Risk of Second Primary Malignancies in Women with Papillary Thyroid Cancer

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Second malignancies in women diagnosed with thyroid cancer are of concern given the young average age at diagnosis and excellent survival. Data from the California Cancer Registry were used to evaluate the risk of second primary cancers among a retrospective population-based cohort of 10,932 women diagnosed with papillary thyroid cancer between 1988 and 1999. Follow-up was calculated from 2 months until the diagnosis of a second primary cancer, death, loss to follow-up, or December 31, 1999, whichever occurred first. Standardized incidence ratios, based on age-specific cancer incidence rates for California women, were calculated. During a total of 50,938 person-years of follow-up (mean: 4.7 years), 279 women developed a second primary cancer. The incidence of invasive breast cancer was not elevated compared with California women overall (standardized incidence ratio (SIR) = 0.9, 95% confidence interval (CI): 0.7, 1.1) or when stratified by age, race/ethnicity, follow-up, or radiation treatment. An excess of in situ breast cancer (SIR = 1.6, 95% CI: 1.0, 2.4), kidney cancer (SIR = 3.9, 95% CI: 2.2, 6.3), and melanoma (SIR = 2.1, 95% CI: 1.3, 3.2) limited to the first 5 years after diagnosis was observed. Women with papillary thyroid cancer are at increased risk of in situ, but not invasive, breast cancer, kidney cancer, and melanoma.

Thyroid cancer disproportionately affects women at almost three times the rate of men and is one of the most common cancers in young women aged less than 45 years (1). The incidence of thyroid cancer in women has increased by 34 percent in the last decade (compared with 17 percent in men): The age-adjusted incidence rate per 100,000 women in California was 9.9 in 2000 compared with 7.4 only a decade earlier (2, 3). In areas without endemic goiter, over 80 percent of all thyroid cancers are of papillary histology (or its variant, mixed papillary-follicular). The prognosis for this cancer is very good, especially for young women, with a 10-year survival rate of over 99 percent for women diagnosed before the age of 45 years (4). However, because of the young age at which most women are diagnosed with thyroid cancer, the occurrence of second primary cancers is of potential concern.

Other than ionizing radiation and proliferative benign thyroid disease, the causes of thyroid cancer are still largely unknown (1, 5, 6). However, recent studies have suggested that a pregnancy occurring within the 5 years preceding the thyroid cancer diagnosis is associated with increased risk independent of the possible surveillance biases associated with this event (7, 8). Dietary factors may also influence risk. Recent studies have found that greater consumption of soy-based foods and vegetables is associated with a reduction in thyroid cancer risk (9, 10).

Understanding the patterns of how multiple cancers occur within individuals may provide clues to the etiology of this relatively rare cancer. The association between thyroid cancer and breast cancer has received the most attention to date. With the exception of two of the smallest studies (11, 12) and one larger one that found elevated incidence only in certain

Abbreviations: CI, confidence interval; RR, relative risk; SIR, standardized incidence ratio.
MATERIALS AND METHODS

Data from the population-based California Cancer Registry were used to evaluate the risk of second primary malignancies in a large, ethnically diverse cohort of female thyroid cancer patients. The cohort of interest included 13,937 women residing in California and diagnosed with a histologically confirmed thyroid cancer (International Classification of Diseases for Oncology site code C73.9; Surveillance, Epidemiology, and End Results code 32010) between January 1, 1988, and October 31, 1999; the thyroid cancer had to be the woman’s first cancer diagnosis. Reporting to the California Cancer Registry is mandated by law, resulting in a completeness rate of over 97 percent. The California Cancer Registry is also part of the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program, which guarantees that the highest quality standards are met. This study was determined to be exempt by the Northern California Cancer Center Institutional Review Board. Exempt status was granted, in part, because no identifying information was released to the investigators.

