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Breast and Thyroid Cancer: A Multi-Center Study with Accrual to Clinical Trials Network (ACT)

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Abstract

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data collection and validation, manuscript preparation

data analysis, manuscript preparation

data procurement

data collection, manuscript revision

data collection, manuscript revision

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design, data analysis, manuscript preparation and revision

concept, design, manuscript preparation, project management, and revisions

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Supplemental Material Legend

Appendix I: Data Dictionary

Objective: To investigate a possible link between breast and thyroid cancer.

Methods: A multi-center retrospective review of patients in the electronic medical records of six Accrual to Clinical Trial (ACT) institutions with both breast cancer and thyroid carcinoma. Each center queried their data using a predefined data dictionary. Information on thyroid and breast cancer included dates of diagnosis, histology, and patient demographics.

Results: A random effects model was used. There were 4.24 million women's records screened, 44,605 with breast cancer and 11,846 with thyroid cancer. The relative risks observed at each institution ranged from 0.49 to 13.47. The combined risk ratio estimate was 1.77 (95% CI: 0.50 – 5.18).

Conclusion: There was no association between risk of developing thyroid cancer and being a breast cancer survivor compared to no history of breast cancer, but the range of relative risks among the participating institutions was wide. Our findings warrant further study of more institutions with a larger sample size. Additionally, further analysis of the significance of regional risk ratio differences may be enlightening.

Level of Evidence: 3

Keywords

thyroid cancer; breast cancer; epidemiology

Introduction

Breast cancer is the most common malignancy among American women, excluding those of the skin. The American Cancer Society estimates 281,550 new cases of invasive breast cancer will be diagnosed in the U.S. in 2021.[1] When a patient is diagnosed and treated for breast cancer, they may undergo post therapy surveillance for recurrence with whole body 18 FDG Positron emission tomography (PET) scanning. Uptake may be noted anywhere on these scans, including the thyroid, which may indicate inflammation, infection, or a second primary cancer (SPC). This is further compounded by the prevalence of microcarcinomas in the female population that may otherwise be clinically insignificant. This may create additional clinical issues for the medical team to interrogate in order to wholistically care for the patient.

PET thyroid gland uptake above background levels may prompt evaluation of the thyroid. PET positivity within the thyroid gland may be either, diffuse or focal.[2–5] Diffuse thyroid uptake on PET is typically reflective of thyroiditis, most commonly autoimmune thyroid disease (Hashimoto's Thyroiditis), and is confirmed by thyroid function and directed antibody testing.[6,7] These patients are often prescribed thyroid supplementation and returned to the care of the breast and primary care teams. Patients with focal thyroid uptake on PET should be evaluated according to the latest American Thyroid Association (ATA) guidelines for thyroid nodules.[8] The unintended result in these cases is essentially a thyroid cancer screen which is not currently recommended.[8]

Thyroid nodule evaluation typically includes thyroid function testing (to rule out a hyper functional nodule), ultrasonography of the thyroid and cervical lymphatics, and ultrasound

directed fine needle aspiration biopsy for a cytologic diagnosis of the nodule(s) and any lymphadenopathy which might be of sonographic concern. Cytology results are managed based on their Bethesda classification and a surgical treatment plan is formulated.[9–11]

Our interest as head and neck surgeons is the thyroid gland and any association between breast cancer and thyroid cancer has been sporadically reported but not been established. Based on anecdotal experience from multiple patients with both thyroid and breast carcinoma, our group investigated whether breast cancer survivors have a greater risk of developing thyroid cancer. Our hypothesis was that this observed clinical pattern may indicate a more significant connection between these two malignancies than coincidence. Recent studies have suggested a link might exist between breast and thyroid cancer.[12–15] This knowledge further bolstered our observations and was formative to formulating our hypothesis. This study expands investigation of this potential association to a cohort of multiple tertiary centers in the United States.

