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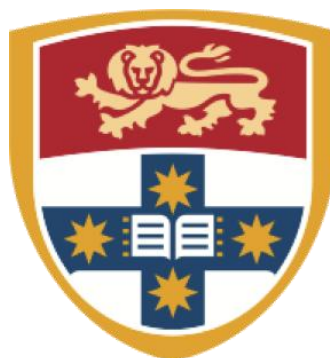
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The effect of Benign Thyroid Disease, Diabetes Mellitus, Weight Loss and Physical Activity on Breast Cancer Risk

Prudence J Hardefeldt

**A thesis submitted in fulfillment of
the requirements for the degree of**

Master of Philosophy (Medicine)



**Department of Medicine
The University of Sydney ©
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“From little things, big things grow”

Paul Kelly

Statement of Originality

The contents of this thesis represents original research undertaken by the author from the Whiteley-Martin Research Centre, Sydney Medical Program, University of Sydney, Australia.

The author was responsible for the design, development and conduct of the work which was performed under the joint supervision of Associate Professor Guy Eslick and Dr Senarath Edirimanne.

All literature searches, data extraction and interpretation were completed by the author unless otherwise acknowledged. Data analysis was completed by the Associate Professor Guy Eslick in conjunction with the author.

Certification

I hereby certify that the work embodied in this thesis is the result of original research and has not been submitted for a higher degree to any other University or Institution.



Prudence J Hardefeldt

Prudence J Hardefeldt

Publications

The following manuscripts have been published, accepted for publication or submitted for publication from the work embodied in this thesis.

Journal Papers

Hardefeldt PJ, Edirimanne S, Eslick, GD. (2012). Diabetes mellitus increases the risk of Breast Cancer. *Endocrine Related Cancer*, 19, 793-803.

Hardefeldt PJ, Eslick GD, Edirimanne S. (2012). Benign thyroid disease is associated with breast cancer: A meta-analysis. *Breast Cancer Research and Treatment*, 133 (3), 1169-1177.

Hardefeldt PJ, Edirimanne S, Eslick, GD. (2013) Goitre is associated with benign breast disease: A meta-analysis. *The Breast Journal*, 19 (3), 346-348.

Hardefeldt PJ, Edirimanne S, Eslick, GD. (2013) Physical activity and weight loss reduce the risk of breast cancer. *Journal of the American Medical Association* (submitted).

Oral Presentation

2012 Sydney International Breast Cancer Conference

Hardefeldt PJ, Edirimanne S, Eslick, GD. Diabetes mellitus increases the risk of breast cancer.

Poster Presentations

2012 San Antonio Breast Cancer Symposium

Hardefeldt PJ, Edirimanne S, Eslick, GD. Physical activity reduces the risk of breast cancer: A meta-analysis.

2012 San Antonio Breast Cancer Symposium

Hardefeldt PJ, Edirimanne S, Eslick, GD. Diabetes mellitus increases the risk of breast cancer.

2011 San Antonio Breast Cancer Symposium

Hardefeldt PJ, Edirimanne S, Eslick, GD. Benign thyroid disease is associated with breast cancer: A meta-analysis.

Published Abstracts

Hardefeldt PJ, Eslick GD, Edirimanne S. (2011). Benign thyroid disease is associated with breast cancer: A meta-analysis. *Cancer Research*, 71 (24 suppl), P4-11-11.

Hardefeldt PJ, Edirimanne S, Eslick, GD. (2012). Diabetes Mellitus increases the risk of Breast Cancer. *Cancer Research*, 72 (24 suppl), P4-12-07.

Hardefeldt PJ, Edirimanne S, Eslick, GD. (2012) Physical activity and weight loss reduce the risk of breast cancer. *Cancer Research*, 72 (24 suppl), P1-11-01.

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Abstract

The aetiology of breast cancer has been the topic of numerous observational studies with benign thyroid diseases, diabetes mellitus, physical activity and weight loss associated with altered breast cancer risk. However, there has been a degree of inconsistency in the results of the primary studies, with a consensus on the exact nature of the association between breast cancer and these four risk factors yet to be determined. The aim of this study was to complete a meta-analysis of primary observational studies clarifying the risk of breast cancer associated with benign thyroid diseases, diabetes mellitus, physical activity and weight loss.

A comprehensive database search was completed with MEDLINE, EMBASE, PubMed, Current Contents Connect and Google Scholar searched with additional cross checking of reference lists. Inclusion criteria depended on the risk factor investigated but general requirements included the use of an internal control group and reporting of both an odds ratio, relative risk or hazards ratio and 95% confidence interval. Collated data was assessed for heterogeneity and a pooled odds ratio calculated.

The results of this study identified an increased risk of breast cancer associated with type 2 diabetes mellitus while both physical activity and weight loss were found to be protective in terms of breast cancer risk. These findings are in keeping with the “lifestyle” approach to breast cancer risk. While sub group analyses were completed wherever possible, there were insufficient studies to

analyse the risk of breast cancer associated with graves disease and type 1 diabetes mellitus.

In conclusion, type 2 diabetes mellitus and autoimmune thyroiditis are associated with an increased risk of breast cancer while physical activity and weight loss was found to be protective. Prospective longitudinal studies of high quality are required to further explore these risk factors.

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List of Abbreviations

AITD- Autoimmune thyroiditis

NIS- sodium-iodine symporter

Anti-TPO- Anti-thyroid peroxidase antibodies

Anti-TG- anti thyroglobulin antibodies

OR- odds ratio

CI- confidence interval

CS- cross section

CC- case-control

CO- cohort

RCT- randomized controlled trial

n- classic fail safe

1. Introduction

Breast cancer is the most common form of cancer facing women in Australia. On average, 333 per 100,000 women aged between 50 and 70 years old are diagnosed with breast cancer each year, a number which has gradually increased over the last 20 years (figure 1)[1]. Consequentially, breast cancer presents a significant physical, psychological and financial burden on both the individual and the healthcare system as a whole. For this reason, primary prevention, or the management or avoidance of known risk factors, is more important than ever.

The aetiology of breast cancer can broadly be split into three categories: risk factors known to modulate the bodies' exposure to sex steroids, familial or genetic risk factors and finally personal and lifestyle risk factors. The increased exposure to sex steroids, predominantly oestrogen, can be a result of a number of factors including early menarche, late menopause, null parity and weight gain, with each of these known to increase the risk of breast cancer[2].

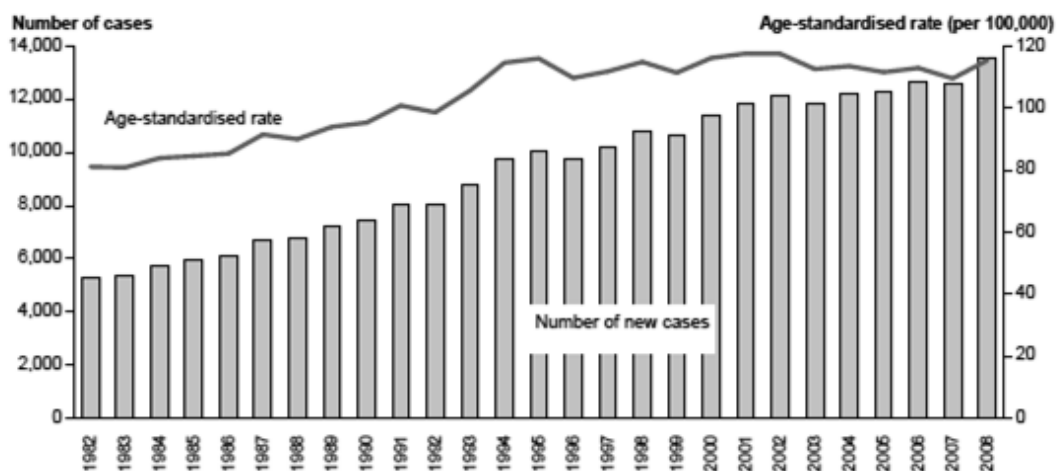


Figure 1. Trend in breast cancer risk in Australia between 1982 and 2008. Published in 2012 by the Australian Institute of Health and Welfare & Cancer Australia[1].

