

THYROID DISORDERS AND BREAST CANCER

A Research Project by

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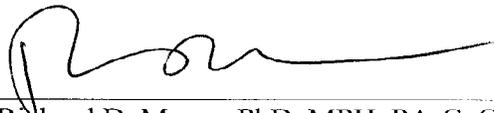
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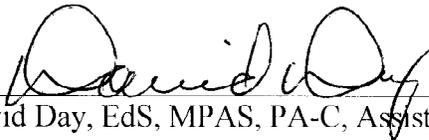
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We hereby recommend that the research project prepared under our supervision by Michelle Menke entitled Thyroid Disorders and Breast Cancer be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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DEDICATION

To my fiancé, Tony,
and all of my friends and family
for their support during this endeavor

ABSTRACT

Introduction: A possible link between thyroid disorders and breast cancer has been a subject of debate, since thyroid extract was first used to treat breast cancer in 1896. Many researchers have suggested an increased risk of breast cancer in women with thyroid disorders and others have indicated a decreased risk. **Purpose:** To determine if there is a relationship between thyroid disorders and breast cancer in women. **Method:** An evidence based literature review using Medline, AbstractsFirst, and Cochrane using the terms: hypothyroidism, hyperthyroidism, thyroid dysfunction, breast cancer, and breast carcinoma. Criteria for article selection: publication in a peer reviewed journal, level 3 evidence or higher, and the relevance of the data to this study. **Results:** Twenty articles met criteria for this study: 11 show an association and 9 show no association. **Conclusion:** The current data is inconclusive in determining the possibility of an association between thyroid disorders and breast cancer risk, thus no recommendation can be made at this time. Further evaluation is needed.

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LIST OF ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
E2	Estradiol
FT3	Free triiodothyronine
FT4	Free thyroxine
¹²⁵ I	Radio-labeled iodine
NIS	Sodium-iodine symporter
RT3	Reverse triiodothyronine
RT3U	Resin triiodothyronine uptake
SIR	Standardized incidence ratio
SMR	Standardized mortality rate
T2	Diiodothyronine
T3	Triiodothyronine
T4	Thyroxine
Tg Ab	Antithyroglobulin antibody
TPO.Ab	Antiperoxidase antibody
TR α 1	Thyroid receptor alpha 1
TR β 1	Thyroid receptor beta 1
TR β 2	Thyroid receptor beta 2
TRH	Thyroid releasing hormone
TSH	Thyroid-stimulating hormone

CHAPTER I

INTRODUCTION

The association between thyroid conditions and breast cancer has been a topic of debate and study for many years. In 1896, Beatson first treated metastatic breast cancer with thyroid extract and oophorectomy. Since then other researchers have extensively investigated the relationship between the two conditions.¹ Cristofanilli et al. reported a decrease in the risk of developing invasive breast cancer in women with primary hypothyroidism.² In another study, Gogas et al. suggested that there was evidence of an increase in Hashimoto's thyroiditis in patients with breast cancer.³ In contrast, a meta-analysis by Sarlis et al. revealed no association between Hashimoto's thyroiditis and breast cancer.⁴ Simon et al. reported that neither disorders of the thyroid nor the treatment for these conditions substantially alters the risk of breast cancer.⁵ The debate continues today with this current study.

According to the American Association of Clinical Endocrinologist (AACE), up to 27 million Americans may have overactive or underactive thyroid glands and 8 out of 10 of these patients are women.⁶ Some of the more common thyroid conditions include hyperthyroidism, hypothyroidism, autoimmune thyroiditis, goiter, and thyroid nodules which can be benign or malignant and lead to neoplasms (adenoma and/or carcinoma).⁷ Several laboratory tests are used to evaluate and diagnose patients with these conditions. These tests include serum levels of thyroid stimulating hormone (TSH), thyroxine (T4), free thyroxine (FT4), triiodothyronine (T3), free triiodothyronine (FT3), and thyroid releasing hormone (TRH). Other serum levels tested to determine the presence of these conditions include the autoantibodies, antiperoxidase antibody (TPO.Ab), thyroglobulin antibody (Tg.Ab), and thyroid stimulating hormone receptor antibody (TSH(R) Ab).⁷

