The Breast–Thyroid Cancer Link: A Systematic Review and Meta-analysis

Sarah M. Nielsen1, Michael G. White2, Susan Hong3, Briseis Aschebrook-Kilfoy4, Edwin L. Kaplan2, Peter Angelos2, Swati A. Kulkarni5, Olufunmilayo I. Olopade1, and Raymon H. Grogan2

Abstract

Rates of thyroid cancer in women with a history of breast cancer are higher than expected. Similarly, rates of breast cancer in those with a history of thyroid cancer are increased. Explanations for these associations include detection bias, shared hormonal risk factors, treatment effect, and genetic susceptibility. With increasing numbers of breast and thyroid cancer survivors, clinicians should be particularly cognizant of this association. Here, we perform a systematic review and meta-analysis of the literature utilizing PubMed and Scopus search engines to identify all publications studying the incidence of breast cancer as a secondary malignancy following a diagnosis of thyroid cancer or thyroid cancer following a diagnosis of breast cancer. This demonstrated an increased risk of thyroid cancer as a secondary malignancy following breast cancer [OR = 1.55; 95% confidence interval (CI), 1.44–1.67] and an increased risk of breast cancer as a secondary malignancy following thyroid cancer (OR = 1.18; 95% CI, 1.09–1.26). There is a clear increase in the odds of developing either thyroid or breast cancer as a secondary malignancy after diagnosis with the other. Here, we review this association and current hypothesis as to the cause of this correlation.

Introduction

With increased survival following improvements in the diagnosis and treatment of various malignancies, the rates of secondary cancers have increased in recent years. To date, secondary malignancies comprise approximately 18% of all cancers in the United States (1). Regardless of whether this effect is due to common risk factors, sequelae of radiation or chemotherapy, or genetic predisposition, survivors of breast and thyroid cancer have higher rates of developing the other as a secondary malignancy than those observed in the general population (2–7).

The most common endocrine malignancy, differentiated thyroid cancer, has increased in incidence worldwide over the last three decades—nearly 3-fold in the United States (8, 9). Similarly, breast cancer is the most commonly diagnosed malignancy in women. With an overall favorable prognosis for the majority of breast and thyroid cancers, greater attention is being paid to improving quality of life and screening for secondary malignancies in these groups of survivors. As our understanding of the association between thyroid and breast cancer improves and more of these women live longer, the increase in risk of a second malignancy is becoming increasingly important to clinicians.

Despite large national and multinational cohorts of breast and thyroid cancer survivors being described, the existence and exact magnitude of an increased risk for breast or thyroid cancer as secondary malignancy following a diagnosis for the other is yet to be defined. Here, we perform a meta-analysis to verify and quantify this suggested increased rate of secondary malignancies in both groups of cancer survivors. In addition, we undertook a review of the literature to describe the proposed mechanisms of any increase in breast and thyroid cancer risk as secondary malignancies following each other.

Materials and Methods

This review includes English-language studies from 1966, the year when the breast–thyroid cancer association was first published, through 2015. Electronic searches of the PubMed and Scopus databases were queried for articles containing the terms “BREAST” and “THYROID” and “SECOND” or “SECONDARY” and “MALIGNANCY” titles including “METASTATIC” were excluded on initial database search. These articles were hand reviewed by two independent reviewers and bibliographies of selected publications reviewed for additional sources. The final data were reviewed by all authors for accuracy. The most recent publication representing the largest number of described patient-years of follow-up was utilized in instances in which the same database or patient cohort in overlapping time periods was described. This systematic review is summarized in Fig. 1. Number of observed and expected secondary malignancies were reported or calculated from available studies and used to calculate ORs for...
the development of secondary malignancies for each study. Meta-analysis of the data was performed using Stata (Version 13; ref. 10).

Results

After review, 19 unique cohorts of breast cancer patients were identified. These studies and associated standardized incidence ratios are summarized in Table 1. Meta-analysis of the OR of developing thyroid cancer after a diagnosis of breast cancer is summarized in Fig. 2. Although the general population would be projected to have an OR of 1.0, breast cancer survivors have an increased risk of developing thyroid cancer after a diagnosis of breast cancer (OR = 1.55; 95% CI, 1.44–1.67). This analysis describes follow-up of 956,672 breast cancer patients and 611 secondary thyroid cancers (6, 11–28).

