Lack of association between Hashimoto thyroiditis and breast cancer: A quantitative research synthesis

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ABSTRACT

Several authors have suggested a positive association between Hashimoto thyroiditis (HT) and breast cancer (BrCa). Others have refuted these findings; hence, this subject remains controversial. We therefore reviewed the world literature on this subject accumulated over the last 50 years and performed a quantitative research synthesis, a meta-analysis variant. The incidence risk ratios and 95% confidence intervals (CI's) were calculated for each study and the combined relative risk (RR) was estimated. We found 37 relevant studies, of which only 13 were accessible to analysis. A significant association (RR=1.40; CI=1.29-1.53, P<0.022) was found for 6 of the 13 studies pertaining to 1,431 women. However, in the cumulative population of 14,226 women (from all 13 studies), we failed to demonstrate an association between the diagnoses of HT and BrCa (RR=1.07; CI=0.99-1.15; P=0.08). In conclusion, we believe that selection bias or institutional referral bias, in at least some of the "positive" studies, may have led to the spurious recognition of an association between HT and BrCa, especially as both of these conditions are highly prevalent in women between the 4th and 7th decade of life.

Key-words: antithyroidal antibodies, breast cancer, Hashimoto thyroiditis, meta-analysis, thyroid gland

INTRODUCTION

Breast cancer (BrCa) is the most common cancer in women in the Western world, but despite intensive research only a part of its incidence is believed to be attributable to known risk factors, either genetic or epige-

netic[1]. Several common medical conditions are associated with changes in the endocrine milieu, which secondarily may influence the risk of development and progression of BrCa[2]. One of these conditions, which has been positively linked by some authors to BrCa, is Hashimoto thyroiditis (HT). The mechanism for this association is not clear, although some studies have shown increased prevalence of antithyroidal auto-antibodies in women with BrCa, compared to healthy controls, thus leading to the hypothesis that the mammary tumor and the thyroid gland may share common antigens, such as thyroid peroxidase (TPO) and sodium-iodide (Na+/I-) symport-

er[3]. However, the above findings have been refuted by other authors[4,5]. Hence, the subject remains controversial.

We therefore reviewed the relevant world literature spanning the last 50 years, and performed a quantitative research synthesis, a variant of meta-analysis. Despite a strong association suggested by some of the studies, these involved only a small proportion of the total number of cases cumulatively reported. When considering the total population of women in the analysis of the statistically evaluable studies, no significant association became evident between these two disorders.

DATA SOURCE, OPERATIONAL DEFINITIONS AND METHODS

Biomedical literature

MEDLINE and manual literature searches (1950-2001) were conducted using the Medical Subject Headings (MESH) "Hashimoto", "thyroiditis", "hypothyroidism", "thyroid disease", "anti-thyroidal antibodies", and "goiter" in conjunction with the MESH terms "breast cancer" and "breast neoplasms". Both English and non-English-language articles were reviewed. We selected case series, cross-sectional studies (or prevalence surveys), "case-control" (retrospective) studies, as well as retrospective cohort/clinical cohort studies examining: either (i) the prevalence of thyroid disease (or in some cases, HT specifically) in women with BrCa (as well as "healthy controls" - whenever applicable) or (ii) the prevalence of BrCa in women with HT (as well as "healthy controls" - whenever applicable). Notably, in some of the studies focusing on the prevalence of thyroid disease in women with BrCa versus "control" patients, the latter population also included women with benign breast disease.

Abbreviations

Antibodies	Ab's
Breast cancer	BrCa
Free thyroxine	fT4
Hashimoto thyroiditis	HT
Not available	N/A
Non-significantly different	NSD
Patients	Pts
Thyroidal % radioiodine uptake (24H)	%RAIU
Relative risk	RR
Tri-iodothyronine	T3
Thyroxine	T4
Thyroid peroxidase	TPO
Thyrotropin	TSH
Ultrasound	U/S