Excluded from the analysis (in a hierarchical manner) were the following: 1) women whose thyroid cancer was of a histologic type other than papillary (or its variant, mixed papillary-follicular) (International Classification of Diseases for Oncology histology code 8050, 8260, or 8340) \(n = 2,515; 18\) percent); 2) women for whom the month or year of the thyroid cancer diagnosis, any second cancer diagnosis, or the date of last follow-up/death was not recorded \(n = 53; <1\) percent); and 3) women who were followed for less than 2 months \(n = 437; 3\) percent). Follow-up was calculated from 2 months after the thyroid cancer diagnosis until the earliest of one of the following: diagnosis of a second primary malignancy at any site (invasive or in situ), death, loss to follow-up by the California Cancer Registry, or December 31, 1999. As censoring occurred at a second cancer, subsequent cancers (i.e., third, fourth, etc., primaries) were not counted in the analysis. Of the 10,932 women with papillary thyroid cancer included in the analysis, 279 were diagnosed with a second primary malignancy during 50,938 person-years of follow-up (mean: 4.7 years).

Incidence rates per 100,000 female thyroid cancer patient-years were calculated adjusting for age (in 5-year age groups) and were standardized to the 2000 US standard million population. Subjects contributed person-years of follow-up to all age categories through which they were followed. Since age and date of diagnosis, but not date of birth, were available to us, we calculated birth year and assumed a birthday of January 1 for all subjects; assuming a birthday of July 1 instead resulted in only slight differences in approximate birth year and did not impact the study results. To assess whether the incidence of specific cancers for the women in our cohort differed from the incidence of those cancers in the general population of California women, standardized incidence ratios were calculated. The expected number of cancers at each site was determined by multiplying the age-specific (and for analyses involving race/ethnicity, race/ethnic-specific) California incidence rates for women (which ignore cancer sequence) by the corresponding person-years of follow-up among our thyroid cancer patients. The 95 percent confidence intervals were based on Byar’s approximation of the exact Poisson test (22). To examine differences within overall standardized incidence ratios, stratification by age, race/ethnicity, follow-up time, and radiation treatment was conducted. When stratifying the standardized incidence ratios by radiation treatment, we limited analyses to women followed for 5 or more years to account for the latency of radiation-induced effects. To formally evaluate whether the standardized incidence ratios across different factors were significantly different from each other, we computed relative risks by use of univariate and multivariate Poisson regression models with the log of the stratum-specific expected number of cancers as the offset (22). As the multivariate Poisson regression model for lung cancer showed evidence of under-dispersion, we adjusted the confidence intervals by using the Pearson chi-square divided by the degrees of freedom as an estimate of the dispersion parameter rather than setting it to 1. For melanoma, all analyses were limited to White women.

RESULTS

Of the 10,932 women with a first primary papillary thyroid cancer diagnosed between January 1, 1988, and October 31, 1999, in California and included in this analysis, the mean age at diagnosis was 43 years; 60 percent were White, 3 percent were Black, 22 percent were Hispanic, 14 percent were Asian or Pacific Islander, and race/ethnicity was other or unknown for less than 1 percent. Of the women followed for 5 or more years, 49 percent received radiation treatment (45 percent isotopes, 2 percent implants, 1 percent beam, 1 percent combination of beam with implants or isotopes, and <1 percent type not specified).

Table 1 presents the age-adjusted incidence rates and age-adjusted standardized incidence ratios compared with the general California female population for specific cancers following thyroid cancer. Only cancers with 12 or more
observed second primary malignancies were included. No overall increase in cancer incidence (all sites combined) was observed among this cohort nor was there an association with invasive breast cancer. However, a significant increased incidence of in situ breast cancer (standardized incidence ratio (SIR) = 1.6, 95 percent confidence interval (CI): 1.0, 2.4), kidney cancer (SIR = 3.9, 95 percent CI: 2.2, 6.3), and melanoma (SIR = 2.1, 95 percent CI: 1.3, 3.2) following thyroid cancer diagnosis was observed.