Breast cancer is another common disorder of women with an estimated 2.3 million women alive in January 2002 who had a history of breast cancer.⁸ There was an estimated 212,920 new cases of breast cancer in women in 2006. Several known risk factors for breast cancer, some modifiable and others not modifiable, exist and include age, family history, age at first full-term pregnancy, early menarche, late menopause, HRT, alcohol consumption, and physical inactivity. The systemic effect of thyroid hormones and thyroid conditions on breast cancer risk is still being debated in the literature. The purpose of this study is to evaluate the current evidence and to determine if there is an association between thyroid conditions and breast cancer.

CHAPTER II

LITERATURE REVIEW

Several studies⁹⁻¹¹ have suggested an association between breast cancer and thyroid disorders. In 1993, Smyth et al. used diagnostic thyroid ultrasound to determine thyroid volumes and morphology in 184 breast cancer patients and 150 controls.⁹ They found a significant increase in thyroid volume in breast cancer patients compared to controls ($p < 0.01$) and a significantly higher number of patients with enlarged thyroids and breast cancer compared to controls ($p < 0.001$). The study also found that patients with breast cancer had a significantly higher percentage of thyroid abnormalities, defined as nodules and cysts, as compared to controls ($p < 0.001$).

In 1996, Smyth et al. further investigated the relationship between thyroid enlargement and breast cancer in the prospective arm of a case control study with 100 women who underwent high resolution ultrasound to evaluate the volume of their thyroid glands at the time of excisional biopsy for a breast mass. These findings were compared to a control group of 200 non-hospitalized women and found that the mean thyroid volume in breast cancer patients was significantly greater than that in the healthy controls ($p < 0.01$).¹⁰

In a prospective study of 102 breast cancer patients and 100 healthy age-matched controls, Giani et al. found an increase in the overall prevalence of thyroid disease in breast cancer patients. Both cases and controls underwent clinical and ultrasound evaluation of thyroid volume in addition to having blood samples taken to evaluate thyroid hormone levels. A significantly higher number of breast cancer patients had thyroid disease as compared to controls ($p < 0.0001$).¹²

In 2003, Turken et al. conducted a study of 150 women with breast cancer and 100 age matched controls to determine the prevalence of thyroid diseases in the breast cancer patients as compared to the general population. Participants underwent clinical and ultrasound evaluation of their thyroid glands, serum thyroid hormone and antibody levels, and fine-needle aspiration of their thyroid glands. The results showed an increased prevalence of autoimmune and non-autoimmune thyroid diseases in breast cancer patients ($p < 0.001$, $p < 0.001$).¹³

A prospective study conducted by Cengiz et al. of 136 breast cancer patients and 68 controls found an increased frequency of thyroid pathology in breast cancer patients as compared to controls. Participants underwent thyroid ultrasound and blood sampling for thyroid hormone and antibody levels. Breast cancer patients had a significantly higher frequency of thyroid pathology as compared to controls ($p = 0.000035$).¹⁴

Saraiva et al. conducted a study to determine the profile of thyroid hormones in breast cancer patients and to compare those results with normal age-matched controls. Serum samples were collected prior to surgery, radiotherapy, or chemotherapy and analyzed for free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), antithyroid peroxidase antibody (TPO.Ab), and estradiol (E2). Further serum samples were collected after surgery to confirm the results. This study concluded that there is an increased incidence of thyroid disease in breast cancer patients as compared to controls.¹⁵

Cristofanilli et al. conducted a retrospective case control study with 2224 participants (1136 cases, 1088 controls) to investigate whether primary hypothyroidism is associated with invasive breast carcinoma and to evaluate the “clinicopathologic characteristics of breast carcinoma in patients with hypothyroidism.” It was found that patients with primary breast carcinoma were 57% less likely to report a history of primary hypothyroidism as compared with

healthy women. Thus the conclusion was that there is a reduced risk of primary breast cancer in women with primary hypothyroidism.²