Operational Definitions and Systematic Evaluation of Studies

In view of the variety of parameters studied and the conflicting results among published reports (due, in part, to the heterogeneity of the corresponding patient populations), we selected only those studies that were amenable to statistical analysis. The criteria for selection of studies were defined a priori. For the purposes of our analysis, we defined HT as the presence of: (i) positive anti-thyroidal antibodies (ATA's), i.e. high titers of anti-microsomal or antithyroglobulin (anti-Tg) antibodies (measured as inverse fractions of dilution in hemagglutination assays in earlier studies) or high levels of anti-thyroid peroxidase (anti-TPO) or anti-Tg antibodies levels (measured as mU/l in specific immunoassays in more recent studies), or (ii) elevated serum thyrotropin (TSH) levels or (iii) decreased serum total triiodothyronine (T3) levels or (iv) the presence of nodular goiter by physical exam and/or ultrasonographic evaluation. We took into consideration the fact that the cardinal cause for conditions (ii)-(iv) in the study populations would be HT (6). Additionally, data were extracted for further analysis from studies meeting all of the following criteria: (i) a "healthy control" group of patients was included, (ii) clinical characteristics of various patient groups were reported, and (iii) the diagnosis of BrCa was based on either histopathologic confirmation of the malignancy or patient record review. Each study was independently reviewed by two of the authors (L.G. and N.J.S.) and, subsequently, the methodology and results thereof were summarized into tables prior to formal statistical analysis.

Statistical analysis

The method of quantitative research synthesis, a meta-analysis variant, was used to analyze the available data[7,8]. This method features the following components: (i) incidence risk ratio calculation: for each individual study, a treatment effect size (relative incidence risk ratio) and 95% confidence interval (CI) were calculated by commercially available statistical software (SAS/STAT®, Cary, NC)[9]; (ii) common relative risk (RR) calculation: the Mantel-Haenszel test was used for that purpose; (iii) common treatment effect estimation. Additionally, the Breslow-Day test of homogeneity (χ^2-test statistic) was used to assess whether any inter-study differences would be attributable to random sampling alone (depending on the distribution of effect sizes among studies). If all studies are homogeneous (e.g., the presence of HT consistently increased the risk of detection/diagnosis of BrCa), this χ^2-statistic would be non-significant. Conversely, with this method, if the heterogeneity (in-

Table 1. Characteristics of published studies (n=29)

