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

Sarah M. Nielsen^{*1}, Michael G. White^{*2}, Susan Hong³, Briseis Aschebrook-Kilfoy⁴, Edwin L. Kaplan², Peter Angelos², Swati A. Kulkarni⁵, Olufunmilayo I. Olopade¹, and Raymon H. Grogan²

¹Center for Clinical Cancer Genetics and Global Health, Department of Medicine, The University of Chicago, Chicago, IL, US

²Endocrine Surgery Research Program, Department of Surgery, The University of Chicago Pritzker School of Medicine, Chicago, IL, US

³Breast Cancer Survivorship Program, Center for Clinical Cancer Genetics and Global Health, Department of Medicine, The University of Chicago, Chicago, IL, US

⁴Department of Public Health Sciences, The University of Chicago, Chicago IL, US

⁵Department of Surgery, Northwestern University, Feinberg School of Medicine, Chicago, IL, US

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% CI [1.44,1.67]) and an increased risk of breast cancer as a secondary malignancy following thyroid cancer (OR= 1.32, 95% CI [1.23,1.42]). 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.

Keywords

second primary malignancies; breast neoplasms; thyroid neoplasms; risk factors; radiation exposure; genetic susceptibility

Corresponding Author: Raymon H. Grogan, MD, The University of Chicago Medicine & Biological Sciences, 5841 S. Maryland Ave. | Rm. G-214, MC 4052 | Chicago, IL 60637, Office: 773-702-7125, Fax: 773-834-5295.

^{*}These authors contributed equally to this work

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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 three-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. Additionally, 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 Pub-Med 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 were described. This systematic review is summarized in Figure 1. Number of observed and expected secondary malignancies were reported or calculated from available studies and used to calculate odds ratios for the development of secondary malignancies for each study. Meta-analysis of the data was performed using Stata (Version 13, College Station, TX) (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 odds ratio of developing thyroid cancer after a diagnosis of breast cancer is summarized in Figure 2. While the general population would be projected to have an odds ratio of 1.0, breast cancer survivors have an increased risk of developing thyroid 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 odds ratio developing breast cancer after a diagnosis of thyroid cancer is summarized in Figure 3. While the general population would be projected to have an odds ratio 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 has been accumulated on the possible link between breast and thyroid cancer, however prior to our study it has been difficult to clearly identify whether or not a link between breast and thyroid cancer truly exist, 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.

Surveillance Bias

It has been postulated that increased rates of second primary cancers, such as thyroid and breast, can be explained in part by surveillance bias. Thyroid cancer is often an indolent asymptomatic tumor that may go undetected for many years and whose prevalence correlates with the degree of screening (45). Because of thyroid cancer's association with breast cancer and because breast cancer survivors receive increased surveillance in the form of clinical examinations and imaging (CT scans and mammography), it is possible that the increase in surveillance is responsible for higher rates of thyroid cancer detection. Similarly, as most thyroid cancers occur in women under 50 years, women with a history of thyroid cancer are more likely to be compliant with screening tests such as mammograms, thus increasing the rates of its detection (46).

It should be noted, however, that while 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 non-thyroid 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 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 have 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).

While 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 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). Additionally, evaluating breast cancer risk in a cohort of thyroid cancer patients, multi-parity was found to have a protective effect on the development of breast cancer while nulli-parity was associated with higher rates of subsequent breast cancer (42). Demonstration of this association suggests 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 appears to play a role in the development of either breast or thyroid cancer as a secondary malignancy.

While 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 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 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). While a number of hormonal pathways have been suggested as possible mechanisms of this observed interaction, none have been conclusively determined.

Radiation Exposure

In the 1930's and 1940's 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 10–50% greater risk of developing a non-breast second primary cancer as compared to the general population (17). While 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 hematological 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 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). Since typical latency periods of thyroid cancer after radiation exposure are 20–

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).

Based on 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 (RAI) for Thyroid Cancer and the Risk of Breast Cancer

RAI has been used since the 1940's as an adjuvant treatment of thyroid cancer; ablating residual thyroid tissue, involved 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 ^{131}I 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 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) (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 (CLS). SDH is comprised of four subunits (SDHA, B, C and D) that encode mitochondrial complex II of the electron transport chain in the Krebs'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 to 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 CLS. *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 to *PTEN* mutation carriers, these individuals may have a 2–3 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 to 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 40. Whether or not these women require earlier more aggressive surveillance such as annual breast MRIs in addition to mammograms remains to be seen.

While 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). While 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 become evident as the incidence of thyroid cancers continues to rise and the treatments for both cancers continue to improve.

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Figure 1. Summary of systematic review performed querying both Scopus and PubMed databases

Figure 2. Odds ratio of developing thyroid cancer as a secondary malignancy following diagnosis and treatment for breast cancer. Odds ratio on meta-analysis is 1.55 (95% CI [1.44, 1.67])

Figure 3.