Materials and Methods

An invitation for collaboration based on our hypothesis of a connection between thyroid and breast cancer was circulated to academic otolaryngologists on faculty of the Accrual to Clinical Trails (ACT) member institutions. Six institutions (Table 1) within the ACT network responded and volunteered to provide data on women in their electronic medical record (EMR) systems who had been diagnosed with breast cancer and thyroid cancer using a predefined data dictionary (Appendix I) provided by University of Arkansas for Medical Sciences (UAMS). The Accrual to Clinical Trials network is a nationwide federation of leading academic research institutions that share aggregate patient counts from electronic health data (https://www.actnetwork.us). Information on thyroid and breast cancer included dates of diagnosis, histology, and patient demographics. The UAMS Institutional Review Board approved the study (217844).

Women whose cancer diagnoses were made 6 months apart or less were excluded from analysis, as were males. Cancers presenting within 6 months of each other are not considered to be SPC. As breast cancer is rare in men, they are not screened for it like women, and represent a distinct cohort. Study data from the EMR were collected and managed using REDCap electronic data capture tools hosted at UAMS.[16,17] No molecular data was available for any patients.

Relative risks and corresponding 95% confidence intervals were calculated for each institution participating in the study. A random effects model was used to combine the results from the institutions and produce an overall relative risk estimate. We borrowed from meta-analysis work of Higgins' I^2 statistics, which measures the heterogeneity in relative risk estimates among institutions.[18] Typically, I^2 statistics greater than 75% are indicative of high heterogeneity. Data analyses were conducted using R version 4.0.3 and the metafor package.[19–21]

Results

Clinical data sought relative risk of thyroid cancer as a SPC for breast cancer from participating institutions' EMR data. The institution-specific and overall relative risks are presented in Figure 1. Descriptive statistics for both groups are summarized in Table 2. All patients were female, and demographics for race, ethnicity, and cancer histology are given in Table 3. EMR systems identified patients diagnosed with breast cancer and thyroid cancer using a predefined data dictionary (Appendix I) provided by UAMS. There was a total of 4.24 million women who had an appointment with a head and neck surgeon from the EMRs of each institution. Based on this sample, there were 44,605 women who had a diagnosis of breast cancer and 11,846 women who had a diagnosis of thyroid cancer, of whom 376 were diagnosed with breast cancer prior to thyroid cancer. The average age at breast cancer diagnosis was 56.79 years old while the average age at thyroid cancer diagnosis was 60.65 years old.

The relative risks observed at each institution ranged from 0.49 at University of Kentucky and University of California at San Francisco to 13.47 at University of California at Irvine. The I^2 estimate was 98.5% (95% CI: 96.3% to 99.7%), indicating a high degree of heterogeneity in the relative risk estimates. The combined risk ratio estimate is 1.77 (95% CI: 0.50 – 5.18), which indicates that the risk of developing thyroid cancer in women with a history of breast cancer is 71% higher than women with no history of breast cancer, but this result is not statistically significant.

Not all institutions were able to provide histologic diagnoses for all cancers, but broad trends shared across sites that reported these diagnoses showed predominantly mixed histology among breast cancers and papillary histology among thyroid cancers.

Discussion

Cancer, in general, is understood to be a disease with a pathogenesis that is fundamentally genetic, whether it arises from point damage to DNA (inherited or environmentally caused) in individual cells, or from missing or defective gene copies or gene products (proteins) that regulate expression or control cell proliferation. As such, researchers are increasingly demonstrating that certain types of cancers tend to occur in clusters. Examples include Cowden syndrome, Li-Fraumeni syndrome, Lynch syndrome, BRCA1 and BRCA2, MEN syndromes, and many others.[21] We also know that environment and exposures can play a strong role in gene mutations and expression, which also has implications. These effects can be challenging to identify with a highly mobile western lifestyle. The question of whether breast and thyroid cancer may be genetically linked has been suggested but not definitively answered. [22–24] A molecular postulate for a possible linkage of these two cancers exceeds the original purpose and scope of this work.

