

# A Linkage Between Thyroid and Breast Cancer: A Common Etiology?

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## Abstract

Breast and thyroid cancers are two malignancies with highest incidence in women. These cancers often occur metachronously. Women with thyroid cancer are at increased risk for subsequent breast cancer; women with breast cancer have an increased incidence of later development of thyroid cancer, suggesting a common etiology. This bidirectional relationship is reported worldwide; however, the underlying reasons for this co-occurrence are unknown. In this review, we summarize the current epidemiologic evidence and putative mechanisms of these metachronous or synchronous

cancers. Key potential causative factors are chemotherapy and radiotherapy of the primary tumor, genetic variants linking the two diseases, hormonal signaling both from the thyroid gland and from estrogens, and lifestyle and environmental factors. There is a critical need for additional epidemiologic studies focused on gender and regional incidence together with molecular investigations on common tumorigenic pathways in these endocrine cancers. Understanding the putative mechanisms will aid in the diagnosis and clinical management of both diseases.

## Introduction

Breast cancer is the most common cancer diagnosed in women in the United States with over 250,000 cases per year (1). Survivors of breast cancer are at increased risk of a second cancer, frequently thyroid cancer (2–4). Thyroid cancer, which also predominantly affects women, is of great concern as the incidence in the United States has more than tripled over the past decades, including the aggressive variants (5, 6). The higher incidence is not due to enhanced surveillance and advances in diagnostics; increases in tumors of all sizes as well as indolent and aggressive tumors are reported (7). Male thyroid cancer rates have doubled since 1975, whereas female rates have tripled (6). As 5-year survival rates after thyroid cancer are in excess of 90% (1) and the incidence of the disease is increasing, there are now more survivors of thyroid cancer than in the past. The risk of a subsequent second primary cancer, most often breast cancer, is increased for thyroid cancer survivors (3, 4, 8). Understanding health risks following treatment is critical for improving the public health.

Because of the rising incidence of thyroid cancer in the United States and globally (9), it is critical to understand the risk factors for thyroid cancer and long-term risks associated with the disease. Intriguingly, the increase in incidence can vary dramatically depending upon location (9). An increase in thyroid cancer incidence is most pronounced in Asia, particularly in South

Korea, as compared with other regions. Contributing factors likely include improved health care networks and surveillance, environmental influences, hereditary factors, radiation exposure, and lifestyle factors. Iodine deficiency is an important public health problem in several Asian countries (10), and has been linked to an increased chance of developing thyroid cancer, in addition to the increased risk of thyroidal disorders (reviewed in ref. 11).

In contrast to the global increase in thyroid cancer incidence, changes in breast cancer incidence vary globally. The U.S. incidence has been stable for the past few decades. Strikingly, in the 1980s, there was a 30% increase in female total breast cancer diagnoses, which is attributed to heightened surveillance (12). In China, breast cancer incidence has also increased; however, it is difficult to determine a precise figure due to the varying quality of studies (13). This may be a pattern similar to what was observed in the United States during the 1980s; the rise of breast cancer rates may be a result of China's rapid growth in recent decades and improvements to health care technology and access. Low- and middle-income nations, such as South American nations, have exhibited the greatest increase in incidence of breast cancer (12). This may also be due to changes in surveillance and a result of improvements in health care access and technology. Regardless, a myriad of factors may underlie the observed increase in breast cancer rates in some regions of the world and the cause is not yet clear.

Over the last 40 years, studies reveal compelling evidence of a bidirectional and potentially causative relationship between breast cancer and thyroid cancer. Women with breast cancer are at increased risk for developing thyroid cancer; survivors of thyroid cancer are more likely to develop breast cancer suggesting common etiologic features in the development of both tumor types (14). A metachronous relationship between thyroid and breast cancers has significant implications for clinical surveillance and management of both diseases. In addition, understanding the etiology of the second primary tumor is vital for the development of new preventive strategies, diagnostics, and therapeutics.

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## What Is the Epidemiologic Evidence of the Relationship between Breast and Thyroid Cancer?