While the first three reproductive factors listed above directly increase the bodies' lifetime exposure to oestrogen, weight gain modulates the oestrogen pathway via the aromatase enzyme. Here, adipose tissue converts androgens to oestrogens at peripheral sites to increase plasma oestradiol and promote proliferation[3, 4].

A significant family history of breast cancer increases the risk of breast cancer whether or not there is a known genetic mutation. Current estimates quantify this risk at an odds ratio greater than two meaning someone with a family history of breast cancer is more than twice as likely to develop breast cancer than the general population[5]. A known genetic mutation, on the other hand, results in a slightly higher risk of breast cancer. The two most common genetic mutations are the BRCA1 gene on chromosome 17 and the BRCA2 gene on chromosome 13. A mutation to one of these genes results in a 60% risk of developing breast cancer before age 70 for a BRCA 1 mutation and 45% risk for BRCA2 [6-8] compared with a 12% lifetime risk of developing breast cancer in the general population[1].

The association between personal and lifestyle factors and breast cancer risk has been the topic of a numerous observational studies. Ageing is the personal factor known to have the greatest effect on breast cancer risk with the risk of acquiring breast cancer gradually increasing across the lifetime to peak between the age of 65 and 69 years (figure 2)[1]. Here the risk of breast cancer is 378 per 100,000 women, an risk rate over 10 times greater than the risk for a young adult aged below 30[1]. Furthermore, studies have identified an increased risk of breast

cancer associated with lifestyle decisions including the use of both cigarettes and alcohol[9, 10]. It should be noted, however, that the magnitude of this increased risk is quite small, with only a 10% increased risk associated with smoking[11] and a 30% increased risk associated with alcohol use[9, 10, 12].

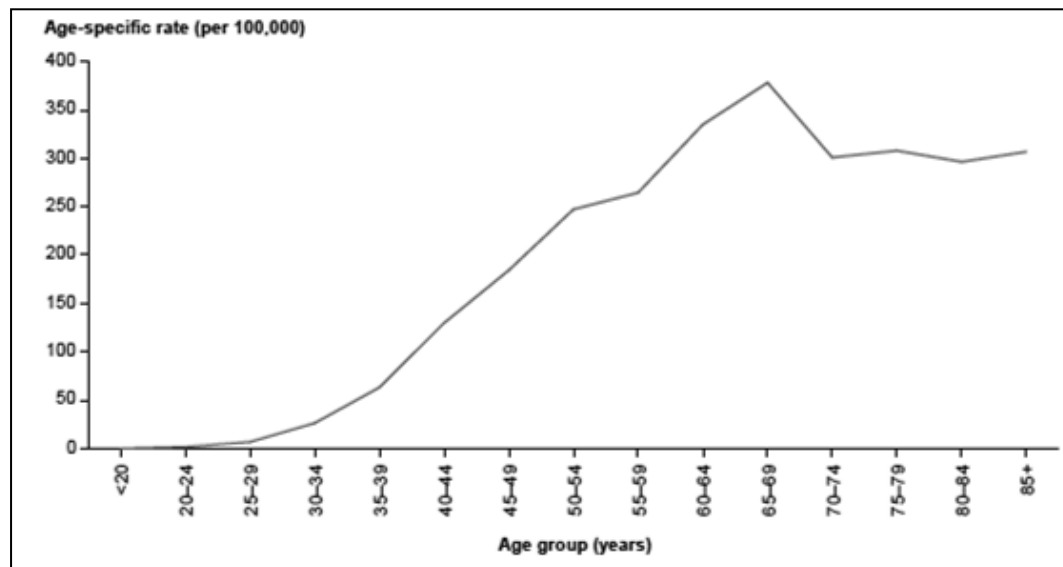


Figure 2. Age at diagnosis and corresponding breast cancer incidence rates in Australia. Published in 2012 by the Australian Institute of Health and Welfare[1].

A number of other risk factors have been identified within primary studies however a consensus is yet to be reached on the impact they have on breast cancer risk. These include benign thyroid diseases, diabetes mellitus and physical activity; the three risk factors to be investigated in this analysis.

An association between benign thyroid diseases and breast cancer has been discussed in the literature since as early as 1896 where Beatson postulated that surgical removal of the thyroid gland, in addition to the ovaries, may assist in the management of metastatic breast cancer[13]. Since this case series, a number of observational studies have been undertaken with a degree of inconsistency in

the results. While some studies have identified an increased risk associated with benign thyroid diseases[14-16], others have failed to find an association between the two[17, 18].

Diabetes mellitus has long been hypothesised to increase the risk of breast cancer secondary to the hyperinsulinemia associated with type 2 diabetes mellitus[19]. A meta-analysis of observational studies, published in 2007 by Larsson et al[20], confirmed this increased risk however there was no subgrouping completed by type of diabetes. In addition, a number of new studies have now been published which were not incorporated in this initial review.

Physical activity and weight loss are two predominantly beneficial lifestyle choices hypothesised to reduce the risk of breast cancer[21-26]. A number of mechanisms have been implicated in this reduction of risk: the main two involving a reduction in both hyperinsulinemia[27] and circulating oestrogen[28] associated with increased physical activity or weight loss. Despite over 100 primary studies investigating the association between physical activity and breast cancer risk, there is yet to be a consensus formed regarding intensity of the exercise, timing of the exercise in terms of the different stages of life (adolescence, adulthood and post menopause) nor the best method or extent of weight loss in women to achieve a reduction in breast cancer risk.

The aims of this study were to complete a thorough literature review of the association between benign thyroid diseases, diabetes mellitus, physical activity, weight loss and breast cancer risk. We aimed to include all types of breast

cancer, not only invasive breast cancer. In addition we aimed to complete a quantitative analysis of the primary studies, updating any prior reviews and completing subgroup analyses wherever possible to further investigate the etiology of breast cancer.

2. Benign Thyroid Diseases and Breast Cancer Risk

2.1 Introduction

The controversial relationship between benign thyroid diseases and breast cancer has been investigated for over 50 years. Despite extensive population studies, the results as a whole have been inconsistent. To date a relationship between specific benign thyroid diseases and breast cancer has not been quantified with the exception of Autoimmune Thyroiditis (AITD), which was investigated in a meta-analysis published in 2002 [29]. This study by Sarlis et al. [29] found no association between AITD and breast cancer despite significant findings in a number of primary studies [15, 30-32].

The effect of hypothyroidism on breast cancer risk has also proved a point of contention. Cristofanilli et al. (2005)[33] found primary hypothyroidism reduced the risk of breast cancer despite other studies reporting an increased risk of breast cancer[34, 35] or no association at all [36-38]. This variation in results is also present when investigating the relationship between goitre and breast cancer. Although numerous studies have reported an increased risk of breast cancer associated with goitre [15, 38-40], other studies have failed to find a relationship between the two [36]. In regards to Benign Thyroid Diseases and breast cancer, this disparity in results appears relatively commonly throughout the literature.

