, and any first- through fifth-degree relatives and spouses; and a significantly higher rate of BRAF v600e mutation in patients with both PTC and CM than would be expected for each individual condition alone.

RESULTS Patients with CM had a 2.3-fold increased risk (P < .001) of being diagnosed as having PTC compared with population-based matched controls. Conversely, patients with PTC had a 1.8-fold increased risk (P < .001) of developing CM. First- through fifth-degree relatives and spouses of patients with PTC or CM did not show a statistically significant increased risk. Eight patients with both cancer diagnoses had tissue specimens tested, of which 4 (50%) were found to be positive for the BRAF v600e mutation in either their PTC or CM specimen, and 3 (38%) were found positive in both.

CONCLUSIONS AND RELEVANCE Patients with either PTC or CM have an increased risk of developing the other cancer as a second primary malignant neoplasm. Tissue specimens from patients with both cancers show a high rate of BRAF v600e mutation. Translational studies are needed to better define the associated genetic predisposition between PTC and CM and to test the efficacy of and implementation techniques for treatment plans using BRAF mutation as a therapeutic target.

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In contrast to most other cancers worldwide, the incidences of papillary thyroid carcinoma (PTC) and cutaneous malignant melanoma (CM) have been increasing over the last few decades. The average annual increase in incidence in the United States from 1999 to 2008 was 6.2% to 7.3% for thyroid cancer and 2.1% to 2.3% for melanoma.\(^1\) The observed change in thyroid cancer incidence has been attributed almost entirely to the most common histologic subtype, PTC.\(^2\)

There are well-recognized risk factors associated with PTC and CM, including external irradiation for PTC and UV irradiation and presence of nevi for CM. Although there is little commonality between these risk factors, these cancers are similar in that they both display a familial pattern of inheritance. The thyroid gland demonstrates the highest estimate of familial relative risk, between 5.0 and 10.4 fold, compared with all other organs.\(^3\) From 5% to 10% of CM cases are familial as well.\(^4\)\(^5\) Although this represents a minority of cases, first-degree relatives of patients with CM have a significantly higher risk of developing melanoma than those with a negative family history,\(^4\)\(^5\) indicating that some patients and their families may have a genetic predisposition from known or undiscovered variants.\(^5\)

In addition to an apparent inherited susceptibility, PTC and CM also share a high rate of BRAF v600e mutation in their lesions. This is a mutation of the B isoform of the Raf kinase protein, a component of the RAS/Raf/MAPK kinase/MAPK signaling pathway, which plays a key role in regulation of cell growth, division, and proliferation.\(^7\)\(^8\) Although the BRAF mutation is exhibited in a variety of cancers, by far the highest frequencies of the mutation are observed in CM, at a rate of 5% to 10%,\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\)\(^15\)\(^16\) Studies have also shown that BRAF-positive PTCs and CMs tend to display more aggressive features. Specifically, BRAF-positive PTC has been shown to have a significantly higher rate of aggressive histologic subtype, extrathyroidal extension, lymph node metastases, and advanced clinical stage.\(^13\)\(^14\)\(^15\)\(^16\) A higher rate of tumor ulceration and increased Breslow depth has been seen in BRAF-positive CM, as well as increased lymphocytic infiltration, although these factors did not influence overall survival rates.\(^13\)\(^14\)\(^15\)\(^16\)

The high BRAF mutation rate, associated aggressive clinicopathologic features, and familial pattern shared by PTC and CM highlight this tumor mutation as a likely genetic link between the underlying cause of these 2 cancers. Given similar clinicopathologic features, we would expect to see an increased risk of developing CM in patients previously diagnosed with PTC, and vice versa. Our objective in this study was to analyze the associated risk between these 2 cancers using a unique population database linked to a statewide cancer registry. The Utah Population Database (UPDB) is a dynamic, shared resource located at the University of Utah containing computerized genealogical records for 6.5 million individuals linked to statewide vital and medical records. It is the only database of its kind in the United States and one of a few in the world; most families living in Utah are represented in the UPDB.\(^17\) For example, of 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.

Comprehensive cancer records from the Utah Cancer Registry (UCR) are record-linked to the UPDB. The UCR is a Surveillance Epidemiology and End Results (SEER) registry of statewide cancer records dating back to 1966. For over 30 years, researchers have used the UPDB and linked UCR information to identify and study individuals and their family members that 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 associated risk between PTC and CM.

**Methods**

This study was approved by the institutional review board at the University of Utah. Using a software suite developed specifically for the UPDB,\(^18\) we determined the risk of PTC in patients with CM and their first- through fifth-degree relatives and spouses diagnosed in Utah between 1966 and 2011. We also determined the risk of CM in patients with PTC and their first- through fifth-degree relatives within these same time and location parameters.