In the past few years alone, population studies in Asia, Europe, and the United States reveal increased incidence of breast cancer among women previously diagnosed with thyroid cancer (15–21). Of note, aggressive follicular thyroid cancer is detected in patients with a history of breast cancer more often than the more common papillary thyroid cancer (18). Furthermore, and importantly for determining etiology, nonmalignant thyroid nodules are more common in women with breast cancer than those without breast tumors (19). There is an increased risk of developing thyroid cancer following breast cancer (16, 20). Women with prior benign breast disease also are reported to be at a greater risk of thyroid cancer (21). The increased risk of thyroid cancer following breast cancer and breast cancer following thyroid cancer is reported in both women and men (22). Women with breast cancer are 2-fold more likely to develop future thyroid cancer and women with thyroid cancer have a 67% greater chance of developing breast cancer than the general population. These recent studies are summarized in Table 1. Importantly, the metachronous relationship was evaluated in nations with widespread cancer screening and nations where screening is becoming more common. In particular, Zhang and colleagues evaluated patients with cancer between 2001 and 2010 in China, which corresponded with investments into cancer registries (17, 23).

The clinical characteristics of the initial and metachronous tumors exhibit distinctive features compared with nonmetachronous cancer patients. The metachronous breast tumors following thyroid cancer are more likely to be hormone receptor–positive than patients with breast cancer without this history (16). The metachronous thyroid tumors following breast cancer are smaller but more aggressive than the control population of females with thyroid cancer without a history of breast cancer. Metachronous thyroid cancer is also more common when the initial breast tumor was HER2-positive (24). Analysis of Surveillance, Epidemiology, and End Results data revealed patients who developed metachronous breast cancer following a thyroid tumor typically were diagnosed with breast cancer at a younger age than average and exhibited histologic features associated with hormone replacement therapy, implicating a potential role for estrogen (18).

These recent studies highlight the trends observed in prior research and meta-analyses (25, 26). Studies to date have primarily focused on metachronous cancer incidence in women as both cancers occur primarily in women (100:1 for breast and 4:1 for thyroid, female:male). Remarkably, the co-occurrence of these diseases is even greater in men. Men with a prior history of breast cancer are 19 times more likely to develop thyroid cancer. This link is bidirectional; men with prior thyroid cancer are 29 times more likely to develop breast cancer (22). Independent confirmation of the metachronous risk in male cases is needed. The epidemiologic linkage between thyroid cancer and breast cancer is bidirectional and data from patients collected globally has consistently demonstrated the metachronous relationship. However, larger studies are needed to increase confidence as to how much greater a risk there is of a second primary tumor as the various studies presented in this review do not report increased risk using the same parameters. Further research is needed to determine whether certain demographics are at greater risk, the role of socioeconomic factors, or whether there are geographic hotspots at greater risk of metachronous disease.

## What Genetic Factors Link the Diseases?

There is a strong familial component in the development of cancer. A recent, large study examining twins in the Nordic nations estimated heritability to be approximately 33% of cancer risk (27). There does appear to be some familial link between thyroid and breast cancer; a study on Swedish patients found that first-degree relatives of women diagnosed with breast cancer are at an increased risk of developing thyroid cancer (28). Similar results were observed in a U.S. population (29). Among other factors that could drive a familial association, genetics has potentially the greatest explanatory power in the link between breast tumors and thyroid tumors as many driver mutations are similar in both cancers. Cowden Syndrome is an already recognized genetic disorder, arising from mutations to the tumor suppressor *PTEN*, which increases the risk of both breast and thyroid cancer, among other cancers including endometrial and gastrointestinal (30, 31). *PTEN* encodes for phosphatase and tensin homolog (PTEN), which inhibits the catalytic activity of the enzyme PI3K (32). PI3K upregulates the downstream effector AKT, which then phosphorylates an array of proteins, ultimately changing gene

**Table 1.** Summary of studies linking breast and thyroid cancer incidence

Sex	Breast → thyroid	Increased risk breast → thyroid	Thyroid → breast	Increased risk thyroid → breast	Sample size
Female			Prinzi et al., 2013	15.24 OR	3,921
Female and male	Van Fossen et al., 2013	Female 2-Fold Male 19-Fold	Van Fossen et al., 2013	Female 1.67-Fold Male 29-Fold	74,650 (Breast) 15,940 (Thyroid)
Female	An et al., 2015	2.18 SIR	An et al., 2015	2.45 SIR	6,833 (Breast) 4,243 (Thyroid)
Female			Kuo et al., 2016	2.07–2.60 IRR (AD)	53,853
Female	Zhang et al., 2016	4.75 SIR	Zhang et al., 2016	2.40 SIR	18,732 (Breast) 12,877 (Thyroid)
Female	Jung et al., 2017	2.29 SIR			3,444
Female	Luo et al., 2017 <sup>a</sup>	1.38 HR			133,875
Female	Shi et al., 2017 <sup>b</sup>	2.5-Fold			4,189