Improved treatments for cancer have led to more patients who survive to develop recurrence and SPC.[25–33] In 2006, the Institute of Medicine called for the creation of survivorship care plans for cancer survivors to address these patients' growing long-term care needs.[26] The Childhood Oncology Group (COG) and American Cancer Society (ACS) responded

by providing evidence-based guidelines for clinicians to utilize in creating these plans for their patients.[29–31] The COG guidelines recommend screening for SPCs in survivors of childhood, adolescent, and young adult cancers, specifically for breast and colorectal cancers.[27] The ACS developed survivorship guidelines for 4 primary cancers, namely breast, colorectal, prostate, and head and neck cancer (HNC).[28–31] These guidelines state that those with average cancer risk undergo the same screening for SPCs as the general public, whereas patients with high risk for cancers are recommended to undergo additional vigilence.[28–31] Per the ACS, breast cancer survivors are considered high risk if they have a strong family history of breast cancer, a genetic mutation such as BRCA1 or BRCA2, or if they received radiation therapy for another cancer, such as Hodgkin lymphoma.[32] The breast cancer exception for screening is not reflected in the ATA guidelines.[8] Yet there is a growing body of evidence that suggests these guidelines may be incomplete, and that clinicians should have a higher level of suspicion that their breast cancer patient may have, or may yet develop, a SPC.[12–15, 35–38]

A higher-than-expected incidence of thyroid cancer has been observed in breast cancer patients. One recent meta-analysis reports an odds ratio (OR) of a female developing thyroid cancer after a breast cancer to be 1.55 (expected OR 1.0 in the general population).[12] With this increased incidence having been observed, many have begun to speculate on the impact that routine thyroid cancer screening would have on this select patient population1.[2, 35–37] Currently, neither the US Preventive Task Force[39] nor the ATA[8] recommends routine thyroid cancer screening in any population other than those defined as high-risk, which includes only patients with a history of radiation exposure to the neck (seen in some cases of HNC) or a family history of differentiated thyroid cancer. Perhaps, hereditary breast cancer survivors (identified by ACS as high risk) should also be the group that merits thyroid cancer screening? A more generalized thyroid cancer screening has been tried in Korea and resulted in a significant uptick in thyroid cancer incidence, the majority of which were incidental microcarcinomas. Korea later reversed their policy of thyroid screening and now no longer does it because they were identifying low risk papillary microcarcinomas which may or may not ever be of clinical significance.

The results observed in our study indicate that risk may vary geographically, sometimes even between centers within the same state. We have no hypothesis regarding this at present. Patients in contemporary society are known to be highly mobile which would confound possible geographic effects. Additionally, variation in clinical practice may explain differences between centers, especially the ones from the same/similar states. Looking at the California institutions alone, a patient’s RR could vary from 0.4 in San Francisco to 13.47 in Irvine 400 miles away, with patients nearer by in Sacramento, about 70 miles outside San Francisco, demonstrating a RR of 5.34. This phenomenon has been observed by other researchers.[15] Studies examining the link between breast and thyroid cancer have found an elevated risk of SPC in thyroid cancer survivors of Asian descent, which may explain the regional difference in RR in part. A more detailed assessment of the catchment trends and comparative ethnic demographics of each institution was beyond the scope of this study but would be of significance for future studies.[40]

In the meta-analysis conducted by Joseph et al, the risk for thyroid cancer as a SPC following breast cancer ranged from 0.92 to 4 among studies published from the United States, Europe, Israel, and Japan.[15] Even though our overall finding of an elevated relative risk for the entire cohort was not found to be significant, the fact that each environment demonstrated markedly different relative risks is of clinical interest. The number and geographical distribution of the participating institutions is not enough to help clinicians know whether they practice in a higher-risk region or not. What it does establish is that there is variability across the United States, warranting further study of associations among various populations.