For our analysis, PTC was defined as International Classification of Diseases for Oncology (ICD-O) site code C73.9 and morphology codes 8050, 8260, 8340 through 8344, 8350, and 8450 through 8460; CM was defined as ICD-O site codes C44.0 through 44.9, 51.0 through 51.9, 60.0 through 60.2, 60.8, 60.9, and 63.2, and morphology codes 8720 through 8790. The risk of PTC in patients with CM and their first- through fifth-degree relatives, as well as the risk of CM in patients with PTC and their first- through fifth-degree relatives was compared with that of matched, population-based controls within categories of relationship: first-degree relationship included parents, children, and siblings; second-degree: grandparents, grandchildren, aunts and uncles, and nieces and nephews; third-degree: first cousins; fourth-degree: first cousins, once removed; and fifth-degree: second cousins. We also examined risk of these cancers in spouses of patients to determine evidence of shared environment in disease cause.

A review of University of Utah clinic records from June 2006 to March 2012 was performed, and 9 patients linked to UPDB data were identified to have both PTC and CM diagnoses as well as associated tissue specimens for BRAF testing. The formalin-fixed PTC and CM tissue specimens from surgical excision were able to be located from 8 of these 9 patients. These specimens were prospectively tested for BRAF v600e mutation through polymerase chain reaction (LightCycler; Roche Diagnostics) with allele-specific fluorescent melting curve analysis. These cases serve as an illustration of potential BRAF mutation rates in a small, convenience subsample and were included in the study analysis.

The magnitude of familial risk was estimated by calculating odds ratios (ORs) using conditional logistic regression and adjusting for number of biological relatives, their degree of relatedness, and their person-years at risk, as described elsewhere.\(^19\)\(^20\) Randomly selected controls with a follow-up year in Utah equal to or greater than the case year of diagno-
sis were matched 5:1 with cases on the basis of sex, year of birth, and place of birth (in Utah or outside of Utah). To appropriately match exposure periods, a control had to have follow-up (known to reside in Utah) at least as long as the date of diagnosis for their respective case, as previously described.20 All relatives of patients with PTC and of matched controls with adequate follow-up in Utah who linked to a UPDB pedigree comprising at least 2 generations were included in the calculations, even if a relative had been counted previously. For example, in sibships that contain multiple patients with PTC and CM, each case was included as a separate proband, and risk among all siblings of each case was calculated separately. This approach has been shown to lead to unbiased estimates of familial risk.23 Because observations within families are not independent, a robust variance estimator for clustered data similar to a generalized estimating equations approach was incorporated.22 The 9 cases of both PTC and CM, identified through clinic-record review as having tissue available for BRAF testing, had UPDB pedigree information and were included in the data analysis.

### Results

There were 4426 PTC and 14 565 CM cases identified in Utah with family information in UPDB and first-primary cancers not in UCR from 1966 through 2009. An additional 34 cases of PTC, including 4 patients with PTC who also had CM, were identified through the University of Utah Healthcare system of hospitals and clinics in 2010 and 2011, for a total of 4460 PTC and 14 569 CM cases available for study (Table 1). Patients with CM had a 2.3-fold increased risk (95% CI, 1.8-3.0) (<.001) of being diagnosed with PTC compared with population-based matched controls with pedigree information in UPDB. Conversely, patients with PTC similarly had a 1.8-fold increased risk (95% CI, 1.4-2.3) (<.001) of developing CM (Table 2).

#### Table 1. Characteristics of Patients With PTC and CM and Matched Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PTC</th>
<th>Controls (5:1)</th>
<th>CM</th>
<th>Controls (5:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4460</td>
<td>22 300</td>
<td>14 569</td>
<td>72 845</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>984 (22)</td>
<td>4990 (22)</td>
<td>8086 (55)</td>
<td>40 405 (45)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>3476 (78)</td>
<td>17 310 (78)</td>
<td>6483 (45)</td>
<td>32 440 (45)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD), ya</td>
<td>44 (15.9)</td>
<td>NA</td>
<td>56 (18.2)</td>
<td>NA</td>
</tr>
<tr>
<td>First-degree relatives evaluated per case or control, mean No.</td>
<td>5.1</td>
<td>4.5</td>
<td>5.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Second-degree relatives evaluated per case or control, mean No.</td>
<td>10.7</td>
<td>9.4</td>
<td>13.3</td>
<td>11.1</td>
</tr>
</tbody>
</table>