NOTE: Only the studies published in the past 5 years (since 2013) are presented, organized by which cancer was the initial disease. Some studies explored the bidirectional relationship and are listed twice. Fold refers to the fold change of risk for the second tumor compared with people who do not have a history of the initial cancer. The sample size classifies patients based upon the site of the earlier cancer.

Abbreviations: AD, age-dependent; IRR, incidence rate ratio; SIR, standard incidence ratio.

<sup>a</sup>Luo and colleagues examined the benign breast disease rather than a breast malignancy.

<sup>b</sup>Shi and colleagues studied thyroid nodules, rather than thyroid cancer.

expression. The PI3K–AKT pathway promotes survival, proliferation, and migration to drive tumorigenesis. Cowden syndrome can also be worsened by co-mutations to *KLLN* and genes that make up the succinate dehydrogenase complex (*SDHx*; ref. 25). *KLLN* is a transcription factor that shares the *PTEN* promoter and upregulates *TP53* to promote apoptosis (33). *SDHx* mutations also dysregulate *TP53* through enhanced proteasomal degradation of p53 (34). Other genes that feed into the PI3K pathway and apoptosis may be involved in the link between thyroid and breast cancers.

In addition, germline mutations in *PARP4* were identified in women treated for both cancers (35). Heightened expression of *PARP4* also correlated with longer disease-free survival and overall survival in patients with breast cancer. *PARP4* belongs to a family of genes, poly-ADP-ribose polymerases (PARPs), that encodes enzymes to catalyze synthesis of poly-ADP-ribose (36). Levels of poly-ADP-ribose increase in response to genetic insults and is a critical component of DNA repair. PARP inhibitors are used clinically to treat ovarian tumors and are in clinical trials for breast cancer (37). However, existing drugs do not target *PARP4*. *PARP4* is unique in that it can also be found in the cytoplasm, unlike the other members of the PARP family (36). Unfortunately, *PARP4* is not well characterized and more research is needed to determine the biochemical and physiologic processes it regulates.

To date, no other mutations have been demonstrated to be causal agents linking metachronous breast and thyroid tumors. More studies to examine patients with histories of both diseases are needed to uncover new gene variants. Furthermore, epigenetic changes including altered expression of miRNAs and long-noncoding RNAs (lncRNA), covalent modification of DNA, and mutations to regulatory elements in the genome could be critical. Recently, the mitotically associated lncRNA (MANCR), has been demonstrated to be upregulated and a driver of aggressive breast cancer (38). MANCR is also upregulated in thyroid cancers (39). Such information from these two studies exemplifies common transcriptional regulation in both diseases.

## What Is the Impact of Cancer Treatment on Future Risk?

Radiation, despite being a treatment option for breast cancer, is a well-documented risk factor in the development of cancer and is a major risk factor for thyroid cancer (40–42). Multiple recent clinical studies demonstrate alteration of the ability of the thyroid to produce hormones following radiotherapy (43–45). Despite this evidence that radiotherapy harms the thyroid, a very large study from Taiwan of over 55,000 patients did not report any association between treating breast cancer with radiation and subsequent thyroid cancer, nonetheless the results did corroborate the previously discussed relationship between thyroid and breast cancers (46). Another study revealed that although the use of radiotherapy to treat breast cancer was associated with an increased risk of certain tumors, including leukemia and lung cancer, there was not an observed increase in the risk of thyroid cancer (47).