Despite numerous studies investigating the association between Benign Thyroid Diseases and breast cancer, the exact mechanism behind any such relationship

has not yet been identified. Hypotheses have focused on common elements to both the thyroid and the breast such as the Sodium-Iodide Symporter (NIS)[41] and the proliferative effects of thyroid hormones[42]. However, a reversal in the relationship with breast cancer acting as the predecessor in triggering thyroid dysfunction has not been excluded[43, 44].

The purpose of this study was to collate and analyse literature investigating the relationship between benign thyroid diseases and breast cancer. In addition, we aimed to incorporate data from recent studies to re-assess the relationship between autoimmune thyroid disease and breast cancer, offering an updated analysis, since that completed by Sarlis et al in 2002, of whether the presence of autoimmune thyroid disease may indicate a higher risk of breast cancer.[29]

2.2 Methods

Study Protocol

One reviewer (PH) following the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE)[45] completed a database search. The databases, MEDLINE (from 1950), EMBASE (from 1949), PubMed (from 1946), Current Contents Connect (from 1998) and Google Scholar (from 1992), were searched using medical subject headings, text word and keyword searches wherever possible (figure 3). The search terms used were “thyroid disease” or “hyperthyroid” or “hypothyroid”, “thyroiditis” or “graves” AND “breast disease”, or “breast carcinoma”, or “breast cancer” or “breast neoplasm”. While there was no language restriction placed on the search, we did not search for unpublished literature. The reference lists of relevant studies were checked manually to locate any missing studies.

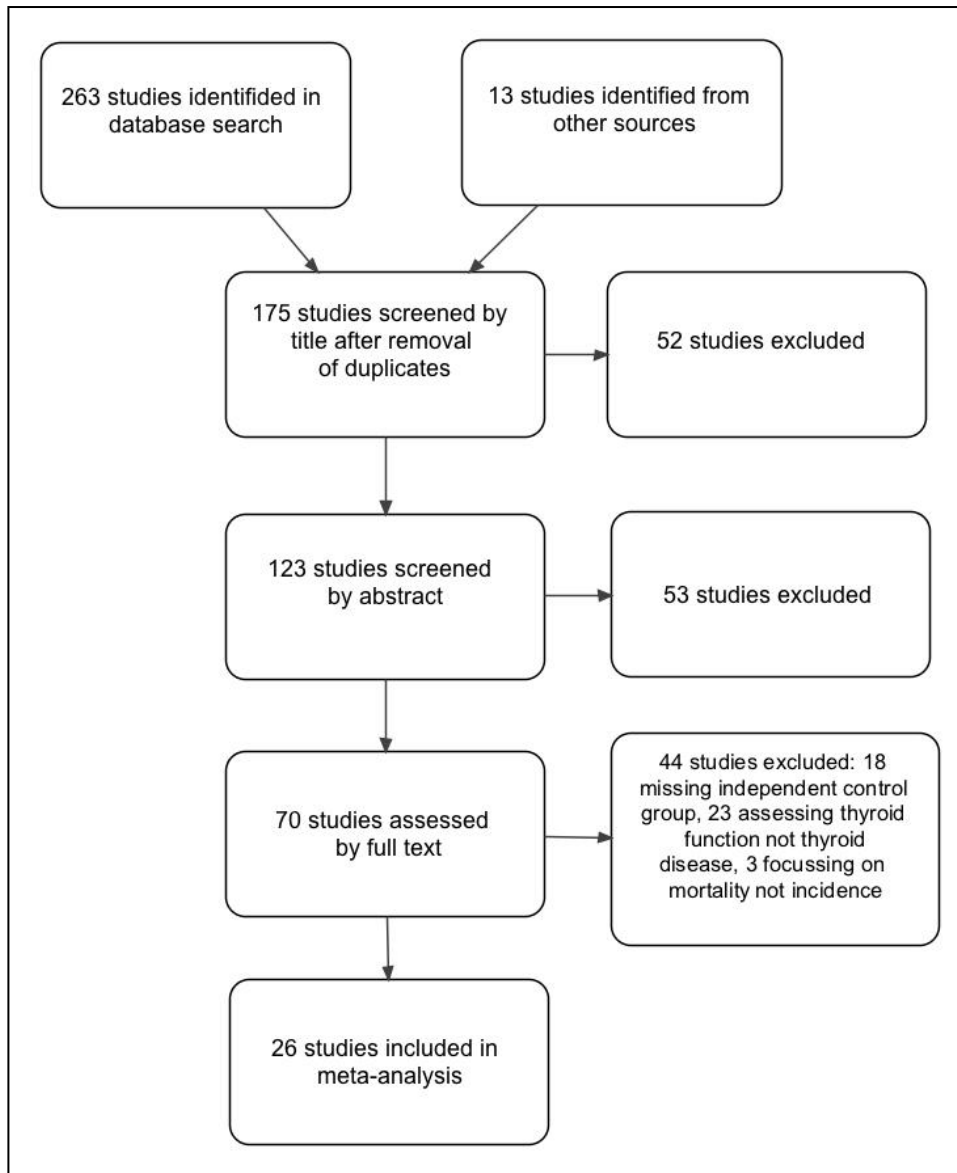


Figure 3. Results of the literature search of Benign Thyroid Disease and Breast Cancer.

Study Selection

Studies which met the following inclusion criteria were included in the meta-analysis: (1) The risk point estimate was reported as an odds ratio (OR), relative risk (RR) or hazard ratio (HR) or the OR could be calculated from the presented data; (2) the 95% confidence interval (CI) was reported or the CI could be calculated from the presented data; (3) an internal control group was used to calculate the OR and the internal control group had been diagnosed with neither

breast disease nor thyroid disease; (4) the diagnosis of benign thyroid disease adhered to the criteria in the table 1. Any study that did not meet the above criteria was excluded from the meta-analysis.

Table 1. Inclusion criteria.

Thyroid disease	Diagnostic criteria
Auto-immune thyroiditis	Positive serum antibody (anti-TPO, anti-TG or microsomal) and evidence of thyroid dysfunction (goitre, altered serum thyroid function tests) and/or histological confirmation of the diagnosis
Antibody presence	Presence of Anti-TPO, Anti-Tg or Microsomal antibodies in serum
Goitre	Increased thyroid volume on ultrasound, palpable goitre on clinical examination, or confirmation of diagnosis in medical record
Hyperthyroid	Thyroid function tests indicating thyrotoxicosis (i.e. decreased TSH and raised T3/T4)
Hypothyroid	Thyroid function tests indicating hypothyroidism (i.e. increased TSH and decreased T3/T4)
Graves Disease	Presence of TSH-receptor antibody and thyroid function tests indicating thyrotoxicosis

Data Extraction

Data was extracted by a single reviewer (P.H) and entered into a standardised data spread sheet (table 2). For each article, data collected included publication date, time-frame for data collection, study type (cross section (CS), Cohort (CO) or case control (CC)), sample size, mean age, country (geographical and economic status), odds ratio, relative risk or hazard ratio, confidence interval and adjusted variables. Where applicable, adjusted odds ratios were recorded. However, where no odds ratio was given, an unadjusted odds ratio and confidence interval was calculated by the reviewer (P.H). Where multiple odds ratios were given within the same study, i.e. from two different geographical locations[46], the data was entered as two separate odds ratios. Studies that did

not define the specific type of benign thyroid disease were analysed as “non-specific thyroid disease”.