Eighteen unique cohorts of thyroid cancer patients were identified. These studies and associated standardized incidence ratios are summarized in Table 2. Meta-analysis of the OR developing breast cancer after a diagnosis of thyroid cancer is summarized in Fig. 3. Although the general population would be projected to have an OR of 1.0, thyroid cancer survivors have an increased risk of developing breast cancer (OR = 1.18; 95% CI, 1.09–1.26). This analysis included 44,879 thyroid cancer patients and 5,791 secondary breast cancers (22, 24, 29–44).

Discussion

There is a large amount of data that have been accumulated on the possible link between breast and thyroid cancer; however, before our study it has been difficult to clearly identify whether or not a link between breast and thyroid cancer truly exists, and in which direction. Our meta-analysis confirms and quantifies the existence of the increased co-occurrence of breast and differentiated thyroid cancer. Although we were unable to quantify the time to diagnosis of these secondary malignancies due to heterogeneity in the studies, the significant increase in risk is bidirectional, and suggests that surveillance bias alone cannot explain the link entirely, and there is likely a pathophysiologic risk. In order to understand this possible pathophysiologic cause of this link, we have included an extensive review of the current hypotheses for this increase in risk. We hope that the combination of this meta-analysis and literature review will open up new directions of study for this important group of patients.

Table 1. Standardized incidence ratios of thyroid cancer after breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Location(s)</th>
<th>Study period</th>
<th>Mean follow-up period (y)</th>
<th>Cases (n)</th>
<th>BC</th>
<th>TC</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molina-Montes 2013</td>
<td>Spain</td>
<td>1985–2007</td>
<td>6.4</td>
<td>5,897</td>
<td>8</td>
<td>1.01</td>
<td>(0.02–2.01)</td>
</tr>
<tr>
<td>Mellemkjær 2006</td>
<td>Denmark, Finland, Norway</td>
<td>1943–2006</td>
<td>8.8</td>
<td>304,703</td>
<td>347</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Lee 2008</td>
<td>Taiwan</td>
<td>1979–2003</td>
<td>5.4</td>
<td>59,001</td>
<td>45</td>
<td>1.42</td>
<td>(1.04–1.90)</td>
</tr>
<tr>
<td>Kirova 2008</td>
<td>France</td>
<td>1988–1997</td>
<td>10.5</td>
<td>16,705</td>
<td>20</td>
<td>0.87</td>
<td>(0.55–1.35)</td>
</tr>
<tr>
<td>Raymond 2006</td>
<td>USA (SEER)</td>
<td>1973–2000</td>
<td>NA</td>
<td>335,191</td>
<td>314</td>
<td>2.23</td>
<td></td>
</tr>
<tr>
<td>Mellemkjær 2006</td>