Childhood radiotherapy is documented to increase the chance of a woman developing breast cancer later in life (48, 49) Thyroid tumors are not typically treated with beam radiotherapy, but one of the most commonly prescribed treatments for thyroid cancer is to treat the patient with radioactive iodide ( $^{131}\text{I}$ ).  $^{131}\text{I}$  selectively targets the tumor via the sodium-iodide symporter (NIS) to kill

the diseased thyroid tissue. However, breast tissue expresses NIS to transport iodide into milk and so could be impacted by radioactive  $^{131}\text{I}$  (50). There is also evidence that dietary iodide intake is protective against the development of breast cancer (51). Since the 1960s, numerous studies denote a concern for secondary tissue effects with the use of  $^{131}\text{I}$  treatment for thyroid diseases (52). Although increased risk for development of leukemia was determined, no association with breast cancer was noted (53–55). In addition, meta-analysis of studies specifically examining  $^{131}\text{I}$  treatment for thyroid cancer revealed no association between the use of  $^{131}\text{I}$  and subsequent development of breast cancer (56). A recent study found no difference in breast cancer risk between patients with thyroid cancer treated with and without  $^{131}\text{I}$ , confirming the prior observations (57).

Although the impact of radiotherapy on thyroid function has been extensively studied, data on chemotherapy is sparse. Studies on patients with breast cancer receiving different chemotherapeutic treatments reveal a reduction in serum  $T_4$  levels, but subsequent recovery of thyroid function and thyroid cancer risk was not assessed (58–60). Critically, the impact of chemotherapeutic agents on thyroid function and cancer risk needs further study.

## Are Thyroid Disease and Disruptions of Thyroid Hormone Signaling Risk Factors?

Thyroidal status may be an important factor in second tumor development, although studies are limited. Clinical implications of thyroid hormone–mediated effects altering the initial tumor development are unclear, and the data on the impact of thyroid hormone levels on the likelihood of developing a tumor are inconsistent (61–63). Regardless, in a small clinical study utilizing the patients with advanced cancers, including breast tumors, ablation of *de novo* thyroid hormone synthesis and supplementation with  $T_3$  prolonged patient survival (64). Strikingly, in a mouse xenograft study, more metastases were observed in hypothyroid than euthyroid animals and the hypothyroid mice developed smaller primary tumors, suggestive of an important role for thyroid hormones on tumorigenesis (65). In addition, the impact of tyrosine kinase inhibitors on thyroid function has predictive value in determining patient outcomes; patients with cancers other than thyroid cancer rendered hypothyroid after tyrosine kinase inhibitor treatment have a more favorable prognosis, as defined by overall survival (66). The subpopulation of patients who experienced drug-induced hypothyroidism and received the supplemental  $T_4$  exhibited greater odds of overall survival than those with untreated hypothyroidism. The authors note that thyroidal dysfunction may be indicative of the effectiveness of the cancer treatment but the mechanisms are unknown (66). Overall, studies of the drug-induced hypothyroidism indicate that thyroid hormone signaling may protect against advanced breast cancer.

The canonical pathway for thyroid hormone action is through the nuclear hormone receptors thyroid hormone receptor alpha ( $\text{TR}\alpha$ ) and thyroid hormone receptor beta ( $\text{TR}\beta$ ). Of these receptors,  $\text{TR}\beta$  is expressed in both breast and thyroid tissue (67).  $\text{TR}\beta$  has also been implicated as a tumor suppressor (68). The pathways that  $\text{TR}\beta$  regulates have not yet been thoroughly explored; however, there is evidence that it represses PI3K in both breast and thyroid cancer cells (69, 70).  $\text{TR}\beta$  also represses transcription of the oncogene *RUNX2* in thyroid cancer through an interaction with a chromatin-remodeling complex (71, 72). *RUNX2* is a

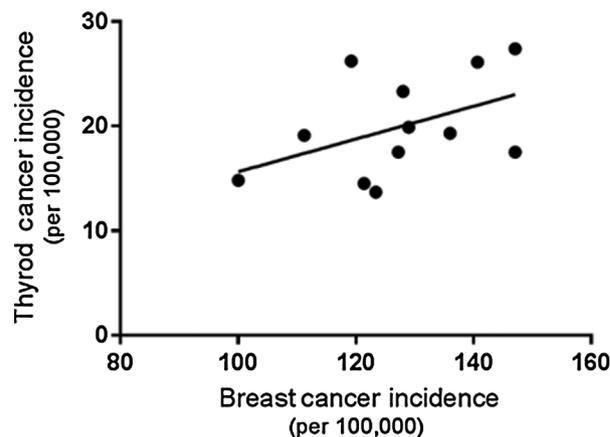
driver of both breast and thyroid cancers and common thyroid hormone-mediated mechanisms may be active in both tissues (73, 74). There is also a nonclassical thyroid hormone receptor, the integrin  $\alpha V\beta 3$ , which responds to  $T_4$  rather than  $T_3$ , and activates the prooncogenic MAPK pathway (75). It is probable that the response a tumor has to thyroidal status depends upon the genes expressed in the cells due to the multiple receptors that feed into many different pathways.