Study Limitations

Limitations of our study include that it is retrospective, how the data (and its accuracy) was entered into the EMR, that patients came from head and neck practices, and how both breast and thyroid cancer have been diagnosed and treated over the extended period under consideration in this study. As outlined in the introduction, a common scenario that prompts workup for thyroid cancer in patients with breast cancer is increased uptake on PET. However, the use of PET scans was not introduced as routine screening for metastatic disease in breast cancer until the late 1990's;[10,41,42] therefore many women may have developed clinical thyroid pathology that was not found earlier because they never received a PET scan. Further, advancements in treatment of breast cancer have increased survivorship among women,[25,28] and it is possible that women who would have developed thyroid cancer might have succumbed to their breast cancer prior to the possibility of developing a thyroid cancer if they were treated in the past. Finally, there could be confounders in the data for which we did not control. One example is genetic predisposition. While we requested family history of thyroid or breast cancer, we did not collect data on known cancer syndromes, such as Cowden's. It is possible that some of the geographic variability could be explained if one of the centers specialized in a condition that impacted risk of either cancer.

Pathology results in this data were not controlled. This would have been onerous to review all pathology by a select group of pathologists using pre-determined standards. Reports from local pathologists were used assuming accuracy and compliance with their national standards for diagnosis in place at the time of diagnosis. With that, it is still possible that thyroid cancer was being over read as has been documented by the proliferation in diagnosis of thyroid microcarcinomas since the early 2000's.[43] Therefore, some thyroid cancers diagnosed could have been incidental and clinically insignificant. Furthermore, the area of thyroid uptake on PET was not confirmed to be correlated with the thyroid malignancy reported on pathology.

During the chart review process, the reviewer often relied on physician notes or reported patient recollection of dates of diagnosis and interventions. As a result, documentation of thyroid or breast pathology in these records may be inaccurate. For example, the specific type of pathology and date of diagnosis was not always recorded. Molecular pathology was not available for analysis. A definite molecular mechanism for the relationship between breast and thyroid cancer has yet to be reported and exceeds the capacity and mission of this report.[44]

While the various contributing institutions had the data dictionary provided by UAMS to use as a guideline, it is possible that this guideline was incompletely followed. For example, 2 institutions returned data showing that all patients presented with breast cancer before thyroid cancer. While it is possible that these patients' diagnosis of breast cancer led to the discovery of occult thyroid cancer, it is also possible that the data was pulled with parameters that inadvertently excluded patients presenting with thyroid cancer first.

Differences between institutions might be driven by differences in levels of intensity for cancer screening. Again, this is a reference to differences in clinical practice. Cancer survivors are often screened for other malignancies with a greater intensity.[45] These could result in a screening bias which might explain the co-occurrence of these two types of malignancy. This difference was not studied or accounted for in our data. Since different institutions have different approaches to care, this could generally be addressed by increasing our sample from more centers across the country that are ACT institutions.

Finally, there is not a well-defined time period during which subjects are followed for the event of interest., development of thyroid cancer. The time frame for events to occur is open-ended and varies by site, which may lead to differences attributed to clinical practice and a biased estimate of risk.

Conclusion

Our finding of relative risk of developing a thyroid malignancy was not statistically significant, but the range of relative risks among the participating institutions was wide. We offer no mechanistic explanation for this possible linkage.[46–7] Further investigation should center on enrolling more centers and increasing the sample size as well as identifying where the relative risk of developing thyroid cancer as a SPC is particularly high. This information may inform practice guidelines by specialty organizations on screening[48] and it may help researchers better identify what risk factors may contribute to the higher incidence of thyroid cancer as an SPC in certain populations. This study does not presently justify for a change in current guidance on thyroid cancer as an SPC to breast cancer. The immediate implication for clinical practice should be a consideration of thyroid cancer as a SPC to breast cancer among breast cancer providers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

Data was maintained and is available through Dr. King and Mr. Spencer. Dking3@uams.edu.

Data from our study is available upon request. Contact Dr. Deanne King at DKing3@uams.edu.