Study [**]	Study [***] Design	Total # of Pts with BrCa	Cumulative # of Pts Reported	Parameters Studied for the Assessment of Thyroid Status in the Pt Population	Study Conclusions
Studies Reporting a Positive Correlation Between BrCa and HT					
Rose et al., 1978 (13) [*]	PS	127	271	TSH, T4	TSH levels are increased in women with BrCa *versus* normal controls
Rose et al., 1979 (14) [*]	PS	92	169	TSH, T3, T4	
Edelstyn et al., 1958 (10)	PS	67	67	%RAIU	%RAUI is lower in women with BrCa and systemic metastasis *versus* those with locally invasive disease only
Shering et al., 1996 (16) [*]	CC	150	350	Thyroidal Volume (by neck U/S)	Thyroidal volume is increased in women with BrCa *versus* normal controls
Giani et al., 1996 (15) [*]	CC	102	202		
Smyth et al., 1996 (17)	PS	200	554		
Smyth et al., 1998 (18) [*]	CC	356	760		
Itoh & Maruchi, 1975 (12)	RC	18	18	Historical Diagnosis (Chart Review)	RR of BrCa is increased in women with HT *versus* normal controls
Abe et al., 1975 (11) [*]	CS	52	52		
Shering et al., 1996 (16) [*]	CC	150	350	Anti-TPO Ab's	The incidence of anti-TPO Ab's is increased in women with BrCa *versus* normal controls
Giani et al., 1996 (15) [*]	CC	102	202		
Smyth et al., 1998 (18) [*]	CC	356	760		
Study Reporting a Negative Correlation Between BrCa and HT					
Kapdi et al., 1976 (19)	PS	380	5,505	History of previous thyroid hormone therapy	Hypothyroid state is "protective" against BrCa development
Studies Reporting a Lack of Association Between BrCa and HT					
Abe et al., 1980 (28)	PS	25	36	TSH, T3, T4	TSH levels are NSD between women with BrCa and normal controls
Lemaire et al., 1985 (32)	PS	226	578		
Adamopoulos et al., 1986 (33)	PS	97	218	TSH, T3, fT4	T3 and fT4 levels are NSD between women with BrCa and normal controls
Reeve et al., 1961 (20)	PS	62	62	%RAIU	%RAUI is NSD between women with BrCa and normal controls
Stoll, 1965 (22)	PS	183	183		
Abe et al., 1980 (28)	PS	100	149		
Schottenfeld, 1968 (23)	CS	226	779	Thyroidal Volume (by physical examination)	Thyroidal volume is NSD between women with BrCa and those with benign breast disease or normal controls
Adamopoulos et al., 1986 (33)	PS	97	218	Thyroidal Volume (by neck U/S)	
Humphrey et al., 1964 (21) [*]	PS	369	630	Historical Diagnosis (Chart Review)	The incidence of thyroidal disease is NSD between women with BrCa and normal controls OR The incidence of BrCa is NSD between women with HT and normal controls
Schottenfeld, 1968 (23)	CS	226	779		
Moosa et al., 1973 (24)	RC	462	713		
Maruchi et al., 1976 (26) [*]	RC	5	508		
Kurland et al., 1976 (25)	RC	5	486		
Hedley et al., 1981 (29)	RC	42	2,523		
Kalache et al., 1982 (30) [*]	CC	1,176	2,352		
Brinton et al., 1984 (31) [*]	CC	1,362	2,612		
Fukuda et al., 1987 (34)	RC	4	4,531		
Goldman et al., 1990 (36)	RC	83	7,338		
Goldman, 1990 (35)	Meta-analysis	N/A	N/A		
Goldman et al., 1992 (4) [*]	RC	100	9,520		
Weiss et al., 1999 (5) [*]	CC	2,173	4,163	Clinical Questionnaire (History of Diagnosis of Thyroidal Disease)	The incidence of thyroidal disease is NSD between women with BrCa and normal controls
Mittra et al., 1976 (27) [*]	CC	362	669	Anti-TPO Ab's	The incidence of anti-TPO Ab's is NSD between women with BrCa and those with benign breast disease or normal controls
Adamopoulos et al., 1986 (33)	PS	97	218		
Maruchi et al., 1976 (26) [*]	CC	28	348	Autopsy	The incidence of BrCa is NSD between women with lymphocytic thyroiditis at autopsy and normal controls

* : Studies evaluated in the quantitative research synthesis/meta-analysis

** : CC=Case-Control; CS=Case Series; PS: Prevalence Survey (Cross-Sectional Study); RC=Retrospective Cohort

***: Some of the studies appear more than once in this table, as they report on several different parameters of thyroid status assessment

ter-study variability) was large, then the Breslow-Day χ^2-statistic was significant. Further, in this analysis, CI's are typically wider than those derived by a simpler statistical method, such as the inverse-variance weighted average comparison[7]. For all statistical tests, a two-tailed P value of <0.05 was considered significant.

RESULTS

From our literature search, we found 34 relevant reports on the subject, 29 of which (85%) are summarized in table 1[4,5,10-36]. The remaining 5 reports (15%) were editorials, comments, letters and opinion statement type of publications and, hence, were not amenable to quantitative analysis[37-41]. Taking into account the selection criteria mentioned in the Methods section above, only 13 of the 29 studies (45%) cited in table 1 were evaluable (designated by an asterisk [*] in Table 1)[4,5,11,13-16,18,21,26,27,29,31]. The primary reason for excluding >50% of the published studies was the rather poor quality of the reported data, which led to their failure to meet the defined selection criteria for our analysis. Six of the 13 statistically evaluable studies (46%) showed a significant association between HT and BrCa (RR=1.40, CI=1.29-1.53, P<0.022, by Fisher's exact test)[11,13-16,18]. These results were perti-

nent for a cumulative population of 1,431 women (Figure 1).

However, in the cumulative number of 14,226 women (from all 13 evaluable studies), we failed to demonstrate an association between the diagnoses of HT and BrCa (RR=1.07; CI=0.99-1.15, P=0.08, by Fisher's exact test), as is clearly evident in figure 1.