### Does Hormonal Disruption Alter Metachronous Cancer Susceptibility?

Breast cancer is often hormonally driven through the upregulation of estrogen and progesterone receptors and mimetics of these compounds can be carcinogenic (reviewed in ref. 76). This relationship has been extensively studied, and although there are still many unanswered questions regarding the mechanistic details, there is little doubt concerning whether estrogenic signaling can promote breast tumorigenesis. Estrogen is also implicated in the development of thyroid cancer, and may explain why women develop the disease at roughly 4 times the rate as men (reviewed in ref. 77). Numerous studies have linked endocrine disrupting chemicals (EDC) to obesity, developmental perturbations, and hormone-dependent cancers (78). Exposure to EDCs at prenatal and early developmental stages are associated with later development of cancers (79), which could predisposition the same individual to developing both tumor types; potentially explaining why the same person develops both diseases in a short time frame and at a younger age. For example, EDCs may stimulate thyroid and breast cancer development through estrogenic signaling. Bisphenol A (80) and flame retardants (81), mimetics of endogenous estrogen or xenoestrogens, have been implicated in the development of thyroid cancer as well as breast cancers (82). Bisphenol A binds to TRs and antagonizes thyroid hormone action (83, 84). As  $TR\beta$  is a tumor suppressor in both thyroid and breast cancers, this inhibition may be a common mechanism.

Epidemiologic analysis of hotspots for thyroid cancer development is consistent with the hypothesis that an increase in thyroid cancer may be linked to environmental as well as lifestyle factors (85). We performed an exploratory analysis in Vermont, comparing the breast and thyroid cancer incidence rates in different counties, and observed a weak correlation between the two cancer types (Fig. 1). A linear trend line fit to the data indicated that an increase of breast cancer incidence by 10 per 100,000 women corresponded to an increase in thyroid cancer of 1.6 per 100,000 people. An investigation into hotspots where breast and thyroid cancers cooccur could reveal environmental factors, including EDCs, which drive both tumor types.

Approximately 80% of breast tumors are hormone receptor-positive. Endocrine therapies via selective estrogen receptor modulators (SERM) that target estrogen receptor alpha are a cornerstone of breast cancer treatment for most patients (86, 87). The prototypical SERM, tamoxifen, has been reported to stimulate thyroid stimulating hormone production (88) and, in a rat model, to induce thyroid tissue proliferation (89). In patients on both endocrine therapy and  $T_4$  replacement therapy for hypothyroidism, there is an increase to levels of thyroxine-binding globin, total  $T_4$ , and thyroid-stimulating hormone (90). What effect SERMs have on thyroid tumorigenesis has not been adequately investigated.



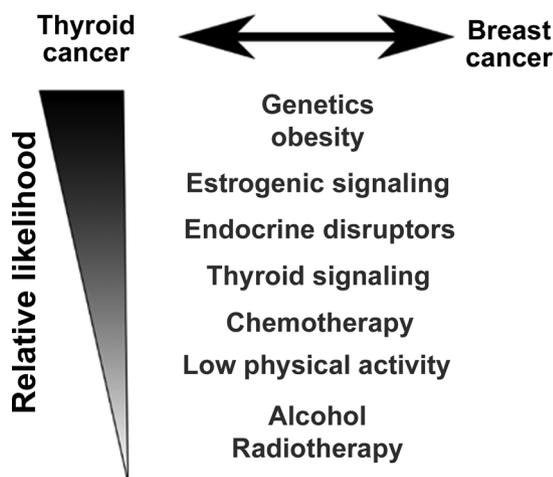
**Figure 1.**

Thyroid and breast cancer incidences are positively correlated among Vermont Counties. County-specific age-adjusted thyroid cancer and invasive breast cancer incidence for 2010–2014 among Vermont females was obtained from the state of Vermont Environmental Public Health Tracking Data Explorer. A linear regression was performed to yield a slope of 0.1565 with an  $R^2$  value of 0.2102. The counties of Essex and Grand Isle were excluded because of insufficient numbers of thyroid cancer cases in these small population counties.