Table 2 presents the incidence ratio for breast cancer, kidney cancer, and melanoma stratified by age, race/ethnicity, time since diagnosis, and receipt of radiation therapy. No particular subgroup of thyroid cancer patients was at significantly elevated or reduced risk of invasive breast cancer. A significantly increased incidence of in situ breast cancer was observed among the following subgroups of women: those aged 45–69 years at thyroid cancer diagnosis (SIR = 2.0, 95 percent CI: 1.1, 3.2), Asian/Pacific Islanders (SIR = 3.1, 95 percent CI: 1.0, 7.3), and those during the period of 1–2.9 years of follow-up (SIR = 2.3, 95 percent CI: 1.1, 4.3). However, none of these effects was statistically different across the levels of each subgroup (incidence among women aged 45–69 years compared with those aged <45 years: relative risk (RR) = 2.1, 95 percent CI: 0.7, 6.2; for Asian/Pacific Islanders compared with Whites: RR = 2.2, 95 percent CI: 0.8, 6.1; for follow-up time of 1–2.9 years compared with <1 year: RR = 1.7, 95 percent CI: 0.5, 6.0).

An elevated incidence of kidney cancer was evident in the majority of the subgroups examined (table 2), and no significant relative risks comparing subgroups were observed. The incidence of melanoma was highest during the first year of follow-up (SIR = 3.9, 95 percent CI: 1.4, 8.4) and remained elevated for the first 5 years before returning to expected levels. Compared with women followed 5 or more years, those recently diagnosed with thyroid cancer were 4.2 times more likely (95 percent CI: 1.0, 16.6) to be diagnosed with melanoma. The risk during the first 5-year period was 2.8 (95 percent CI: 0.8, 9.4; p = 0.10) compared with the later period.

Similar analyses were conducted for endometrial, ovarian, lung, and colon cancers (data not shown). No increased or decreased incidence of endometrial, ovarian, or colon cancer was seen in any subgroup of thyroid cancer patients, although the number of cases observed in some subgroups was quite small. However, in comparison with other California women, women aged 70 or more years showed a reduced incidence of lung cancer among thyroid cancer patients (SIR = 0.3, 95 percent CI: 0.0, 0.9), but an increased incidence was observed among non-White women (SIR = 1.9, 95 percent CI: 1.0, 3.3). These subgroup differences were independent and statistically significant (for women aged ≥70 years compared with <70 years, adjusting for race/ethnicity: RR = 0.2, 95 percent CI: 0.1, 0.4; for non-White women compared with White women, adjusting for age: RR = 2.4, 95 percent CI: 1.8, 3.3).

**TABLE 1.** Age-adjusted incidence rates with 95% confidence intervals, observed and expected numbers of cases, and standardized incidence ratios with 95% confidence intervals for specific cancers following papillary thyroid cancer, California women, 1988–1999

<table>
<thead>
<tr>
<th>Cancer site*</th>
<th>Age-adjusted incidence rate</th>
<th>95% confidence interval</th>
<th>Observed no. of cases</th>
<th>Expected no. of cases</th>
<th>Standardized incidence ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>439.3</td>
<td>383.7, 494.9</td>
<td>279</td>
<td>272.6</td>
<td>1.0</td>
<td>0.9, 1.2</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>121.7</td>
<td>92.7, 150.6</td>
<td>78</td>
<td>87.4</td>
<td>0.9</td>
<td>0.7, 1.1</td>
</tr>
<tr>
<td>In situ</td>
<td>31.6</td>
<td>18.6, 44.7</td>
<td>23</td>
<td>14.4</td>
<td>1.6</td>
<td>1.0, 2.4</td>
</tr>
<tr>
<td>Endometrium</td>
<td>20.2</td>
<td>9.3, 31.0</td>
<td>14</td>
<td>14.8</td>
<td>1.0</td>
<td>0.5, 1.6</td>
</tr>
<tr>
<td>Ovary</td>
<td>18.4</td>
<td>8.1, 28.7</td>
<td>13</td>
<td>11.3</td>
<td>1.2</td>
<td>0.6, 2.0</td>
</tr>
<tr>
<td>Lung</td>
<td>46.4</td>
<td>28.8, 64.0</td>
<td>30</td>
<td>31.6</td>
<td>1.0</td>
<td>0.6, 1.4</td>
</tr>
<tr>
<td>Colon</td>
<td>23.4</td>
<td>8.5, 38.3</td>
<td>12</td>
<td>18.5</td>
<td>0.7</td>
<td>0.3, 1.1</td>
</tr>
<tr>
<td>Kidney</td>
<td>22.5</td>
<td>11.3, 33.6</td>
<td>16</td>
<td>4.1</td>
<td>3.9</td>
<td>2.2, 6.3</td>
</tr>
<tr>
<td>Melanoma‡</td>
<td>48.4</td>
<td>26.0, 70.8</td>
<td>21</td>
<td>10.2</td>
<td>2.1</td>
<td>1.3, 3.2</td>
</tr>
</tbody>
</table>