In a case control study by Lemaire et al. the thyroid function of 226 breast cancer patients was compared to the thyroid function of 3 groups used as controls: 125 patients with other malignancies, 61 patients with benign breast disease, and 166 healthy patients. T3 and T4 levels were significantly higher ($p < 0.01$) in the breast cancer patients as compared to the other control groups. The study concluded that breast cancer patients experience thyroid dysfunction distinct from the thyroid dysfunction experienced by patients with various acute or chronic diseases.¹⁶

Gogas et al. studied 600 Greek women to determine whether there is an increased prevalence of autoimmune thyroiditis in women with breast cancer compared to the general Greek female population. They evaluated the thyroid gland volume and performed serologic testing for thyroid autoantibodies on 310 breast cancer patients and two control groups: 100 age-matched women with benign breast disease and 190 age-matched women who were admitted to surgery for other conditions. The findings showed an increase in autoimmune thyroiditis in patients with breast cancer.³

A prospective study conducted by Giustarini et al. confirmed that there is a strong relationship between thyroid autoimmunity and breast cancer. The study included 61 women with nodular breast pathology suspected for malignancy prior to surgery and 100 age-matched controls. Thyroid autoimmunity was determined by clinical and ultrasound evaluation of thyroid volume and serologic evaluation of thyroid hormone and antibody levels. This study confirmed the high prevalence of autoimmune thyroid disorders in breast cancer patients and demonstrated that this finding is independent of stressful events such as surgery, treatment, or anesthetic procedures.¹⁷

Another prospective study¹¹ found that thyroid autoimmunity was increased in patients with breast cancer. The study consisted of 566 participants divided into three groups: 356 breast cancer patients, 122 women with benign breast disease, and 88 healthy women with no clinical evidence of breast disease. TPO.Ab were detected in 34.0% of the breast cancer patients compared with 18.5% of the controls ($p < 0.001$). These results indicate an association between TPO.Ab positivity and breast cancer that suggests the presence of subclinical autoimmune thyroid disease in some breast cancer patients.¹¹

In contrast to the studies previously described, several studies^{4, 5, 18-24} found no association between thyroid dysfunction and breast cancer. Among these is a study conducted by Moseson et al. in which various medical conditions related to hormone abnormalities were associated with breast cancer risk. This study is a retrospective case control study of 354 breast cancer patients and 747 matched controls conducted by telephone interview regarding physician diagnosed thyroid conditions, etc. It was determined that there is no association between any thyroid dysfunction and breast cancer risk ($P = 0.88$).¹⁸

Weiss et al. also concluded that there is no association between thyroid disease and breast cancer risk in a population based case control study of 2173 breast cancer patients and 1990 random controls conducted to evaluate the relationship between breast cancer and selected medical conditions. This study was performed by structured face-to-face interviews which covered a detailed questionnaire to include medical history. In this study, thyroid disorders as a group were not associated with breast cancer risk ($OR = 0.94$).¹⁹

In a similar study, Talamini et al. interviewed 2569 women with histologically confirmed breast cancer and 2588 women admitted to the hospital for a wide spectrum of acute disorders to determine the relationship between several medical conditions and the risk for breast cancer.