Statistical Analysis

A random effects model was used to calculate a pooled odds ratio for the effect of thyroid disease on the risk of developing breast cancer. Heterogeneity was assessed using Cochran’s Q statistic with a p value of less than 0.10 indicating significant heterogeneity. The extent of heterogeneity was further quantified using the I² statistic with results of 25%, 50% and 75% correlating with low, moderate and high levels of heterogeneity respectively. Egger’s regression model was used to calculate publication bias with the extent of bias documented using the “fail safe” method whereby the number of studies required to nullify our results was calculated. A fail safe (n) with a p value less than 0.05 was considered significant. Data was analysed using Comprehensive Meta-analysis (version 2.0).

Table 2. Summary of included studies.

Study	Year	Study Design	Cases	Control	Diagnostic tests ^a	Summary of findings ^f
Autoimmune Thyroiditis						
Giani[15]	1996	CS	102	100	TFT, ultrasound, TPO, TG, FNA	Increased prevalence of AITD associated with breast cancer
Jiskra[31]	2007	CS	84	49	TFT, ultrasound, TPO, TG	Increased prevalence of AITD associated with breast cancer
Gogas[30]	2001	CS	310	190	TFT, ultrasound, TPO, TG, FNA	Increased prevalence of AITD associated with breast cancer
Turken[40]	2003	CS	150	100	TFT, ultrasound, TPO, TG, FNA	Increased prevalence of AITD associated with breast cancer
Presence of Anti thyroid antibodies						
Mittra[46] ^b	1976	CS	85	96	Microsomal antibodies	No increased prevalence of microsomal antibodies in breast cancer

CS

Mitra[46] ^c	1976	CS	277	211	Microsomal antibodies	No increased prevalence of microsomal antibodies in breast cancer
Kuijpers[34]	2005	CO	278	2738	TFT, TPO	No relationship between risk of breast cancer and anti-TPO antibody presence
Kuijpers[34]	2005	CS	278	2497	TFT, TPO	Increased prevalence of breast cancer with presence of anti-TPO
Giustarini[47]	2006	CS	36	100	TFT, TPO, TG, ultrasound	Increased prevalence of anti-thyroid antibodies in patients with breast cancer
Rasmussen[48]	1987	CS	58	75	TFT, TPO, TG, TSH-R	Increased prevalence of anti-thyroid antibodies in breast cancer patients
Smyth[49]	1998	CS	356	194	TFT, TPO, ultrasound	Increased prevalence of anti-TPO antibodies in breast cancer patients
Goitre						
Adamopoulos[39]	1986	CS	97	60	TFT, microsomal antibodies, ultrasound	Increased prevalence of goitre in breast cancer patients
Smyth[38]	1996	CS	200	200	TFT, ultrasound	Increased prevalence of goitre in patients with breast cancer, no relationship between hypothyroidism or hyperthyroidism
Adami[36]	1978	CC	179	179	TFT, medical record search	No relationship between presence of goitre, hypothyroidism or hyperthyroidism and breast cancer
Hypothyroidism						
Singh[35]	1982	CS	34	40	Radioactive iodine uptake	Increased prevalence of hypothyroidism in breast cancer patients
Ditsch[37]	2010	CS	65	38	TFT, antibodies	No relationship between BTB and breast cancer
Overall Benign Thyroid Disease						
Cengez[14]	2004	CS	136	68	Ultrasound, TFI, antibodies	Increased prevalence of goitre and BTB in breast cancer
Purde[50] ^d	1990	CC	148	149	Medical record search	No relationship between BTB and breast cancer
Purde[50] ^f	1990	CC	216	160	Medical record search	Increased risk of breast cancer in patients with BTB
Brinton[51]	1984	CC	1552	1375	Self reporting	No relationship between BTB and breast cancer
Franceschi[52]	1990	CC	2663	2344	Self reporting	No relationship between BTB and breast cancer
Kalache[53]	1982	CC	1176	1176	Self reporting	No relationship between BTB and breast cancer
Moseson[54]	1993	CC	370	783	Self reporting	No relationship between BTB and breast cancer
Talamini[17]	1997	CC	2569	2588	Self reporting	No relationship between BTB and breast cancer

Weiss[18]	1990	CC	2173	1990	Self reporting	No relationship between BTB and breast cancer in younger women
Simon[55]	2002	CC	4575	4682	Self reporting	No relationship between BTB and breast cancer
MacFarlane[56]	1980	CS	162	72	TFT	No relationship between BTB and breast cancer
Saraiva[16]	2005	CS	26	22	TFT, antibodies	Increased prevalence of BTB in breast cancer patients
Schottenfield[57]	1968	CC	73	102	Medical record search, TFT	No relationship between BTB and breast cancer

^aDiagnostic tests: Serum thyroid function tests (TFT), immunoassay for anti-TPO antibodies (TPO), immunoassay for anti-TG antibodies (TG), Fine needle aspiration (FNA) ^bJapanese population ^cBritish population ^dEstonian population ^eSlovakian population ^f Benign thyroid diseases (BTB), Breast Cancer (breast cancer), Autoimmune Thyroiditis (AITD)

2.2 Results

263 studies were identified in the literature review of which 26 studies were included in the meta-analysis resulting in a pooled population of 17257 cases and 19396 controls with a mean age of 56. Meta-analysis of these 26 studies resulted in an odds ratio of 1.57 (95%CI 1.31-1.87). Heterogeneity was high ($I^2=84.18$) and significant ($p<0.001$) and there was evidence of publication bias ($p=0.002$, CFS 451) (figure 4). The studies were further subgrouped by study design with evidence of an increased risk only in the cross sectional studies (case control OR 1.08 (0.91-1.28), cohort OR 1.10 (0.45-2.70) and cross section OR 2.46 (1.76-3.44)). There was no trend identified when assessing studies by year of publication. Sub group analyses were then completed by the type of benign thyroid disease assessed in the primary studies.