<td>Europe, Canada, Australia, Singapore</td>
<td>1943–2000</td>
<td>7.2</td>
<td>525,527</td>
<td>471</td>
<td>1.62</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Location(s)</th>
<th>Study period</th>
<th>Mean follow-up period (y)</th>
<th>Cases (n)</th>
<th>BC</th>
<th>TC</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soerjomataram 2005</td>
<td>Netherlands</td>
<td>1972–2000</td>
<td>6.6</td>
<td>9,919</td>
<td>2</td>
<td>0.8</td>
<td>(0.1–3.3)</td>
</tr>
<tr>
<td>Sadetzki 2003</td>
<td>Israel</td>
<td>1960–1998</td>
<td>7.3</td>
<td>49,207</td>
<td>59</td>
<td>1.34</td>
<td>(1.05–1.72)</td>
</tr>
<tr>
<td>Levi 2003</td>
<td>Switzerland</td>
<td>1974–2998</td>
<td>6.4</td>
<td>9,729</td>
<td>6</td>
<td>1.01</td>
<td>(0.37–2.20)</td>
</tr>
<tr>
<td>Tanaka 2001</td>
<td>Japan</td>
<td>1970–1994</td>
<td>8.6</td>
<td>2,786</td>
<td>7</td>
<td>3.7</td>
<td>(1.5–7.6)</td>
</tr>
<tr>
<td>Huang 2001</td>
<td>Canada</td>
<td>1973–1993</td>
<td>6.8</td>
<td>194,798</td>
<td>140</td>
<td>1.2</td>
<td>(1.0–1.4)</td>
</tr>
<tr>
<td>Evans 2001</td>
<td>England</td>
<td>1961–1995</td>
<td>5.7</td>
<td>145,677</td>
<td>57</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>Rubino 2000</td>
<td>France</td>
<td>1973–1992</td>
<td>9.5</td>
<td>4,464</td>
<td>4</td>
<td>2.2</td>
<td>(0.7–5.2)</td>
</tr>
<tr>
<td>Volk 1997</td>
<td>Slovenia</td>
<td>1961–1985</td>
<td>7.3</td>
<td>8,791</td>
<td>10</td>
<td>2.5</td>
<td>(1.2–4.6)</td>
</tr>
<tr>
<td>Doherty 1993</td>
<td>Scotland</td>
<td>1954–1964</td>
<td>18</td>
<td>3,926</td>
<td>4</td>
<td>2.33</td>
<td>(0.63–5.95)</td>
</tr>
<tr>
<td>Murakami 1987</td>
<td>Japan</td>
<td>1965–1982</td>
<td>5.7</td>
<td>9,503</td>
<td>9</td>
<td>3.2</td>
<td>(1.5–6.1)</td>
</tr>
<tr>
<td>Teppo 1985</td>
<td>Finland</td>
<td>1954–1979</td>
<td>NA</td>
<td>26,677</td>
<td>22</td>
<td>1.95</td>
<td></td>
</tr>
<tr>
<td>Harvey 1985</td>
<td>USA</td>
<td>1935–1982</td>
<td>6.6</td>
<td>41,109</td>
<td>28</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Schenker 1984</td>
<td>Israel</td>
<td>1960–1977</td>
<td>NA</td>
<td>12,302</td>
<td>33</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BC, breast cancer; CI, confidence interval; n, number of cases (studies with n < 1,000 excluded); NA, data not available; TC, thyroid cancer; y, years.
It should be noted, however, that although thyroid cancer-specific screening leads to increased rates of detection, the same does not appear to be true for screening for other types of malignancies and incidental thyroid nodules are only rarely reported on routine cross-sectional imaging studies (47, 48).