Participants were interviewed using a structured questionnaire and the odds ratios and confidence intervals were calculated via multiple logistic regression models. The results of this study concluded that there is no association between thyroid disorders and breast cancer.²⁰

The mortality rate of women with benign thyroid disease was studied by Goldman et al. in a retrospective follow-up study consisting of 7338 women by calculating the standardized mortality rates (SMR) for these women. The diagnosis of thyroid disease was confirmed by review of medical records and follow-up consisted of ascertainment of death by locating death certificates. The study concluded that women with thyroid disorders, as defined by this study, were not at an increased risk of death from breast cancer.²¹

Simon et al. conducted a population based case control study to determine if thyroid disorders or the treatment of such disorders affect the risk of breast cancer. The study included 4575 breast cancer patients who were enrolled in the National Institute of Child Health and Human Development Women's CARE Study and 4682 women chosen from the same counties as the cases by random digit-dialing and then frequency matched based on 5 year age group, race, and geographic site. In person interviews were conducted by trained interviewers using a detailed interview instrument. The study concluded that a history of any thyroid disorder was not associated with breast cancer (OR=1.1).⁵

Sarlis et al. conducted a meta-analysis of 13 studies and found no association between thyroid dysfunction, specifically Hashimoto's thyroiditis, and breast cancer. This study found 37 relevant studies, but only 13 of them were amenable to statistical analysis and met selection criteria established by the authors. When comparing the studies, 6 of the 13 suggested an association between Hashimoto's thyroiditis and breast cancer, but by comparing cumulative

populations of women in the studies (1,431 to 14,226), Sarlis et al. found that there is no association between Hashimoto's thyroiditis and breast cancer ($p=0.08$).⁴

Further study of thyroid autoimmunity and its association with breast cancer was conducted by Kuijpers et al. in a prospective cohort study of 2775 women from the Eindhoven Perimenopausal Osteoporosis study. Participants underwent detailed gynecological/obstetrical, endocrinological, and general medical histories as well as had venous blood samples collected for thyroid function and antibody testing. The study group was then linked to the Eindhoven Cancer Registry to determine which participants had previous or current breast cancer diagnoses. It was concluded that the presence of TPO.Ab was not associated with the development of new breast carcinoma during the follow-up period ($OR=1.1$).²²

Sadetzki et al. also concluded that there is no association between thyroid dysfunction and breast cancer. This study explored the possible association between breast cancer and thyroid cancer by analyzing data obtained from the Israel Cancer Registry to determine the standardized incidence ratios (SIR) in the nationwide population. It was determined that the SIR for developing a primary breast cancer after a primary thyroid cancer was 1.07 (95% CI: 0.84, 1.34).²³

Morabia et al. concluded that depressed thyroid activity is not clearly associated with breast cancer except among women with a long duration of ovulatory activity. The study consisted of 73 female cases and 75 hospital controls that initially participated in the Breast Tumor Collaborative Study between 1973 and 1975 still had plasma samples available. These participants underwent face-to-face interviews conducted by specially trained interviewers and additional information was abstracted from hospital and physician charts. The overall matched adjusted odds ratio of breast cancer for below normal FT4 levels was 1.7 (95% CI 0.6-5.0).²⁴

CHAPTER III

METHODOLOGY

This project is a systematic evidence based literature review conducted using Medline, AbstractsFirst, and Cochrane databases. The search terms used included: hypothyroidism, hyperthyroidism, thyroid dysfunction, breast cancer, and breast carcinoma. Articles were chosen based on the following criteria: publication in a peer reviewed journal, level 3 evidence or higher, and relevance of the data to this study. Inclusion criteria were studies in which the participants were tested before any treatment was performed not including biopsy or surgery. Articles were excluded if the thyroid disorder was diagnosed after the patients had received chemotherapy, radiation therapy or hormonal therapy for their breast cancer. Thyroid disorders were defined as enlargement or goiter, hypothyroidism, hyperthyroidism, thyroid nodules or adenoma, and autoimmune thyroiditis.

The studies were categorized into two levels of evidence. Studies classified as Level 1 included meta-analyses and prospective cohort and case-control studies. Studies classified as Level 2 included retrospective cohort and case-control studies.

CHAPTER IV

RESULTS

The search resulted in thirty articles, ten of which were excluded because they included participants who were tested after receiving treatment for breast cancer such as chemotherapy, radiation therapy, or hormonal therapy. The remaining twenty articles included nine Level 1 and two Level 2 articles showing there is an association between thyroid disorders and breast cancer risk. It also included three Level 1 and six Level 2 articles showing no association between the two conditions. These numbers combine to be eleven articles concluding there is an association between the two conditions and nine concluding no association between thyroid disorders and breast cancer exists.