Effect sizes for these studies were not homogeneous (p=0.001), as assessed by the Breslow-Day test of homogeneity. As noted above, in this test statistical significance is reached when the population size among studies is heterogeneous[7]. However, homogeneity across studies (p>0.05) was observed after removing 3 studies which, in fact, were those "positive" studies reporting the most significant incidence risk ratio values[14-16].

DISCUSSION

The association between HT and BrCa has been suggested by several epidemiological and clinical cohort studies ever since Sir George Beatson, surgeon at the Glasgow Cancer Hospital, experimented with thyroid hormones as a treatment for BrCa in 1896[42]. Sixty years later, Loeser observed that hyperthyroidism protected
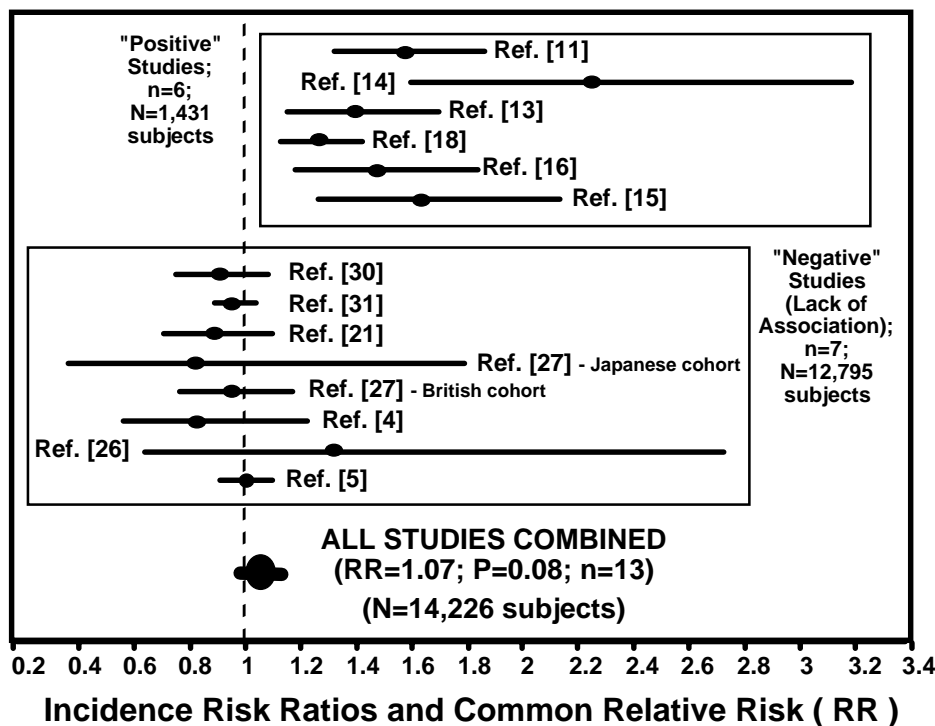

Figure 1. Incidence risk ratios for each individual study and derived common relative risk (RR) for BrCa in women with HT in all studies (n=13). Corresponding confidence intervals for all values are shown as horizontal bars.

against BrCa, whereas women who had undergone subtotal thyroidectomy developed BrCa more often than expected and, thus, recommended administration of thyroid hormone as a treatment for BrCa[43]. This author also postulated that the lack of thyroid hormones permitted the development of malignant cells within the mammary epithelium[43].

Since that time, several reports have suggested an association between thyroid diseases, or their treatments, and the occurrence of BrCa[11,13-16,18]. However, both HT and BrCa are highly prevalent in women between the 4th and 7th decade of life and, hence, there may be adequate reason to attribute the purported association to chance alone[1,6,44-46]. To further clarify the issue, we performed a systematic review of the relevant literature over the last 50 years, which had yielded conflicting results among the various reports.