Despite a clear correlation between nonthyroid or breast screening and increased diagnosis and lack of directed screening for breast or thyroid cancer in survivors of the other, it is possible that

Table 2. Standardized incidence ratios of breast cancer after thyroid cancer

<table>
<thead>
<tr>
<th>Study Location(s)</th>
<th>Study period</th>
<th>Mean follow-up (y)</th>
<th>Cases (n)</th>
<th>BC</th>
<th>TC</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lis 2013 (44)</td>
<td>Taiwan</td>
<td>1976–2006</td>
<td>7</td>
<td>102</td>
<td>19,068</td>
<td>1.42 (1.16–1.72)</td>
</tr>
<tr>
<td>Kim 2013 (43)</td>
<td>U.S.A</td>
<td>1973–2008</td>
<td>NA</td>
<td>1,041</td>
<td>52,103</td>
<td>1.13 (1.06–1.20)</td>
</tr>
<tr>
<td>Mellemkjaer 2006 (24)</td>
<td>Europe, Canada, Australia, Singapore</td>
<td>1943–2000</td>
<td>NA</td>
<td>552</td>
<td>NR</td>
<td>1.31 (1.21–1.43)</td>
</tr>
<tr>
<td>Verkooijen 2006 (41)</td>
<td>Netherlands</td>
<td>1985–1999</td>
<td>10.6</td>
<td>5</td>
<td>282</td>
<td>1.52 (0.46–3.18)</td>
</tr>
<tr>
<td>Berthe 2005 (40)</td>
<td>France</td>
<td>1960–1998</td>
<td>8</td>
<td>12</td>
<td>875</td>
<td>1.19 (0.62–2.08)</td>
</tr>
<tr>
<td>Rubino 2003 (39)</td>
<td>France, Italy, Sweden</td>
<td>1934–1995</td>
<td>13</td>
<td>128</td>
<td>6,841</td>
<td>1.5 (1.0–1.5)</td>
</tr>
<tr>
<td>Adadji 2003 (38)</td>
<td>France</td>
<td>1934–1955</td>
<td>12</td>
<td>48</td>
<td>2,365</td>
<td>1.3 (1.0–1.7)</td>
</tr>
<tr>
<td>Sadetzki 2003 (22)</td>
<td>Israel</td>
<td>1960–1998</td>
<td>9.4</td>
<td>4,911</td>
<td>70</td>
<td>1.07 (0.84–1.34)</td>
</tr>
<tr>
<td>Hennemajeni 2001 (37)</td>
<td>Sweden</td>
<td>1958–1996</td>
<td>NA</td>
<td>113</td>
<td>19,281</td>
<td>1.1 (0.8–1.2)</td>
</tr>
<tr>
<td>Edhemovic 1999 (36)</td>
<td>Slovenia</td>
<td>1971–1993</td>
<td>5.2</td>
<td>4</td>
<td>894</td>
<td>1.12 (0.31–2.87)</td>
</tr>
<tr>
<td>Duttarini 1995 (35)</td>
<td>Italy</td>
<td>1960–1993</td>
<td>8</td>
<td>10</td>
<td>694</td>
<td>2</td>
</tr>
<tr>
<td>Glanzman 1992 (34)</td>
<td>Switzerland</td>
<td>1960–1988</td>
<td>14.5</td>
<td>5</td>
<td>298</td>
<td>1.9 (0.6–4.5)</td>
</tr>
<tr>
<td>Hall 1991 (33)</td>
<td>Sweden</td>
<td>1950–1975</td>
<td>16</td>
<td>24</td>
<td>1,955</td>
<td>1.46</td>
</tr>
<tr>
<td>Osterlind 1985 (30)</td>
<td>Denmark</td>
<td>1943–1980</td>
<td>5.9</td>
<td>11</td>
<td>1351</td>
<td>0.96 (0.76–1.20)</td>
</tr>
<tr>
<td>Ron 1984 (29)</td>
<td>USA</td>
<td>1935–1978</td>
<td>8</td>
<td>24</td>
<td>1618</td>
<td>1.89</td>
</tr>
</tbody>
</table>

Abbreviations: BC, breast cancer; CI, confidence interval; n, number of cases (studies with n < 1,000 excluded); NA, data not available; TC, thyroid cancer; y, years.

*Unreported number of initial thyroid cancer, unable to include in meta-analysis.
this increase in surveillance or improved compliance is responsible for higher rates of detection of secondary malignancies.

The role of hormones

The development of both breast and thyroid cancer has been shown to be affected by hormonal risk factors. Hormonal factors have therefore been hypothesized as a source of the high rates of co-occurrence of these cancers. Often associated with breast cancer development, estrogen, progesterone, and androgen receptors have been shown to be expressed on both normal and malignant thyroid tissue, with neoplastic thyroid tissue having higher receptor levels than normal thyroid tissue (49). This has resulted in the hypothesis that these receptors play a role in thyroid cancer carcinogenesis and increased rates of co-occurrences of these cancers. This hypothesis has been tested in studies involving animal and human thyroid cancer cell lines where estradiol was shown to promote thyroid tumorigenesis and progression (49–51). Estrogens also appear to stimulate the secretion of thyroid-stimulating hormone (TSH), a known thyroid growth factor which has been shown to be higher among thyroid cancer patients (52).

Although established hormonal risk factors for breast cancer have been studied in thyroid cancer, many of these studies are conflicting and many failed to stratify by thyroid cancer type. More recently, evidence suggests that the increased risk for subsequent thyroid cancer seen among breast cancer survivors is specific for papillary thyroid cancer (7). Pooled analysis of 14 case–control studies conducted between 1980 and 1997 evaluated menstrual and reproductive factors in relation to thyroid cancer risk. Positive associations were seen between menstrual and reproductive factors and papillary thyroid cancer risk, especially for women diagnosed at a younger age (53). In addition, evaluating breast cancer risk in a cohort of thyroid cancer patients, multiparity was found to have a protective effect on the development of a primary breast cancer while multiparity was associated with higher rates of subsequent breast cancer (42). Demonstration of this association suggests that the same hormonal risk factors for the development of a primary breast cancer play a role in the development of breast cancer after thyroid cancer. Exposure to estrogens may not only increase the risk of the development of a primary cancer, but also appears to play a role in the development of either breast or thyroid cancer as a secondary malignancy.