Of the eleven articles that concluded there is an association between thyroid disorders and breast cancer, ten articles indicated an increased risk in breast cancer with thyroid disorders and one article indicated a decrease in the risk of breast cancer. A breakdown of the studies suggesting an increased risk of breast cancer into more specific categories resulted in one study suggesting an increase in breast cancer risk with hyperthyroidism, three studies indicating an increase risk with hypothyroidism and autoimmune thyroiditis, and six studies did not differentiate among the different thyroid disorders.

Further analysis of the nine studies concluding no association between thyroid disorders and breast cancer risk resulted in three studies referring to hypothyroidism and autoimmune thyroiditis and six studies referring to thyroid disorders as a group.

No recommendation can be made at this time because the results of this current study are inconclusive for determining if there is an association between thyroid disorders and breast cancer. Further study needs to be done to determine if this association truly exists or if it is merely a coincidence.

CHAPTER V

DISCUSSION

The results of this study show the need for further evaluation of the association between thyroid disorders and breast cancer. Establishing whether or not there is an exact biologic link between thyroid disorders and breast cancer or if the association is merely a result of the coincidence that the two conditions are more common in women, particularly post-menopausal women, should undergo further study.

Laboratory evidence exists indicating that thyroid hormones exert an effect on mammary cells.^{25,26} But there continues to be conflict in the laboratory as well. Gonzalez-Sancho et al found that T3 reduced the proliferation of mammary epithelial cells.²⁶ Dinda et al., on the other hand, found that thyroid hormone exhibits an estrogen-like effect on the regulation of tumor suppressor proteins in breast cancer cells because T3 was shown to regulate cancer cell cycle progression and proliferation.²⁵ Another study may explain these differences. Martinez et al. studied the effect of four different thyroid hormones (T4, T3, T2, and Reverse T3) and how different levels of these hormones affected breast and ovarian cancer cells.²⁷ They found that different levels of the different hormones had differing effects on different breast and ovarian cancer cell lines.²⁷

Another avenue of research that has been pursued involves the thyroid hormone receptors and genetic variations that may be associated with breast cancer.^{28,29} Silva et al. analyzed the expression and mutational status of the thyroid hormone receptor genes (TR α 1, TR β 1, and TR β 2).²⁹ This research suggests that deregulation of thyroid hormone target genes may be involved in the generation of this neoplasia. Conde et al. also studied thyroid hormone receptors and their effect on breast cancer cell proliferation.²⁸ They found that thyroid hormone

receptors, TR α , were found in the nuclei of normal breast duct and acini epithelial cells, but found these receptors in the cytoplasm of pathological breast epithelial cells. These results reveal substantial changes in the expression profile of thyroid hormone receptors suggesting a possible deregulation that could trigger breast cancer development.

Research is also ongoing in regards to tissue iodine content and the sodium-iodine symporter molecule (NIS) and the effect of these on mammary tissue.^{30,31} Kilbane et al. concluded that the tissue iodine content of breast carcinoma specimens was significantly lower than that of tissue from remote sites within the tumor-bearing breast.³¹ This study also found that there was significant inhibition in ¹²⁵I uptake in specimens from patients with TPO.Ab positivity.³¹ Fierabracci et al. on the other hand found that there was no interference by TPO.Ab in the NIS uptake of ¹²⁵I.³⁰

Further investigation is needed to determine the complete molecular effect of thyroid hormone on breast tissue and how that translates to the final effect in vivo. Until we know how thyroid hormones affect breast tissue, we will not be able to determine if there is an association between thyroid disorders and breast cancer.