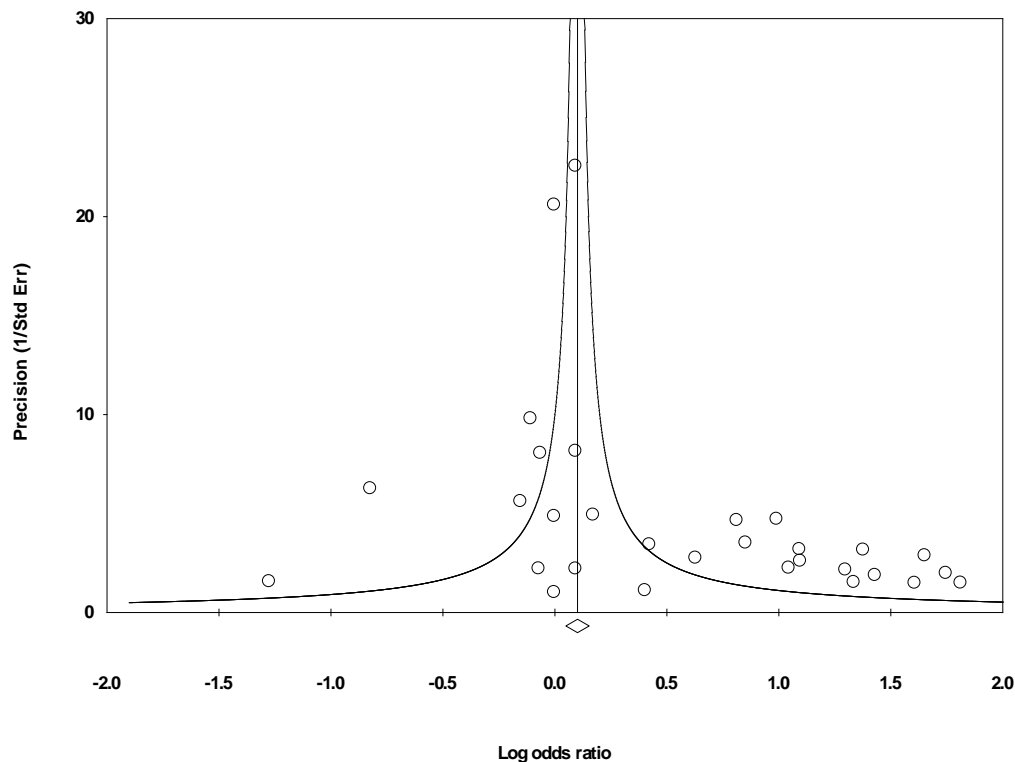


Figure 4. Funnel plot of publication bias

Autoimmune thyroiditis

14 studies were identified investigating the risk of breast cancer in patients with AITD. Ten studies were excluded for failing to meet the inclusion criteria: Two studies were excluded for failing to confirm the diagnosis[55, 58], Four studies were excluded for failing to include an internal control group diagnosed with neither breast nor thyroid diseases[59-62] and two studies were excluded for investigating mortality rather than risk[63, 64]. Jiskra et al. (2007) [31] and Smyth et al. (1996) [38] were included however, Jiskra et al. (2003) [32] and Smyth et al. (1993) [65] were excluded as they appeared to use the same study population evident in the similar characteristics present in case and control groups and the identical study designs.

The four remaining studies were homogenous in their results, each reporting a statistically significant risk point estimate[15, 30, 31, 40] (figure 5). The pooled odds ratio, 2.92 (95% CI 2.13-4.01), demonstrated an increased risk of breast cancer in the AITD population. Minimal heterogeneity was present ($I^2 = 0\%$, $p=0.15$).

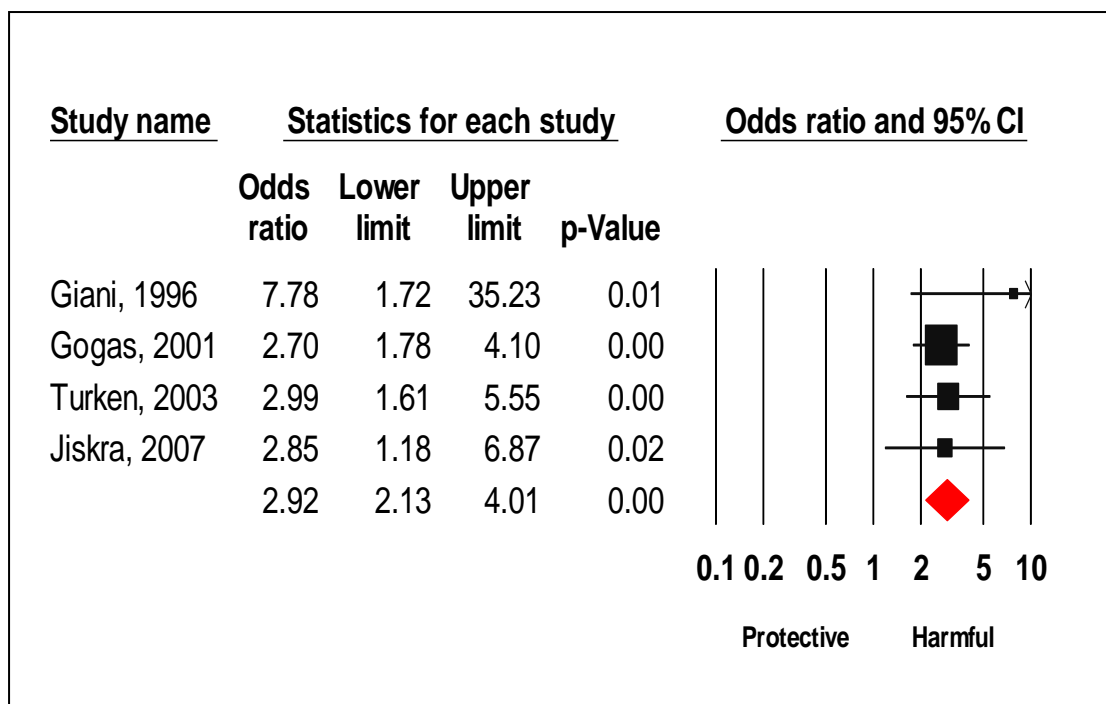


Figure 5. Autoimmune thyroiditis and breast cancer.

Presence of anti-TPO, anti-TG or microsomal antibodies

Eight studies were found investigating the link between thyroid antibody presence and the risk of breast cancer. Six of the eight studies reported a significant increase in the risk of breast cancer. However two studies[34, 46] reported an increased risk point estimate despite non-significant results (figure 6). All eight studies met the inclusion criteria, resulting in a pooled odds ratio of 2.02 (95% CI 1.63-2.50). Heterogeneity was moderate ($I^2=58.3$) but not significant ($p=0.08$).

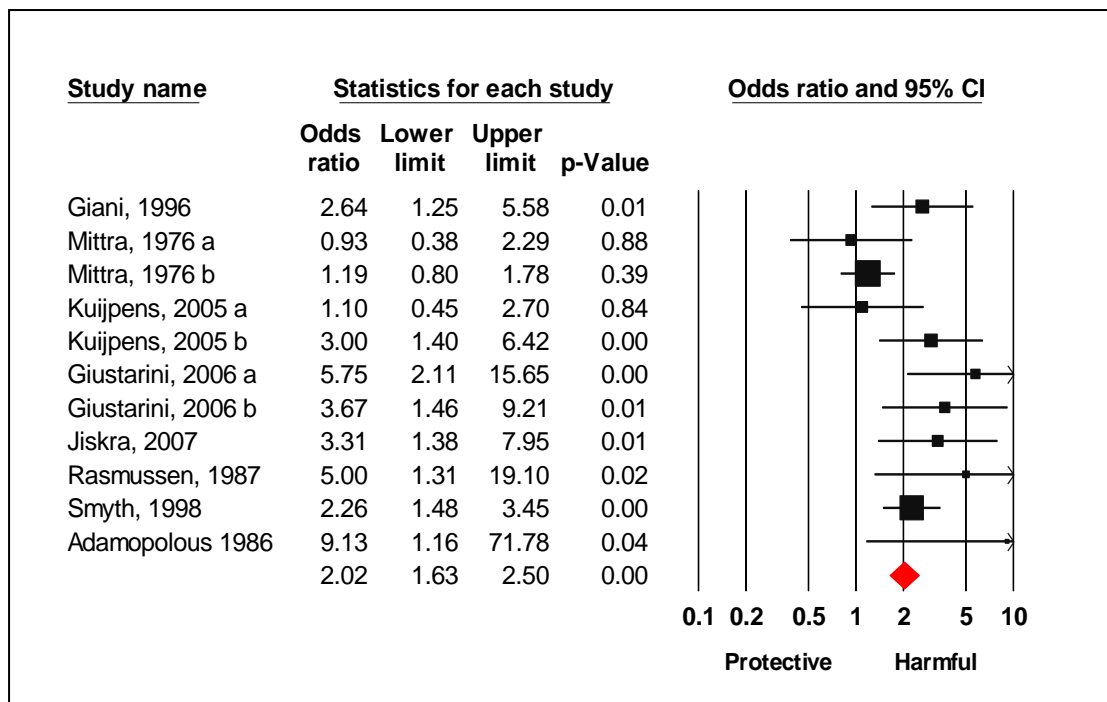


Figure 6. Anti-thyroid antibodies and breast cancer.