### Are Lifestyle-Related Environmental Factors Common between Breast and Thyroid Cancer?

Behaviorally driven environmental factors, include obesity, sedentary lifestyle, alcohol consumption, and tobacco usage have been demonstrated to increase cancer risk (91). Breast cancer risk increases with weight gain, alcohol consumption, and from a lack of regular exercise (92, 93). Shared risk factors with thyroid cancer are candidates to the etiology of metachronous tumors. Obesity is a risk factor to the development of epithelial-derived thyroid cancers, but not to tumors that arise from the thyroid's c cells (94, 95). Despite the association with obesity, there does not appear to be strong evidence of physical activity altering thyroid cancer risk (96, 97). Alcohol-related mechanisms of tumorigenesis are also not shared between the two diseases. A meta-analysis pooled over 7,000 patients with thyroid cancer and demonstrated alcohol consumption does not contribute to a heightened risk of developing a thyroid tumor (98). For the patients that develop metachronous breast and thyroid tumors, specific studies are needed to determine whether lifestyle factors alter the risk of a second cancer.

A factor addressed earlier in this review, thyroid hormones, do have an impact on obesity and metabolism. Changes in signaling resulting from the activity of the tumor suppressor  $TR\beta$  may be related to obesity as a risk factor. A high-fat diet enhanced thyroid tumor growth by the leptin-mediated JAK2-STAT3 pathway in a mouse model exhibiting mutant variants of  $TR\beta$  and PTEN (99). Increased STAT3 activity has been demonstrated to promote breast cancer progression in animal xenograft models and detected at the invasive tumor front in breast biopsy specimens (100, 101). STAT3 activity may be important to the breast–thyroid cancer link.



**Figure 2.**

Summary of possible etiologic factors in the thyroid and breast cancer link. Factors that have the potential to drive the relationship between thyroid and breast cancer are displayed here on an arbitrary scale to represent potential explanatory power. Factors at the top of the figure, darker, are more likely than agents at the bottom of the figure, lighter. Likely etiologic factors include genes, obesity, and hormonal influences such as estrogen, thyroid hormone, and environmental endocrine disruptors. Chemotherapy is a possibility, however there is a lack of studies, so the role it has is unclear. Radioactive iodide or radiotherapy is very unlikely to be etiologic, and both alcohol use and a sedentary lifestyle are unlikely factors for the development of metachronous breast and thyroid tumors.

## Concluding Remarks

There is strong evidence of a relationship between breast and thyroid cancer as survivors of either cancer are at increased risk for development of thyroid or breast tumors compared with the general population. The etiology of these cancers and possible causative factors are at an infancy stage and just beginning to be studied. Further investigation into the genomics and epigenetics underlying both breast and thyroid cancer can yield clues into the specifics of tumorigenesis and identifying who are at greatest risk of a metachronous tumor. A greater understanding of the etiology of male cases of both breast and thyroid cancer also has the potential to uncover important etiologic factors. Different subtypes of breast cancer are more common in men as compared with women (102) and the same is true for thyroid (103). These

differences could account for the greater rate of metachronous occurrence and investigations into molecular differences could reveal novel insights. In addition, although radiotherapy has been investigated and is unlikely to be a significant factor, there is a lack of convincing evidence in either metachronous direction as to a potential role for chemotherapy. Further studies are needed into the effects of chemotherapy and endocrine therapy on thyroid disease and cancer susceptibility. EDCs promote development of hormone-dependent cancers; however, there is a lack of information on EDC exposure and the development of thyroid cancer, an area that merits further investigation. Further research into the role of obesity and JAK-STAT signaling on breast and thyroid tumorigenesis may also provide insights into the metachronous relationship. The potential for the different possible etiologies in the breast–thyroid cancer relationship is summarized (Fig. 2).

Importantly, studies are needed to perform parallel observations in both tumor types to enhance the understanding of which tumorigenic pathways are common to both breast and thyroid and narrow down the risk factors for these metachronous neoplasms. The existing public databases for thyroid cancer characteristics need expansion to allow for the extensive cross comparison between thyroid and breast cancers. There also needs to be a greater focus towards generating thyroid cancer public datasets for comparison with the many existing breast cancer datasets. With the increase in thyroid cancer incidence and improved survivorship of breast and thyroid cancers, it is an important public health concern to identify the linkages between these cancers in both sexes.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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