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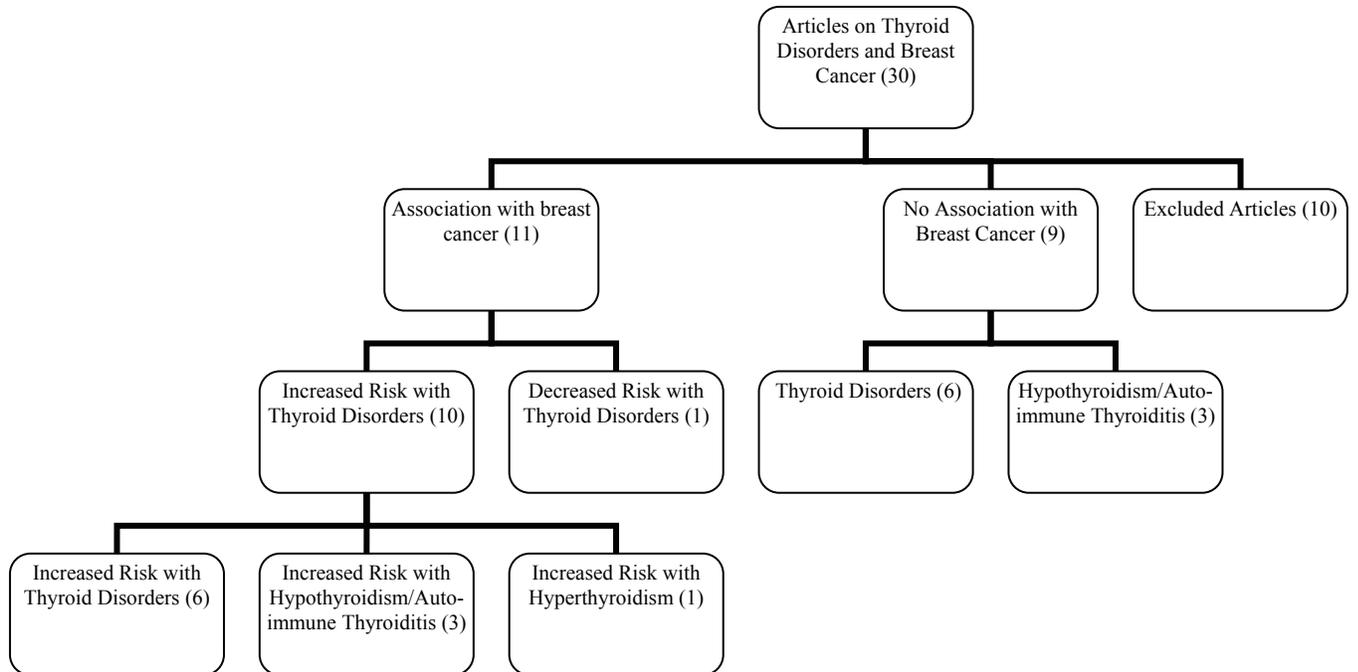
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APPENDIX A