We performed a sub group analysis investigating the risk specific antibodies (anti-TG and anti-TPO) have on the development of breast cancer. Five studies were identified investigating anti-TPO presence, with all studies meeting the inclusion criteria. Four studies supported an increased risk[15, 31, 47, 49] while one study found no significant results in its cohort study, and significant results in the cross sectional study[34]. Anti-TPO was associated with an increased risk (2.64, 95% CI 1.82-3.83) in the pooled odds ratio. Minimal heterogeneity was present ($I^2= 29.34$, $p=.22$).

We identified four studies investigating anti-Tg presence and the associated risk of breast cancer. Three studies showed an increases risk of breast cancer with anti-Tg presence[31, 47, 48], while one study was not significant despite a protective risk point estimate[15]. Overall, an increased risk of breast cancer

was found (OR 2.72, 95% CI 1.58-4.69) further supporting the autoimmune link. Minimal heterogeneity was present ($I^2= 18.10$, $p=0.30$).

Goitre

We found 13 studies investigating the link between goitre and breast cancer. Eight studies were excluded for failing to meet the inclusion criteria, predominantly due to a reliance on self-reporting without confirming either the initial diagnosis or the type of goitre present[17, 51, 54, 55]. Two studies were excluded for failing to include an internal control group[66-68] and one study was excluded for investigating mortality rather than risk[69].

The remaining five studies were included in the meta-analysis. Four of the five studies were homogenous in their findings of an increased risk of breast cancer[15, 38-40], while one study found no evidence of a relationship between the two [36] (figure 7). The goitre was diagnosed by clinical examination alone in one study[39], by clinical examination confirmed by ultrasound in three studies[15, 38, 40] and by self reporting with confirmation from the medical record in the final study[36]. The pooled odds ratio demonstrated an increased risk associated with goitre, evident in an OR of 2.26 (95% CI 1.39-3.69). Moderate and significant heterogeneity was present ($I^2= 56.52$, $p=0.06$).

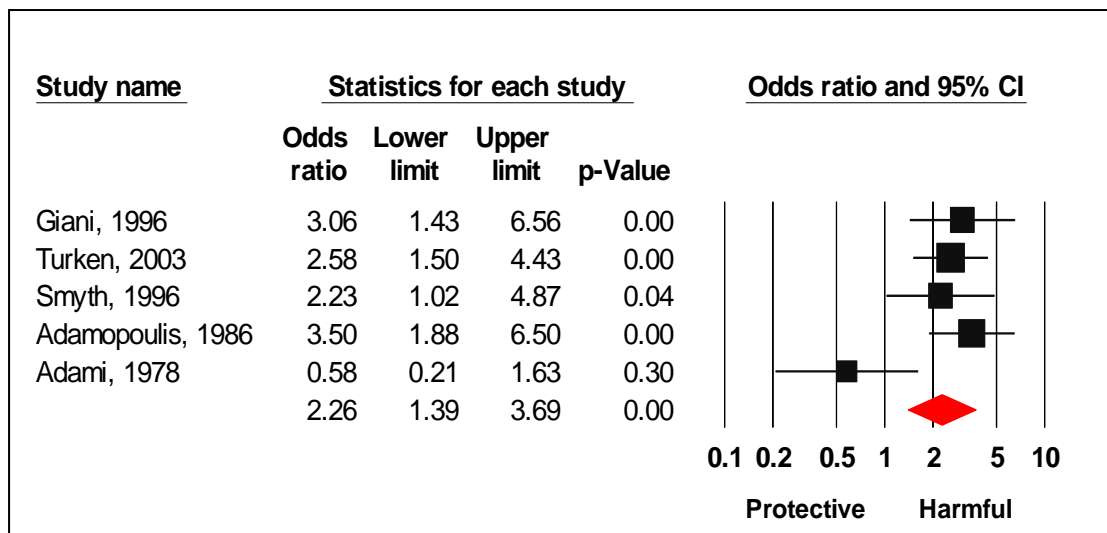


Figure 7. Goitre and breast cancer.

We performed a subgroup analysis investigating the effect diffuse and nodular goitres have on the risk of breast cancer. Of the five studies investigating goitre, three studies presented data on diffuse goitre [30, 39, 40]. The studies were homogenous in reporting a significantly increased risk of breast cancer. This increased risk was confirmed in a pooled odds ratio of 2.84 (95% CI 1.53-5.27) and the absence of heterogeneity ($I^2=0$, $p=0.72$).

The presence of nodular goitre was also associated with breast cancer. Five studies provided data investigating breast cancer risk and nodular goitre [15, 30, 39, 40, 65], Four studies were homogenous in their support of an increased risk [15, 30, 40, 65] while one study found non-significant results [39]. The pooled odds ratio supported an increased risk (OR 3.77, 95%CI 2.30-6.17) with moderate and significant heterogeneity ($I^2=62.6$, $p=0.03$).

Hypothyroidism

The database search identified 15 studies investigating hypothyroidism and breast cancer. Nine studies failed to meet the inclusion criteria due the absence of a control group[70, 71], use of mortality as primary outcome[69] or failure to confirm the benign thyroid diagnosis[17, 51, 53, 54, 62, 72].

The remaining six studies were included in the meta-analysis. There was a degree of heterogeneity in the results with two studies reporting an increased risk[34, 35], one study finding hypothyroidism to be protective[33] and three studies finding no connection between the two[36-38]. The quantitative synthesis did not support a relationship between hypothyroidism and breast cancer evident in a non-significant pooled odds ratio (OR 1.79, 95% CI 0.65-4.97) and high heterogeneity ($I^2=85.43$, $p=0.001$).

Hyperthyroidism

13 studies investigating the risk of breast cancer associated with hyperthyroidism were identified in our literature search. Nine studies were excluded for failing to meet the inclusion criteria: six for failing to confirm the thyroid diagnosis;[17, 51, 53, 54, 62, 72] two for the absence of an internal control group[60, 71] and one for the investigation of mortality rather than incidence[63].

The remaining four studies were included in the meta-analysis. The four studies were homogenous in their finding of no relationship between hyperthyroidism

and breast cancer[35, 36, 38, 40]. This was confirmed in a non-significant pooled odds ratio (OR 1.53, 95%CI 0.77-3.04) devoid of heterogeneity ($I^2=0$, $p=0.59$).

Graves Disease

The database search identified four studies investigating the association between Graves Disease and breast cancer[15, 37, 55, 73]. Three of the four studies failed to meet the inclusion criteria: two for failing to include an internal control group[37, 73] and one for failing to confirm the diagnosis of Graves Disease[55]. The only remaining study did not find a relationship between Grave's Disease and breast cancer[15].