* Breast: International Classification of Diseases for Oncology (ICD-O) site codes C50.0–C50.9 (59% were histologic code 8500 for duct/intraductal carcinoma, not otherwise specified); endometrium: ICD-O codes C54.1 and C54.9 (57% were histologic code 8380 for endometrial adenocarcinoma, not otherwise specified; and 36% were histologic code 8140 for adenocarcinoma, not otherwise specified); ovary: ICD-O code C56.9 (38% were histologic code 8460 for papillary serous cystadenocarcinoma; and 23% were histologic code 8260 for papillary adenocarcinoma, not otherwise specified); lung and bronchus: ICD-O codes C34.0–C34.9 (60% were histologic code 8010 for carcinoma, not otherwise specified; or code 8140 for adenocarcinoma, not otherwise specified); colon excluding rectum: ICD-O codes C18.0–C18.9 (75% were histologic code 8140 for adenocarcinoma, not otherwise specified); kidney: ICD-O code C64.9 (69% were histologic code 8312 for renal cell carcinoma, not otherwise specified); melanoma of the skin: ICD-O codes C44.0–C44.9 and histologic codes 8720–8790 (52% were histologic code 8743 for superficial spreading melanoma, and 43% were histologic code 8720 for malignant melanoma, not otherwise specified). All sites excluded histologic codes 9590–9989.

† Includes all invasive cancers plus in situ bladder cancer.

‡ Invasive and in situ cutaneous melanoma among White women only.
TABLE 2. Observed cases, standardized incidence ratios, and 95% confidence intervals stratified by various factors for cancers of interest following papillary thyroid cancer, California women, 1988–1999

<table>
<thead>
<tr>
<th>Age (years) at thyroid cancer diagnosis</th>
<th>Breast Invasive</th>
<th>In situ</th>
<th>Kidney</th>
<th>Melanoma*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed no. of cases</td>
<td>Standardized incidence ratio</td>
<td>95% confidence interval</td>
<td>Observed no. of cases</td>
</tr>
<tr>
<td>&lt;45</td>
<td>21</td>
<td>0.9</td>
<td>0.6, 1.4</td>
<td>4</td>
</tr>
<tr>
<td>45–69</td>
<td>40</td>
<td>0.8</td>
<td>0.6, 1.1</td>
<td>17</td>
</tr>
<tr>
<td>≥70</td>
<td>17</td>
<td>1.3</td>
<td>0.8, 2.1</td>
<td>2</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57</td>
<td>0.9</td>
<td>0.7, 1.2</td>
<td>15</td>
</tr>
<tr>
<td>Black</td>
<td>2</td>
<td>0.7</td>
<td>0.1, 2.5</td>
<td>1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13</td>
<td>1.4</td>
<td>0.7, 2.3</td>
<td>2</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>6</td>
<td>0.7</td>
<td>0.3, 1.5</td>
<td>5</td>
</tr>
<tr>
<td>Follow-up time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–11 months</td>
<td>13</td>
<td>1.0</td>
<td>0.5, 1.7</td>
<td>3</td>
</tr>
<tr>
<td>1–2.9 years</td>
<td>17</td>
<td>0.7</td>
<td>0.4, 1.1</td>
<td>10</td>
</tr>
<tr>
<td>3–4.9 years</td>
<td>27</td>
<td>1.4</td>
<td>0.9, 2.0</td>
<td>4</td>
</tr>
<tr>
<td>≥5 years</td>
<td>21</td>
<td>0.7</td>
<td>0.5, 1.1</td>
<td>6</td>
</tr>
<tr>
<td>Radiation treatment†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>0.7</td>
<td>0.3, 1.2</td>
<td>2</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>0.8</td>
<td>0.4, 1.5</td>
<td>4</td>
</tr>
</tbody>
</table>