Organization Diagram of Articles



APPENDIX B

Levels of Evidence

Author	N	Title of Study	Study Quality	Results	assoc?
Level 1: Includes inception cohorts					
Cengiz	n=204	The relationship between prognostic factors of breast cancer and thyroid disorders in Turkish women	1	The incidence of thyroid pathology is higher in breast cancer patients compared to controls which suggests a relationship between breast carcinoma and thyroid pathology.	y
Giani	n=202	Relationship between breast cancer and thyroid disease: Relevance of autoimmune thyroid disorders in breast malignancy	1	The overall prevalence of thyroid disease is increased in patients with breast cancer with Hashimoto's thyroiditis accounting for the largest portion of this.	y
Giustarini	n=161	Thyroid autoimmunity in patients with malignant and benign breast disease before surgery	1	Results of this study confirm a strong relationship between thyroid autoimmunity and breast cancer. Also demonstrates that this relationship is present before surgery or any anti-tumoral treatment.	y
Gogas	n=600	Autoimmune thyroid disease in women with breast carcinoma	1	Breast cancer patients showed a high prevalence of thyroid enlargement and presence of nodules, by clinical and ultrasound evaluation as well as an increased prevalence of subclinical autoimmune thyroiditis confirmed by antibody positivity.	y
Sadetzki	n=54,118	Second primary breast and thyroid cancers (Isreal)	1	The overall SIR (1.07) for developing a second primary breast cancer following thyroid cancer was not elevated.	n
Sarlis	n=13 studies with 14,226 population	Lack of associaiton between Hashimoto's thyroiditis and breast cancer: A quantitative research sythesis	1	This study failed to demonstrate a statistical significant association between the diagnosis of Hashimoto's thyroiditis and breast cancer.	n
Smyth	n=566	Serum Thyroid Peroxidase Autoantibodies, Thyroid Volume, and Outcome in Breast Carcinoma	1	Significantly greater number of breast cancer patients were TPO.Ab positive then the control group (p<0.001)	y
Saraiva	n=48	Profile of thyroid hormones in breast cancer patients	1	Thyroid dysfunction was found to be significantly higher in patients with breast cancer (p<0.05).	y
Turken	n=250	Breast cancer in association with thyroid disorders	1	An increased prevalence of autoimmune and non-autoimmune thyroid diseases in breast cancer patients.	y

Author	N	Title of Study	Study Quality	Results	assoc?
Kuijpers	n=2738	Hypothyroidism might be related to breast cancer in post-menopausal women	1	No association was found between TPO.Ab and the development of breast cancer. The presence of TPO.Ab was not associated with development of new breast carcinoma (OR=1.1).	n
Smyth	n=243	Thyroid disease and breast cancer	1	The mean thyroid volume in patients with breast cancer ($p<0.01$) and the number of individual patients with breast cancer having enlarged thyroid glands ($p<0.001$) was significantly greater than that in age matched controls .	y
Smyth	n=778	A direct relationship between thyroid enlargement and breast cancer	1	Both mean thyroid volume and the percentage of individual patients with enlarged thyroid glands were significantly greater in the breast cancer group than equivalent values in age-matched controls ($p<0.01$).	y
Level 2: Includes retrospective cohorts					
Goldman	n=7338	Cancer mortality in women with thyroid disease	2	Women with the thyroid diagnoses included in this study were not at an increased risk of death from breast cancer with the exception of those with nontoxic nodular goiter who used thyroid supplements.	n
Cristofanilli	n=2224	Thyroid hormone and breast carcinoma: Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma	2	Patients with primary hypothyroidism had a 61% reduction in risk of developing invasive disease, thus the association between primary breast cancer and hypothyroidism remains a strong protective factor against diagnosis of invasive breast carcinoma.	y
Simon	n=9257	Do thyroid disorders increase the risk of breast cancer?	2	Neither disorders of the thyroid nor treatment for these conditions substantially alters risk of breast cancer.	n
Moseson	n=1101	The influence of medical conditions associated with hormones on the risk of breast cancer	2	There was no association between any thyroid disorder and breast cancer risk ($p=0.82$).	n
Lemaire	n=578	Thyroid function in women with breast cancer	2	T3 and T4 were significantly higher ($p<0.01$) in breast cancer patients than in the other groups.	y
Weiss	n=4163	Breast cancer risk in young women and history of selected medical conditions	2	Thyroid disorders as a group were not associated with breast cancer risk (OR=0.94).	n
Talamini	n=5157	Selected medical conditions and risk of breast cancer	2	No evidence of relationship between any benign thyroid disease and breast cancer risk (OR=0.9).	n

Author	N	Title of Study	Study Quality	Results	assoc?
Morabia	n=155	Thyroid hormones and duration of ovulatory activity in the etiology of breast cancer.	2	Depressed thyroid activity is not clearly associated with breast cancer except among women with a long duration of ovulatory activity.	n

APPENDIX C

VITA

Name: Michelle L. Menke

Date of Birth: November 4, 1974

Place of Birth: Hutchinson, Kansas

Education:

2004-2006 Master – Physician Assistant (M.P.A)
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