The strongest basis for a positive association between HT and BrCa has been the observation that women with this malignancy have higher prevalence of anti-TPO antibodies, as well as higher mean thyroidal volumes versus healthy controls[17,18]. However, increased prevalence of ATA's has also been observed in women with benign breast disease[33]. Further, the pathophysiologic basis of any association between the presence of ATA's, goiter, or hypothyroidism and mammary epithelial proliferation/tumor formation is very tenuous. Moreover, the "positive" studies (those reporting an association between HT and BrCa) pertain to women from widely divergent ethnic backgrounds (i.e. Western European, US-Caucasian, Japanese) with different iodine sufficiency status, as well as genetic and environmental risk factor profiles. This fact needs to be taken into consideration when raising the possibility of a true biologically pertinent association between these two diseases. Finally, even when the 6 "positive" studies are combined, the cumulative number of subjects therein, i.e. 1,431 women, remains much lower than that in all 13 studies, both "positive" and "negative", i.e. 14,226 women, reflecting the rather small size of individual "positive" studies.

In contrast to the above, 7 additional studies have failed to verify the alleged association between HT and BrCa[4,5,21,26,27,29,31]. Indeed, when data from these studies (showing lack of association between the two disorders) are pooled together with the 6 "positive" ones, no statistically significant association is found. Notably, the combined population sample for our analysis includes 14,226 women and, thus, achieves considerable statistical power for this observation.

The investigation of a possible relationship between HT and, indeed, thyroid disease in general, and BrCa has been pursued vigorously in the literature over many decades[2-5,10-43]. The lack of consistency in the findings of the studies performed heretofore, as well as the possibility of selection bias or institutional referral bias[47] in at least some of the "positive" studies, suggest that HT and BrCa are most probably not causally related, but may share common etiologic factors which remain unidentified.

With regard to the possible etiology of any relationship between thyroid disease and BrCa, a novel insight has recently been provided by studies examining the effect of cytokines, and particularly interleukin (IL)-6, on thyroid function. Serum levels of tumor necrosis factor (TNF) and IL-6 have been shown to be elevated in patients with non-thyroidal illness, including those with assorted malignancies, and to be associated with reduced mean serum total and free T3 levels, as well as occasionally low serum total and free thyroxine (T4) levels[40,41,48-51]. Further, thyroid dysfunction can occasionally be observed in cancer patients receiving IL-2-based immunotherapy[52,53]. Specifically for BrCa, in a study of women with recurrence of this malignancy who did not respond to chemotherapy, serum levels of IL-6 and IL-8 were significantly higher than those seen in women who showed a partial response[41]. Moreover, in this study, a strong negative correlation was observed between serum IL-6 and free T3 (as well as free T4) levels in the non-responders[41]. Thus, it is plausible that circulating (or intrathyroidally produced) IL-6 may lead to a hypothyroid state in at least some of the patients with recurrent metastatic BrCa. Further research in this area, elucidating the relationship between thyroid function and serum levels of IL-6 (or other pro-inflammatory cytokines) is certainly warranted and could potentially explain the wide discrepancies among serum levels of thyroid hormones reported in the published studies.

Limitations of our analysis include the following: (i) the studies taken into consideration reported measurements and assessments of diverse parameters, which were generally not directly comparable; (ii) we cannot rule out the possibility that some of the patients with simple goiter and/or primary hypothyroidism did not have HT as their underlying diagnosis; (iii) more than 50% of the published studies on the subject were excluded due to the rather poor quality of the reported data thus rendering them inaccessible to statistical evaluation; and (iv) in any meta-analysis spanning an extended period of time (50 years in our case), there is a possibility that not all of the relevant publications were traced. In this connection,

data suggestive of lack of association between any two diseases may never be reported due to publication bias; hence, the number of "negative" studies in our analysis may be underestimated.

In conclusion, in a research synthesis, a meta-analysis variant, of 13 studies involving a combined cohort of 14,226 women, we failed to demonstrate a statistically significant association between the diagnoses of HT and BrCa. It is likely that previous reports suggesting a positive correlation between these two entities may have been flawed by analysis design, strong institutional bias, and selection of patient populations with very advanced BrCa exhibiting features consistent with non-thyroidal illness, such as intense hypercytokinemia.

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