* Invasive and in situ cutaneous melanoma among White women only.
† Analysis restricted to papillary thyroid cancer patients followed for 5 or more years after diagnosis.
DISCUSSION

In this large, diverse, population-based cohort of over 10,000 women with papillary thyroid cancer, no overall increased incidence of second primary malignancies was observed nor was invasive breast cancer more common among these women than California women in general. However, thyroid cancer patients were more likely than other California women to be diagnosed with in situ breast cancer, kidney cancer, and melanoma. In addition, non-White women with papillary thyroid cancer were more likely to develop lung cancer than were White women.

Unlike most previous studies (14–20), our study did not demonstrate an increased incidence of invasive breast cancer among thyroid cancer patients. Several of the previous studies have shown this increased risk to be limited to or stronger in younger women (i.e., under the age of 40, 50, or 55 years at the time they were diagnosed with thyroid cancer) (14, 15, 17, 20). This finding suggests the possibility of a heritable component due to the young age of the affected women. Alternately, for women diagnosed after the mid-1980s, this finding may reflect the influence of medical surveillance (i.e., the earlier diagnosis of breast cancers due to the initiation of mammographic screening). Although we did not find an increased incidence of subsequent invasive breast cancer in our population diagnosed during the late 1980s and 1990s, we did find an increased risk of in situ breast cancer. To our knowledge, the present study is the first to examine the risk of in situ breast cancer among thyroid cancer patients. Consistent with the medical surveillance hypothesis, the subgroups at greatest risk for a subsequent in situ breast cancer were women aged 45–69 years at the time of thyroid cancer diagnosis (i.e., those most likely to undergo mammographic screening) and women 1–3 years post-thyroid cancer diagnosis (i.e., the period during which this screening might be most likely to be initiated). However, these subgroup differences were not statistically significant in the present investigation. Further examination in a single study of the reciprocal associations between thyroid cancer and both in situ and invasive breast cancer during the periods preceding and subsequent to the introduction of widespread mammographic screening would be most useful in clarifying the role of mammography in the relation between these two cancers. Such an analysis is possible only by use of the Surveillance, Epidemiology, and End Results Program, Scandinavian, or other cancer registries with long-term, high-quality data. However, screening is likely to be responsible for at least a portion of the pattern of results observed, it does not negate the possibility of a shared etiologic component between breast cancer and thyroid cancer. Associations between the two types of tumors were observed prior to the onset of widespread mammographic screening, and several studies have observed a reciprocal risk of thyroid cancer following invasive breast cancer (13, 17, 21). To improve understanding of this relation, future studies of these associations should examine not only the effects by calendar year but also the histologic type, size, and estrogen-receptor status of the breast cancers. Interpretation of findings should consider not only medical surveillance but also common genetic and hormonal factors.