Odds ratio of developing breast cancer as a secondary malignancy following diagnosis and treatment for thyroid cancer. Odds ratio on meta-analysis is 1.18 (95% CI [1.09,1.26])

Table 1

Standardized Incidence Ratios of Thyroid Cancer after Breast Cancer

Study	Location(s)	Study Period	Mean follow-up period (yrs)	# Cases		SIR (95% CI)
				BC	TC	
Molina-Montes 2013 (28)	Spain	1985–2007	6.4	5,897	8	1.01 (0.02–2.01)
Mellemkjær 2011 (6)	Denmark, Finland, Norway	1943–2006	8.8	304,703	347	1.41
Lee 2008 (27)	Taiwan	1979–2003	5.4	59,001	45	1.42 (1.04–1.90)
Kirova 2008 (26)	France	1981–1997	10.5	16,705	20	0.87 (0.53–1.35)
Raymond 2006 (25)	USA (SEER)	1973–2000	NA	335,191	314	2.23
Mellemkjær 2006 (24)	Europe, Canada, Australia, Singapore	1943–2000	7.2	525,527	471	1.62
Soerjomataram 2005 (23)	Netherlands	1972–2000	6.6	9,919	2	0.8 (0.1–3.3)
Sadetzki 2003 (22)	Israel	1960–1998	7.3	49,207	59	1.34 (1.03–1.72)
Levi 2003 (21)	Switzerland	1974–1998	6.4	9,729	6	1.01 (0.37–2.20)
Tanaka 2001 (20)	Japan	1970–1994	8.6	2,786	7	3.7 (1.5–7.6)
Huang 2001 (19)	Canada	1973–1993	6.8	194,798	140	1.2 (1.0–1.4)
Evans 2001 (18)	England	1961–1995	5.7	145,677	37	1.05
Rubino 2000 (17)	France	1973–1992	9.5	4416	4	2.2 (0.7–5.2)
Volk 1997 (16)	Slovenia	1961–1985	7.3	8,791	10	2.5 (1.2–4.6)
Doherty 1993 (15)	Scotland	1954–1964	18	3,926	4	2.33 (0.63–5.95)
Murakami 1987 (14)	Japan	1965–1982	5.7	9,503	9	3.2 (1.5–6.1)
Teppo 1985 (13)	Finland	1954–1979	NA	26,617	22	1.95
Harvey 1985 (12)	USA	1935–1982	6.6	41,109	28	1.6
Schenker 1984 (11)	Israel	1960–1977	NA	12,302	33	1.7

BC, breast cancer; TC, thyroid cancer; y, year; n, number of cases (studies with n<1,000 excluded); CI, confidence interval; NA, data not available; NE, association not evaluated; a, outcome measured was O/E; b, outcome measured was relative risk.

Table 2**Standardized Incidence Ratios of Breast Cancer after Thyroid Cancer**

Study	Location(s)	Study Period	Mean follow-up (yrs)	Cases (n)		SIR (95% CI)
				BC	TC	
Lu 2013 (44)	Taiwan	1976–2006	7	102	19,068	1.42 (1.16–1.72)
Kim 2013 (43)	USA	1973–2008	NR	1,041	52,103	1.13 (1.06–1.20)
Consorti 2011 (42)	Italy	1996–2009	6.2	7	75	3.58 (1.14–8.37)
Mellemkjaer 2006 (24) *	Europe, Canada, Australia, Singapore	1943–2000	NR	552	NR	1.31 (1.21–1.43)
Verkooijen 2006 (41)	Netherlands	1985–1999	10.6	5	282	1.52 (0.46–3.18)
Berthe 2005 (40)	France	1960–1998	8	12	875	1.19 (0.62–2.08)
Rubino 2003 (39)	France, Italy, Sweden	1934–1995	13	128	6,841	1.3 (1.0–1.5)
Adjadj 2003 (38)	France	1934–1955	12	48	2,365	1.3 (1.0–1.7)
Sadetzki 2003 (22)	Israel	1960–1998	9.4	4,911	70	1.07 (0.84–1.34)
Hemminki 2001 (37)	Sweden	1958–1996	NR	113	19,281	1 (0.8–1.2)
Edhemovic 1999 (36)	Slovenia	1971–1993	5.2	4	894	1.12 (0.31–2.87)
Dottorini 1995 (35)	Italy	1960–1993	8	10	694	2
Glanzman 1992 (34)	Switzerland	1960–1988	14.5	5	298	1.9 (0.6–4.5)
Hall 1991 (33)	Sweden	1950–1975	16	24	1,955	1.46
Johns 1989 (32)	USA	1975–1985	2.7	5	115	8.9
Edmonds 1986 (31)	England	NR	11.2	6	258	2.37
Osterlind 1985 (30)	Denmark	1943–1980	5.9	11	1351	0.96 (0.76–1.20)
Ron 1984 (29)	USA	1935–1978	8	24	1618	1.89

BC, breast cancer; TC, thyroid cancer; y, year; n, number of cases (studies with n<1,000 excluded); CI, confidence interval; NA, data not available; NE, association not evaluated; a, outcome is for in-situ BC, invasive BC risk not significantly elevated; b, outcome measured was relative risk

* Unreported number of initial thyroid cancer, unable to include in meta-analysis