Although serum TSH levels have been shown to correlate with rates of primary thyroid cancers, TSH has also been hypothesized to facilitate breast carcinogenesis, both independently and in combination with estrogen (52, 54, 55). In vitro studies demonstrate that thyroid hormones, particularly T3, can be important in breast cancer initiation and progression, through interactions with the estrogen signaling systems as well as mimicking or enhancing the effects of estrogen on breast cancer proliferation (55). It has been hypothesized that exposure to TSH may play a role in the development of both breast and thyroid cancer as primary and secondary malignancies.

Finally, obesity has been noted to be a risk factor for the development of both breast and thyroid cancer as primary malignancies (56–59). In the absence of significant weight loss, these
patients will remain at increased risk for the development of a secondary malignancy. This is reflected in increased rates of secondary malignancies in obese patients (60, 61). Although a number of hormonal pathways have been suggested as possible mechanisms of this observed interaction, none have been conclusively determined.

Radiation exposure
In the 1930s and 1940s, low-dose external beam radiation to the head, neck, or chest was a common treatment for a number of benign conditions including tinea capitis, acne, tonsillitis, enlarged thymus, and postpartum mastitis. Among these individuals, an increased frequency of thyroid and breast cancer years later was observed (62, 63). Prior mantle field radiation for the treatment of Hodgkin's lymphoma in childhood or adolescence also increases the risk for both breast and thyroid cancers (64, 65). Similarly, victims of exposure to ionizing radiation such as Chernobyl, Hiroshima, and Nagasaki have significantly elevated rates of thyroid and breast cancer, particularly if exposed in childhood (66, 67). A history of external or ionizing radiation is now a well-established risk factor for the development of both breast and thyroid cancers. The role of a common DNA repair pathway involved in the pathogenesis of breast and thyroid cancer has been hypothesized but is yet to be identified.

External Beam Radiation to the Breast and the Risk of Thyroid Cancer

Improvements in adjuvant therapy, combined with better screening and surveillance, has resulted in a higher proportion of early-stage breast cancer and an increase in breast cancer survivors. Early-stage breast cancer is typically managed with breast-conserving surgery and postoperative radiation therapy (RT). Following treatment, breast cancer survivors are at a 10% to 50% greater risk of developing a non-breast second primary cancer as compared with the general population (17). Although some of these second cancers may be sporadic, others may be iatrogenic. Despite improvements in radiation techniques over the past 60 years, minimizing the total radiation exposure to adjacent normal tissues, radiation scatter, and subsequent cancer risk still exists. Thus among cancer survivors, the long-term effects of therapies such as RT is particularly relevant.

Cancers such as lung, esophageal, sarcomas, and hematologic malignancies are strongly associated with RT for prior breast cancer (68). Few studies, however, have specifically evaluated second primary thyroid cancers as a consequence of RT for breast cancer. Two studies examining this association used Cancer Registry and SEER data (2, 19). Both showed no significant increase in thyroid cancer risk. In fact the subsequent thyroid cancer risk was more consistently elevated in the non-RT cohorts. Although some earlier studies suggest that RT for breast cancer significantly increased the risk of a subsequent thyroid cancer, the majority of later studies demonstrated either a modest association or none at all (2, 3, 7, 12, 14, 22, 29, 38, 69–71). Furthermore, higher doses of radiation during breast cancer treatment [<10 grays (Gy) vs. >10 Gy] did not appear to influence this risk (38). In positive correlation studies, increased risk following RT for breast cancer did not persist past 60 months (7). Because typical latency periods of thyroid cancer after radiation exposure are 20 to 30 years, and data on latency periods are conflicting, the effect of radiation treatment alone is unlikely to explain the association between these two malignancies (72).

On the basis of these studies, the risk for radiation-induced thyroid cancer following treatment for breast cancer is likely negligible but requires further evaluation. Special surveillance of the thyroid gland is not currently recommended for breast cancer survivors. In addition, management of thyroid nodules in women with a prior history of breast cancer should not be solely influenced by prior radiation treatment for breast cancer (19).