Consistent with other studies (11, 17–19), our study found a fourfold increased incidence of kidney cancer among papillary thyroid cancer patients. The reason for this increased risk is not clear, although most studies, including our own, suggest that it is not related to exposure to radiation-based treatment, since risk is equally high or higher among thyroid cancer patients not receiving any type of radiation therapy compared with those receiving such therapy (11, 17, 18). In addition, risk is consistently increased over an extended period of follow-up, making it unlikely that this association simply reflects increased medical surveillance. Thus, these two types of cancer may share one or more common etiologic factors. Obesity increases the risk of both thyroid and kidney cancers (1, 23–29), while vegetable consumption decreases the risk for both (9, 27, 30–33). However, it is unlikely that either of these factors alone or in combination accounts for the observed patterns of multiple primary clustering. Indeed, the lack of an association between thyroid and endometrial cancer, which is strongly associated with obesity (34), argues against obesity as the responsible link between thyroid and kidney cancers. In addition, other environmental and demographic characteristics for the two tumors differ. Smoking increases the risk of kidney cancer, while it is associated with a reduced risk of thyroid cancer (23, 26, 27, 29, 35–39). Kidney cancer is more common in men (possibly related to the greater smoking prevalence in men), while thyroid cancer is three times more common in women (suggesting an important hormonal component). In the United States, the incidence of kidney cancer is highest in African Americans, but thyroid cancer is very rare in this population (2, 27). Recent studies, however, have implicated possible genetic links between these two relatively rare tumors. Malchoff et al. (40) identified a distinct inherited tumor syndrome characterized as the familial association of papillary thyroid cancer, nodular thyroid disease, and papillary renal neoplasia. Cybulski et al. (41) showed that mutations in the \(e\)CHK2\(e\) gene, which plays a role in DNA repair in many cell types, were found to be associated with thyroid, breast, and kidney cancers (among others). Kamiya et al. (42) found an association between mutations in thyroid hormone nuclear receptor genes and renal clear cell carcinoma. These results offer promising leads for finally understanding the persistent epidemiologic association between these two cancers.

The twofold increased incidence of melanoma following papillary thyroid cancer observed in the present study is consistent with that of a pooled analysis of three European cohorts (SIR = 2.5, 95 percent CI: 1.6, 3.7) (18). Other studies, however, have not observed such an association (11, 17, 19). A shared environmental etiology is unlikely for these two cancers, because the primary risk factors for melanoma are excessive sun exposure and a history of severe sunburn (43). Several studies have observed mutations in the \(BRAF\) gene in a large portion of melanoma cases (44, 45), as well as a substantial portion of papillary (but not follicular) thyroid cancers (46–53). Intrigued by this possible association, we calculated the standardized incidence ratio for melanoma among 1,105 women with follicular thyroid cancer. The similarity between the melanoma standardized incidence ratios for the two histologic types of
thyroid cancer (papillary: SIR = 2.1, 95 percent CI: 1.3, 3.2; follicular: SIR = 2.5, 95 percent CI: 0.5, 7.3) does not support a shared etiology related to BRAF, if BRAF mutations are truly not present in follicular thyroid tumors. Thus, the most likely explanation, at present, for any relation between these two tumors remains increased medical surveillance, as suggested by the excess incidence of melanoma in the first 5 years after the thyroid cancer diagnosis, being highest within the first year.

The major strengths of this study include the large, diverse, population-based cohort of female thyroid cancer patients available for study and the high-quality data and complete statewide coverage of incident cancers in California. Limitations of the study include the small number of second primary cases at several of the sites and within some of the subgroups of interest, despite the relatively large size of the cohort, and the lack of data with which to examine historical time trends (since the California Cancer Registry was established in 1988, earlier statewide data were not available). A final limitation, as with all cancer registry-based analyses, was the limited confounder data available on individuals. The most informative future studies will be those that are designed to overcome this limitation.

In summary, increased surveillance for early breast cancer, kidney cancer, and melanoma among women with thyroid cancer is warranted, as papillary thyroid cancer patients are at increased risk for these subsequent tumors. Further examination of the connections between these cancers and papillary thyroid cancer may well improve our understanding of the etiology of these diseases.

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The ideas and opinions expressed herein are those of the authors, and endorsement by the California Department of Health Services or the National Cancer Institute is not intended nor should be inferred.

Conflict of interest: none declared.

REFERENCES