2.3 Discussion

The odds ratios associated with AITD, goitre and anti-thyroid antibody support the increased risk of breast cancer associated with thyroid auto-immunity. This finding is a direct contradiction to the findings of Sarlis et al.[29]. Our study differed from the study by Sarlis in two major areas: (1) the inclusion of eight recently published studies and (2) the use of more specific inclusion criteria in regards to the diagnosis of AITD.

We did not consider nodular goitre, antibody presence or reduced thyroid function alone to be indicative of AITD. Instead, our inclusion criteria required a combination of two or more clinical parameters in confirming the diagnosis. In addition, we considered the presence of a diffuse goitre more indicative than nodular in the diagnosis of AITD[74]. At the time of diagnosis AITD is typically associated with hypothyroidism. Interestingly, our results did not demonstrate an increased risk of breast cancer associated with hypothyroidism. A possible explanation for these findings lies in our inability to differentiate between primary hypothyroidism and iatrogenic hypothyroidism secondary to the treatment of thyrotoxicosis.

Sandhu et al. (2009)[58] published one study of note excluded from our meta-analysis. Despite its large population size (n=178,186) the study did not meet our inclusion criteria. The study relied on the linking of a pharmaceutical database with a breast cancer registry to identify breast cancer patients who had previously been prescribed thyroxin. A diagnosis of AITD in this population was

assumed without confirmation. This failure to confirm the diagnosis using conventional methods led to its exclusion from our study.

The increased risk associated with both diffuse and nodular goitre has proven difficult to interpret. While diffuse goitre fits in with the autoimmune model, mechanisms linking nodular goitre to breast cancer are unknown. We cannot exclude the possibility that the increased screening and follow up treatment of breast cancer patients has resulted in an increase in the detection of thyroid dysfunction.

The lack of longitudinal studies forms the basis of the main limitation in our analysis. The majority of studies investigating thyroid autoimmunity were cross sectional in their study design. Furthermore, the few longitudinal studies were predominantly large population studies with poor differentiation between types of benign thyroid disease and a reliance on self-reporting. Finally, the majority of the primary studies were unadjusted analyses, and thus we were unable to exclude potential confounders in our analyses; age is one such confounder we were unable to exclude. Thus, despite demonstrating a relationship between breast cancer and thyroid autoimmunity, we are unable to definitively prove causality.

Strengths of this study include a broad literature search, no restrictions on language and the use of precise inclusion criteria. A comprehensive database search was undertaken with no restrictions on language in place. Furthermore, the use of specific diagnostic criteria in defining the type of thyroid disease and

the requirement for an internal control group improved the quality of our quantitative analysis.

Our results have demonstrated a strong relationship between thyroid autoimmunity and breast cancer. These results have implications in not only screening, but also the development of new prognostic markers and treatment regimes. Recent studies in breast cancer have shown significantly better prognosis associated with the presence of thyroid antibodies. Smyth et al. (1998) found the presence of thyroid antibodies to be as relevant as tumour size and lymph node involvement in predicting disease free and overall survival[49]. Cengez et al however, did not confirm this finding in a study published in 2004[14].

While exact mechanisms linking Benign Thyroid Disease and breast cancer have not yet been identified, a number of hypotheses have been suggested. The presence of the sodium iodine symporter (NIS) in both breast and thyroid tissue led to the hypothesis that the uptake and oxidation of iodine may play a role in the development of breast cancer[75]. Tazebay et al[76] found increased expression of the NIS in breast cancer tissue when compared to surrounding breast tissue and tissue from healthy, non-lactating controls. The presence of the NIS in breast tissue also has implications in the development of future therapies. The up regulation of the NIS in breast cancer may allow use of radioiodine to specifically target carcinogenic cells[41]. This model has been investigated in prostate cancer cell lines with a significant reduction in tumour size achieved[77]. While research into extra thyroidal use of radioiodine therapy is

only in the early stages, it has been used extensively and successfully in the treatment of thyroid cancer and thyrotoxicosis.

A reversal in the relationship with breast cancer acting as a predisposing factor to the development of thyroid disease is an alternate theory into the mechanism linking the two diseases. Oestrogen receptors have been identified in the cytosol of abnormal thyroid tissue while receptors were not present in normal tissue[43, 44]. Receptors for progesterone were also found exclusively in thyroid tissue containing either neoplastic or benign lesions. Despite the majority of studies focusing on thyroid disease as the predisposing factor, we cannot exclude a reversal in the relationship with the oestrogen profile associated with breast cancer triggering thyroid dysfunction.

2.4 Conclusion

In conclusion, we have confirmed a relationship between AITD and breast cancer. In addition we found increased risk associated with a diagnosis of goitre or the presence of serum thyroid autoantibodies. We recommend further high quality prospective studies to definitively prove causality in addition to ongoing investigations into the prognostic and therapeutic benefits of a relationship between benign thyroid disease and breast cancer.

3. Diabetes Mellitus and Breast Cancer Risk

3.1 Introduction

The increased risk of breast cancer associated with lifestyle factors has been the subject numerous observational studies. While there is significant evidence of an increased risk associated with obesity[78, 79], smoking[10, 80-82], alcohol intake[83, 84] and hormone replacement therapy[79, 85, 86], the risk associated with specific types of diabetes mellitus is yet to be determined. In a meta-analysis published in 2007, Larsson et al. reported an increased risk of breast cancer associated with non-specific diabetes mellitus however, due to a lack of primary studies, there was no sub group analysis by type of diabetes completed.

Liao et al. published another relevant study in 2011[87]. This meta-analysis focused on studies published after 2000, investigating the association between diabetes and breast cancer risk with subgrouping by geographical location and menopausal status. Interestingly, this study reported an increased breast cancer risk in Europe and America with no increased risk identified in Asia. Furthermore, this study reported a significant association between breast cancer and diabetes mellitus in only the postmenopausal age group.

In regards to the primary studies, there is a degree of inconsistency in the literature, especially when considering specific types of diabetes. Gestational diabetes has been found to be protective in one study[88] while other studies reported an increased risk[89] or no association between gestational diabetes and breast cancer risk[90-92]. This discrepancy is also present within studies

investigating type 2 diabetes mellitus and studies investigating the aetiology of breast cancer in males.

While the exact mechanism behind any association between diabetes mellitus and breast cancer has not yet been identified, the main hypothesis at this stage has focused on the hyperinsulinemia associated with type 2 diabetes mellitus and consequentially, the proliferative effects of insulin. However, it is difficult to isolate diabetes mellitus from potential confounders with other hypotheses focusing on risk factors known to be associated with both diabetes and breast cancer. Obesity is one such example.

The aim of this study was to quantify the risk of breast cancer associated with Diabetes. Specifically, we aimed to complete a comprehensive literature search updating the findings of Larsson et al. while also subgrouping the identified studies to investigate the individual effect type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes have on the risk of breast cancer.

3.2 Methods

Study Protocol

One Reviewer (P.H), following the meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [45], completed a comprehensive database search. The databases, MEDLINE (from 1950), EMBASE (from 1949), PubMed (from 1946), Current Contents Connect (from 1998) and Google Scholar (from 1992), were searched using medical subject headings, text word and key word searches wherever possible. The search terms used were “diabetes” AND “breast carcinoma” or “breast cancer” or “breast neoplasm”. The reference lists of relevant studies were manually checked for missing studies however we did not search for unpublished literature.