#### Table 2. Risk of PTC or CM in Patients and Relatives of Patients With CM or PTC in Utah

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Patient Genealogy</th>
<th>Control Genealogy</th>
<th>OR (95% CI)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of PTC in CM&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with CM</td>
<td>78</td>
<td>14 491</td>
<td>169</td>
<td>72 676</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>166</td>
<td>77 228</td>
<td>608</td>
<td>318 503</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>278</td>
<td>194 527</td>
<td>1082</td>
<td>789 753</td>
</tr>
<tr>
<td>First- and second-degree relatives</td>
<td>443</td>
<td>271 930</td>
<td>1690</td>
<td>1 098 256</td>
</tr>
<tr>
<td>Third-degree relatives (first cousins)</td>
<td>439</td>
<td>206 146</td>
<td>1572</td>
<td>811 805</td>
</tr>
<tr>
<td>Spouses</td>
<td>39</td>
<td>10 973</td>
<td>135</td>
<td>51 428</td>
</tr>
<tr>
<td>Risk of CM in PTC&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with PTC</td>
<td>78</td>
<td>4382</td>
<td>219</td>
<td>22 081</td>
</tr>
<tr>
<td>First-degree relatives</td>
<td>166</td>
<td>22 490</td>
<td>697</td>
<td>99 307</td>
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<tr>
<td>Second-degree relatives</td>
<td>286</td>
<td>46 933</td>
<td>897</td>
<td>161 466</td>
</tr>
<tr>
<td>First- and second-degree relatives</td>
<td>452</td>
<td>74 063</td>
<td>1587</td>
<td>290 604</td>
</tr>
<tr>
<td>Third-degree relatives (first cousins)</td>
<td>444</td>
<td>47 513</td>
<td>1667</td>
<td>194 720</td>
</tr>
<tr>
<td>Spouses</td>
<td>39</td>
<td>3555</td>
<td>155</td>
<td>16 273</td>
</tr>
</tbody>
</table>

Abbreviations: CM, cutaneous melanoma; OR, odds ratio; PTC, papillary thyroid carcinoma.

* Cases compared with controls matched 5:1 on sex, birth year, and birthplace (in Utah or outside of Utah); unless otherwise indicated, data are reported as number of patients, controls, or relatives.

<sup>b</sup> From conditional logistic regression.

<sup>c</sup> Total of 14 569 patients with CM compared with 72 845 matched controls.

<sup>d</sup> Total of 4460 patients with PTC compared with 22 300 matched controls.
first- and second-degree relatives combined, significant at the $P < .05$ level (Table 2). Spouses of patients with PTC were not at increased risk of CM, nor were spouses of patients with CM at increased risk of PTC (Table 2).

Of the 9 patients diagnosed as having both PTC and CM in the UPDB analysis who were verified through chart review as having tissue available, we were able to procure both thyroid and melanoma tissue specimens of 8 patients for $BRAF$ v600e mutation testing. Four of these 8 patients (50%) tested positive for $BRAF$ v600e mutation in either their thyroid or melanoma specimen, while 3 (38%) tested positive in both specimens. One of these 3 patients was treated with dabrafenib, a $BRAF$ inhibitor, for $BRAF$-positive stage IV melanoma and stage IV thyroid cancer. Although initially responsive to this treatment at both sites, the patient ultimately had progression of disease.

Discussion

This population-based study assesses PTC or CM risk as a second first-primary malignant neoplasm in patients previously diagnosed with the other cancer over a period of more than 50 years in Utah. It evaluates the risk in their families as well. Although the hypothesis is not new, that patients with one of these cancer diagnoses will be predisposed to developing the other given their shared high rate of $BRAF$ mutation, there are few studies that analyze this particular relationship. Using the SEER cancer registry, Goggins et al$^{23}$ observed a 2.2-fold increased risk of thyroid cancer in survivors of CM, and a slightly increased but not statistically significant risk of CM after thyroid cancer. The sample size was well powered in this study. However, all types of thyroid cancer were included in the analysis rather than just the specific histologic subtype examined in the present study, PTC. Our estimates of increased relative risk of PTC in survivors of CM were consistent with those of Goggins et al$^{23}$—2.3-fold and 2.2-fold, respectively. Conversely, we observed a statistically significant increased CM risk of similar magnitude in patients with PTC.

In a population-based study using Connecticut statewide cancer registry data, a standardized incidence ratio of 3.6 was reported for developing thyroid cancer as a second primary in patients with prior CM from 1935 to 1982.$^{24}$ Researchers in Norway reported a 4.2-fold increased risk of CM in male patients with a diagnosis of thyroid cancer.$^{25}$ Similarly, a pooled data analysis from Swedish, French, and Italian thyroid cancer cohorts conducted from 1934 to 1995 resulted in an estimated 2.5-fold increased risk of a second primary CM diagnosis in patients with thyroid cancer.$^{26}$ These prior studies were based on thyroid cancer in general, rather than PTC specifically. Since PTC makes up the vast majority of the thyroid cancers with the $BRAF$ mutation, one could argue that separating out this histologic subtype for analysis would be unlikely to change the overall relative risk values observed in these studies, but it is difficult to know for sure. We believe that our population-based study into a specific histologic subtype of PTC provides a more focused investigation in this regard.