Radioactive Iodine for Thyroid Cancer and the Risk of Breast Cancer

Radioactive iodine (RAI) has been used as an adjuvant treatment after surgical resection of thyroid cancer since the 1940s. RAI acts to ablate residual thyroid tissue, positive unrectsed cervical lymph nodes, and/or distant metastases. Concern about the potential carcinogenic effects of RAI is greatest in organs that concentrate or eliminate iodine or are on the therapeutic route of administration. These organs include the salivary gland, stomach, small intestine, bladder, and bone marrow (73). The mammary gland has the same sodium-iodine symporter as the thyroid gland thus may also be able to concentrate iodine (42). Lactating breast tissue and breast tissue with atypia or malignancy show an increase in RAI uptake (74). However, 131I whole body scanning does not suggest that quiescent breast tissue concentrates significant levels of iodine. Thus the RAI dose delivered to the breast during thyroid cancer treatment is expected to be low (31, 74). A role for RAI in breast carcinogenesis cannot, however, be ruled out.

Most cohort studies examining the risk of breast cancer following RAI treatment for thyroid cancer have failed to find a strong association with RAI treatment (35, 40, 41, 75, 76). A pooled analysis of three of these studies was conducted in 2003. By measuring the cumulative RAI activity as a time-dependent covariate, the investigators were able to assess the role of RAI. Although a 30% overall increased risk for a second primary breast cancer was seen among thyroid cancer patients, when risk was stratified by RAI exposure and dose, risk was actually higher in the non-RAI cohort (39).

Larger scale studies using SEER data are consistent with the previous findings. The risk of breast cancer following thyroid cancer was significantly elevated in both RAI and non-RAI cohorts, and often higher in the non-RAI cohort (2, 3, 38, 39, 71, 77–79). Some studies show a protective effect with higher absorbed doses of RAI for breast cancer risk (17, 38, 39, 75, 77). Thus there appears to be no significant dose-effect relationship of RAI on breast cancer risk.

Genetic susceptibility
In 1994, Goldgar and colleagues published their study examining cancer risk among first- degree relatives of probands with a cancer history. Excess thyroid cancer rates were seen among first-degree relatives of probands with breast cancer, and vice versa (80). This observation suggested that a possible germline mutation could be involved in the breast and thyroid cancer clusters.

Cowden syndrome (CS) is currently the only tumor syndrome known to increase the risk of developing both breast and differentiated thyroid cancer in the same individual (81). The most common cause of CS is a germline mutation in the tumor suppressor gene, PTEN. A recent study highlighted the propensity for second primary malignancies in individuals with PTEN
mutations, with breast and thyroid cancer representing the most significant risks (SIR = 8.92 for breast cancer and 5.83 for thyroid cancer; ref. 81). Therefore, it is important to remember that CS is responsible for an important albeit small proportion of cases of breast and thyroid cancer and should be evaluated for accordingly in these individuals.

More recently, mutations in the tumor suppressor genes, succinate dehydrogenase (SDHx) and KLLN, have been shown to cause CS and Cowden-like syndrome (CLIS). SDH is comprised of four subunits (SDHA, B, C and D) that encode mitochondrial complex II of the electron transport chain in the Kreb’s cycle. In a study cohort of breast, thyroid, and kidney cancers, done in 2012, germline mutations in SDHx were present in 8% of PTEN mutation-negative CS and CSL individuals. Furthermore, co-occurrence of SDHx variants and PTEN mutations in the same individual was found to confer a significantly higher risk of breast cancer compared with individuals with mutations in either SDHx or PTEN alone. In contrast, thyroid cancer prevalence was highest among individuals with SDHx variants alone (82). It is important to note that the association between SDHx variants and increased breast cancer risk has not been observed in all studies (83).

The KLLN gene has also emerged as an important cause and phenotypic modulator of CS and CLIS. KLLN encodes the protein KILLIN, which shares the same chromosomal location (10q23.3), transcription start site, and role in cell-cycle arrest as PTEN. Recent estimates suggest an estimated 30% of CS/CSL individuals without PTEN or SDHx mutations will have KLLN germline epigenetic inactivation of the KLLN promoter. Compared with PTEN mutation carriers, these individuals may have a 2- to 3-fold increased risk of breast and/or papillary renal cancer (84). Thus it is also possible that individuals with both SDHx and KLLN alterations may have an increased risk for papillary thyroid cancer (85).