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Synopsis:

There was no association between risk of developing thyroid cancer and being a breast cancer survivor, but the range of relative risks among the participating institutions was wide. Further study of more institutions with a larger sample size and additional analysis of the significance of institutional practices and regional risk ratio differences should be conducted

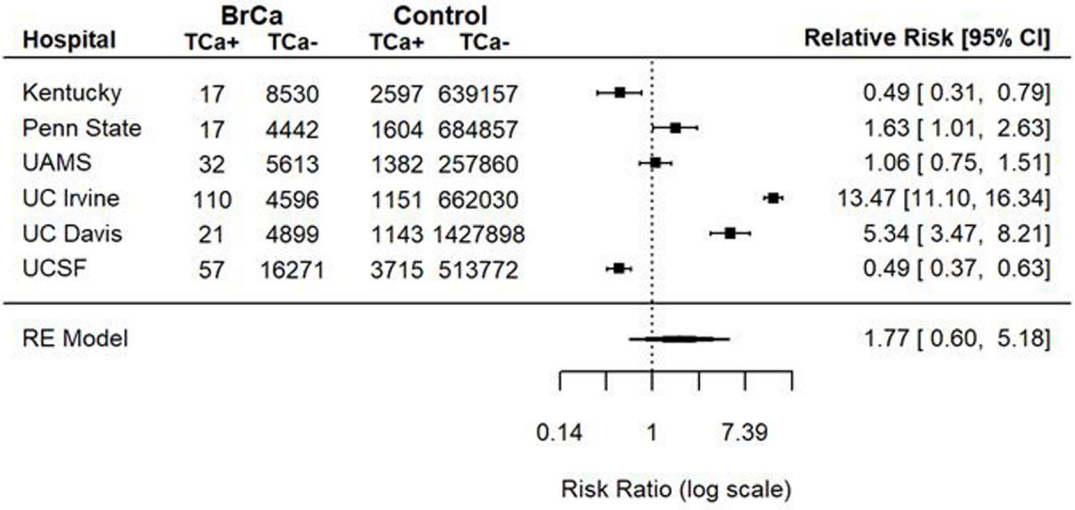

Figure 1: Forest plot of relative risks by site and in the aggregate

The relative risks are show by site and overall; they are highly variable by site.

Table 1:

Participating Institutions

Pennsylvania State University (Penn State)
University of Arkansas for Medical Sciences (UAMS)
University of California, Davis (UC Davis)
University of California, Irvine (UCI)
University of California, San Francisco (UCSF)
University of Kentucky (Kentucky)

Table 2:

Descriptive Statistics

	Kentucky	Penn State	UAMS	UCI	UC Davis	UCSF	Totals
Number of women seen in time period	650,301	690,920	264,887	667,887	1,433,961	533,815	4,241,771
Number of women with breast cancer diagnosis	8,547	4,459	5,645	4,706	4,920	16,328	44,605
Number of women with thyroid cancer diagnosis	2,614	1,621	1,414	1,261	1,164	3,772	11,846
Number of women with breast cancer first	17	17	32	110	21	57	254
Number of women with thyroid cancer first	0	9	12	48	0	53	122
Mean age at breast cancer diagnosis	54.37	60.77	52.68	63.99	51.16	57.74	
Mean age at thyroid cancer diagnosis	61.77	61.28	57.83	64.15	61.21	57.63	

Table 3:

Demographics

	Kentucky	Penn State	UAMS	UCI	UC Davis	UCSF	Totals
N	17	26	44	158	21	110	376
Race and Ethnicity							
American Indian	0	0	0	0	1	0	1
Asian	0	0	1	33	1	25	60
Black	0	1	8	0	0	2	11
Hispanic	0	1	0	21	2	5	29
Pacific Islander	0	0	0	1	0	0	1
White	0	24	35	86	17	68	230
Unknown	17	0	0	17	0	10	44
Breast Cancer Histology							
Carcinoma, unspecified	10	9	2	0	1	0	22
Adenocarcinoma	2	0	4	0	0	4	10
Ductal carcinoma	0	1	8	0	6	3	18
Lobular carcinoma	1	2	5	0	1	6	15
Mixed	4	6	24	0	11	30	75
Other (Mucinous, papillary)	0	8	0	0	1	1	10
Unknown	0	0	1	158	1	66	226
Thyroid Cancer Histology							
Papillary	16	22	29	0	0	2	69
Medullary	0	1	2	0	0	0	3
Follicular	0	2	5	0	0	0	7
Other	1	0	8	0	0	0	9
Unknown	0	1	0	158	21	108	288