A strength of our study is that we were able to analyze risk of either first-primary PTC or CM not only in patients with a first-primary diagnosis of the other cancer (PTC or CM) but in their close and more distant relatives and spouses as well. To our knowledge, this is the only study that has looked at familial risk of cooccurrence of these cancers beyond close relatives. The increased risks we observed of CM or PTC in first- and second-degree relatives of patients with PTC or CM were very modest. However, the increased risk of CM in those with PTC and conversely of PTC in those with CM, along with the lack of association in spouses (who share environment and not genes), suggests a familial basis for the cooccurrence of both cancers.

We acknowledge that the cases and controls linked to UPDB genealogies for assessment of cancer risk in probands and their relatives may differ from people without pedigree information in the UPDB; individuals who link to the genealogies are more likely to be born in Utah and less often relocate outside of Utah. Despite this potential bias, we presented P-values unadjusted for multiple comparisons for specific study hypotheses and performed only a limited number of analyses in PTC and CM subgroups. Our observations of increased proband relative risk were statistically significant and unlikely to represent chance findings.

In addition, detection bias must be a consideration when looking at the rate of second primary malignant neoplasms. This is particularly true when dealing with PTC, a cancer often found incidentally. We are unable to guarantee that this did not contribute to the increased relative risk of PTC seen in survivors of CM. In the study by Goggins et al,$^{23}$ which had very similar relative risk results to those of our study, the size of the PTC nodules in patients with CM was not significantly smaller than the size of nodules for all patients with thyroid cancer (19.2 mm vs 21.6 mm). This could indicate that these cancers are not being detected any earlier in patients with CM than they would be in the general population. Although we were able to readily review medical records for PTC diagnosed after UCR data ending in 2009 and identified 34 additional PTC cases (4 with CM) with UPDB pedigree data, it was beyond the scope of this study to review clinical records to identify additional CM cases after 2009; thus it is possible that we were unable to identify all PTC cases with a recent CM diagnosis. However, given that the cooccurrence of these 2 malignant neoplasms is relatively rare, we believe that our study findings were not substantially impacted.

There does not appear to be a causal link between PTC and CM related to their treatments. Typically, PTC is treated with surgical excision and ionizing irradiation, neither of which is a risk factor for CM. Conversely, CM is most often treated with surgical excision and, much less commonly, external irradiation. Although this irradiation is a PTC risk factor, it is unlikely to affect the rate of second malignant neoplasms owing to its rare use in the treatment of CM.

We identified a subset of individuals who carried both PTC and CM diagnoses and tested their tissue specimens to further elucidate if the $BRAF$ mutation leads to a predisposition for PTC and CM, and therefore a higher-than-expected incidence of developing the second primary tumor after a diag-
nosis of the first. We did, in fact, see a higher-than-average BRAF mutation rate in the tumors of patients with both types of cancer. These numbers are limited, however, because the 8 cases evaluated represented only a pilot project and were identified at a single institution. However, we plan to expand this inquiry in future studies.

In 2010, the incidence of thyroid cancer and cutaneous melanoma was 13.8 and 23.6 per 100 000 for both sexes and all races.27 Therefore, even if either PTC or CM is at double the risk of developing the second primary malignant neoplasm, this risk is still quite modest and likely does not justify any additional directed screening. Similar to the effect that the BRAF mutation can have on cancer predisposition in individuals, it could also manifest in families. Although BRAF is a somatic mutation, there is likely a predisposition to developing this mutation that could be passed on to subsequent generations. We saw an increased tendency toward PTC and CM but no statistically significant increased rates in immediate and extended family members.

Although the BRAF v600e tumor mutation has not yet been definitively identified as a genetic link between PTC and CM, these data support a possible common path of carcinogenesis. Translational studies are needed to better define the associated genetic predisposition between PTC and CM and to test the efficacy of and implementation techniques for treatment plans using BRAF mutation as a therapeutic target.

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Study concept and design: Oakley, Curtin, Hunt.

Acquisition of data: Curtin, Layfield, Jarboe.

Analysis and interpretation of data: Oakley, Curtin, Buchmann, Hunt.

Drafting of the manuscript: Oakley, Curtin.

Critical revision of the manuscript for important intellectual content: Oakley, Curtin, Layfield, Jarboe, Buchmann, Hunt.

Statistical analysis: Curtin.

Obtained funding: Oakley.

Administrative, technical, and material support: Oakley, Layfield.

Study supervision: Buchmann, Hunt.

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REFERENCES