Beyond PTEN/SDHx/KLLN, there is currently little evidence implicating other genes for individuals and families with breast and thyroid cancer clusters. However, as more extensive genetic sequencing is brought into clinical practice, it is likely that new variants and mutations will continue to be identified. Whether or not the vast majority of breast and thyroid cancer patients will turn out to have an identified or yet to be identified mutation remains to be seen. Complete exome sequencing of patients with both breast and thyroid cancers may help elucidate new disease-causing mutations and modifiers of risk in this unique population of patients.

Summary

Women with a prior history of differentiated thyroid cancer are at an increased risk for breast cancer. Furthermore, women with a history of breast cancer are at an increased risk for differentiated thyroid cancer. Despite sometimes conflicting results as to the magnitude and significance of this risk, the above meta-analysis demonstrates a clear association and increase in co-occurrence of these two malignancies. Although further studies are needed, clinicians should consider the increase in risk for second primary cancers when caring for these individuals.

The U.S. Preventative Services Task Force (USPSTF) currently recommends women begin biennial screening mammograms at age 50. For women between 40 and 50 years old, USPSTF recommends discussing the risks versus benefits of screening mammograms (86). Women with a previous history of thyroid cancer appear to be at an increased risk for breast cancer, perhaps via genetic susceptibility, a common receptor pathway, or both. Thus these women should be managed accordingly. For women with a history of thyroid cancer without breast cancer risk factors, a conservative but reasonable surveillance strategy would include initiating screening mammography at age 40. Whether or not these women require earlier more aggressive surveillance such as annual breast MRIs in addition to mammograms remains to be seen.

Although clinicians should be aware of this association in caring for thyroid and breast cancer survivors, the cause of this increase in risk remains unclear. Although surveillance bias is a possible explanation in two indolent malignancies, there is not direct screening in cancer survivors that would explain this increase in risk. This leads one to suspect a pathophysiologic reason for this increase in risk. A number of cell line and clinical studies suggest a common hormonal receptor pathway involving estrogen and/or TSH (42, 49–60). Similarly, obese women with breast cancer have higher rates of subsequent thyroid cancers. As obesity correlates with higher levels of circulating estrogen, this indirectly supports the possible role of a common receptor pathway (87). Furthermore, the association of obesity with breast cancer is strongest in estrogen receptor/progesterone receptor-positive tumors (58). Although further work is needed to correlate thyroid cancer rates and breast cancer hormone receptor status, clinicians should counsel their patients on the increased risk of thyroid cancers among breast cancer survivors and reinforce the importance of achieving (and maintaining) an ideal body weight.

Similarly, shared genetic susceptibility is likely to explain a portion of the higher rates of second primary cancers seen among breast and thyroid cancer survivors. Individuals with a known genetic susceptibility are often diagnosed with primary cancer at younger ages. In population studies, both breast cancer after thyroid cancer and thyroid cancer after breast cancer rates were higher for women diagnosed at younger ages (2, 18, 24, 27, 38, 88). Thus it is possible that in a subset of the subsequent second cancers, these individuals have either an identified or yet unidentified mutation. Complete exome sequencing of patients with both breast and thyroid cancers may help elucidate new mutations and modifiers of risk. In the meantime, a careful and thorough family history can help identify individuals at risk for a known hereditary cancer predisposing syndromes.

The importance of the relationship between breast and thyroid cancer will continue to be evident as the incidence of thyroid cancers continues to rise and the treatments for both cancers continue to improve.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the NIH.

Grant Support

This work was funded by the Ralph and Marion Falk Medical Research Trust and the American Cancer Society (to O.I. Olopade). R.H. Grogan was supported by Award Number K12CA139160 from the National Cancer Institute.

Received August 4, 2015; revised October 20, 2015; accepted October 29, 2015; published online February 5, 2016.
References


The Breast–Thyroid Cancer Link: A Systematic Review and Meta-analysis

Sarah M. Nielsen, Michael G. White, Susan Hong, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/25/2/231

Cited articles
This article cites 86 articles, 13 of which you can access for free at:
http://cebp.aacrjournals.org/content/25/2/231.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/25/2/231.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.