Study Selection

Studies which met the following inclusion criteria were included in the meta-analysis: (1) The included cases must be diagnosed with breast cancer; (2) the risk point estimate was reported as an odds ratio (OR) or relative risk (RR) or the OR could be calculated from the presented data; (3) the 95% confidence interval (CI) was reported or the CI could be calculated from the presented data; (4) an internal control group was used to calculate the OR and the internal control group had been diagnosed with neither diabetes nor breast disease. Any study that did not meet the above criteria was excluded from the meta-analysis.

Data Extraction

Data was extracted by a single reviewer (P.H) and entered into a standardized data spread sheet (table 3). For each article, data collected included publication

date, study period, study type (Cross section (CS), Cohort (CO) or Case control (CC)), sample size, mean age, country (geographical and economic status), OR or RR, CI and adjusted variables. Where applicable, adjusted OR's were recorded. However, where no OR was given, an unadjusted OR or RR and CI was calculated by the reviewer (P.H). Where multiple OR's or RR's were given within the same study, i.e. from two different geographical locations, the data was entered as two separate OR's or RR's. Studies that did not define the specific type of diabetes were analysed as "non-specific diabetes."

Table 3. Summary of included studies.

Study	Year	Design	Cases	Controls	Type of Diabetes	Summary of findings
Type 2 diabetes mellitus						
Bowker et al.[93]	2011	CO	84506	84506	T2DM	No association between breast cancer and DM
Hsieh et al.[94]	2012	CO	61777	677378	T2DM	Increased risk of breast cancer associated with T2DM
Jordan et al. [95]	2009	CC	43	860	T2DM	Increased risk of breast cancer in patients with DM
Khachatryan et al.[96]	2011	CC	150	152	T2DM	Increased risk of breast cancer associated with T2DM
Michels et al.[97]	2003	CO	6220	116488	T2DM	Increased risk of breast cancer associated with T2DM
Resta et al.[98]	2004	CC	1663	4702	T2DM	Increased risk of breast cancer associated with T2DM
Rollison et al. [88]	2007	CC	2324	2523	Non specific, Gestational, T2DM	Gestational diabetes reduces risk of breast cancer, no association between T2DM and non specific DM
Sanderson et al.[99]	2010	CC	190	979	T2DM, Gestational,	No association between DM and breast cancer
Sellers et al. [100]	2007	CO	403	5727	T2DM	No significant risk of breast cancer associated with DM
Wu et al. [101]	2007	CC	1248	1148	T2DM	Increased risk of breast cancer associated with T2DM
Gestational diabetes						
Lawlor et al. [90]	2004	CS	147	3690	Non specific, gestational	No significant association between DM and breast cancer
Perrin et al.[89]	2008	CO	410	37516	Gestational	Increased risk of breast cancer associated with Gestational diabetes
Sella et al.	2011	CO	11,624	174,051	Gestational	No association between gestational

[91]						diabetes and breast cancer
Troisi et al. [92]	1998	CC	1239	1166	Gestational	No association between Gestational diabetes and breast cancer
Overall diabetes mellitus						
Attner et al. [102]	2012	CC	19756	147324	Non specific	Increased risk of breast cancer in patients with DM
Baron et al. [103]	2001	CC	5564	5841	Non specific	Increased risk of breast cancer associated with late onset DM, decreased risk of breast cancer associated with early onset DM
Beji et al.[104]	2007	CC	405	1050	Non specific	Increased risk of breast cancer in patients with DM
Brinton et al.[105]	2010	CO	111	4,501,578	Non specific	Increased risk of breast cancer in patients with DM
Carstensen et al.[106]	2012	CO	23846	346138	Non specific	No association between breast cancer and DM
Chlebowski et al.[107]	2012	CO	3401	64618	Non specific	No association between breast cancer and DM
Chodick et al.[108]	2010	CO	16721	83,874	Non specific	No association between breast cancer and DM
Cleveland et al. [109]	2012	CC	1447	1453	Non specific	No significant association between breast cancer and DM
Ewertz et al.[110]	2001	CC	156	468	Non specific	Increased risk of breast cancer in patients with DM
Franceschi, et al. [52]	1990	CC	2663	2344	Non specific	No association between breast cancer and DM
Garmendia et al. [111]	2007	CC	170	170	Non specific	No association between diabetes and breast cancer
Goodman et al.[112]	1997	CO	161	22039	Non specific	Increased risk of breast cancer in patients with diabetes
Inoue et al. [113]	2006	CO	4668	93,103	Non specific	No association between breast cancer and DM
Jee et al. [114]	2005	CO	21056	270157	Non specific	Increased risk of breast cancer in patients with DM
Khan et al. [115]	2006	CO	1554	31949	Non specific	No association between breast cancer and DM
Lambe et al. [116]	2011	CO	5615	218279	Non specific	Increased risk of breast cancer in post menopausal women with DM
La Vecchia et al.[117]	2011	CC	9991	7834	Non specific	No association between breast cancer and DM
Li et al. [118]	2011	CS	48418	349365	Non specific	Increased risk of breast cancer associated with DM
Lipscombe et al. [119]	2006	CO	73796	391714	Non specific	Increased risk of breast cancer associated with DM
Mink et al. [120]	2002	CO	26	7894	Non specific	No association between breast cancer and DM
Moseson et al.[54]	1993	CC	354	747	Non specific	No significant association between breast cancer and DM
Ronco et al.[121]	2012	CC	367	545	Non specific	Increased risk of breast cancer associated with DM
Rosato et al. [122]	2011	CC	3869	4082	Non specific	Increased risk of breast cancer associated with DM
Sinagra et al. [19]	2002	CS	50	25	Non specific	Increased risk of breast cancer associated with DM
Steenland et al.[123]	1995	CC	1250	11804	Non specific	No significant increased risk of breast cancer associated with DM
Talamini et al.[17]	1997	CC	2769	2588	Non specific	Increased risk of breast cancer in postmenopausal women with DM

Thomas et al.[124]	1992	CC	227	300	Non specific	No significant increase in risk of breast cancer in males with DM
Weiss et al. [18]	1999	CC	2173	1990	Non specific	No association between breast cancer and DM
Yu et al.[125]	2012	CC	103	309	Non specific	No significant increased risk of breast cancer associated with DM

Statistical Analysis

A random effects model was used to calculate a pooled OR for the effect of diabetes on the risk of developing breast cancer. Heterogeneity was assessed using Cochran's Q statistic with a p value of less than 0.10 indicating significant heterogeneity. The extent of heterogeneity was further quantified using the I² statistic with results of 25%, 50% and 75% correlating with low, moderate and high levels of heterogeneity respectively. Egger's regression model was used to calculate publication bias with the extent of bias documented using the "fail safe" method whereby the number of studies required nullifying our results was calculated. A fail safe (n) with a p value less than 0.05 was considered significant. In addition to the Egger's regression model, the Begg and Mazumdar rank correlation was used to assess the symmetrical nature of funnel plot to further assess publication bias. Data was analysed using Comprehensive Meta-analysis (version 2.0).

3.3 Results

The literature search identified 59 studies investigating the association between breast cancer and diabetes, 16 studies were excluded from the meta-analysis for failing to meet the inclusion criteria (figure 8). 11 studies were excluded for failing to include an internal control group[126-136], three studies were excluded for investigating mortality rather than incidence[137-139], one study was excluded for using benign breast disease as a comparator[140] and the final study was excluded for investigating the effect of glycaemic control on breast cancer risk[141]. The remaining 43 studies were included in the meta-analysis.

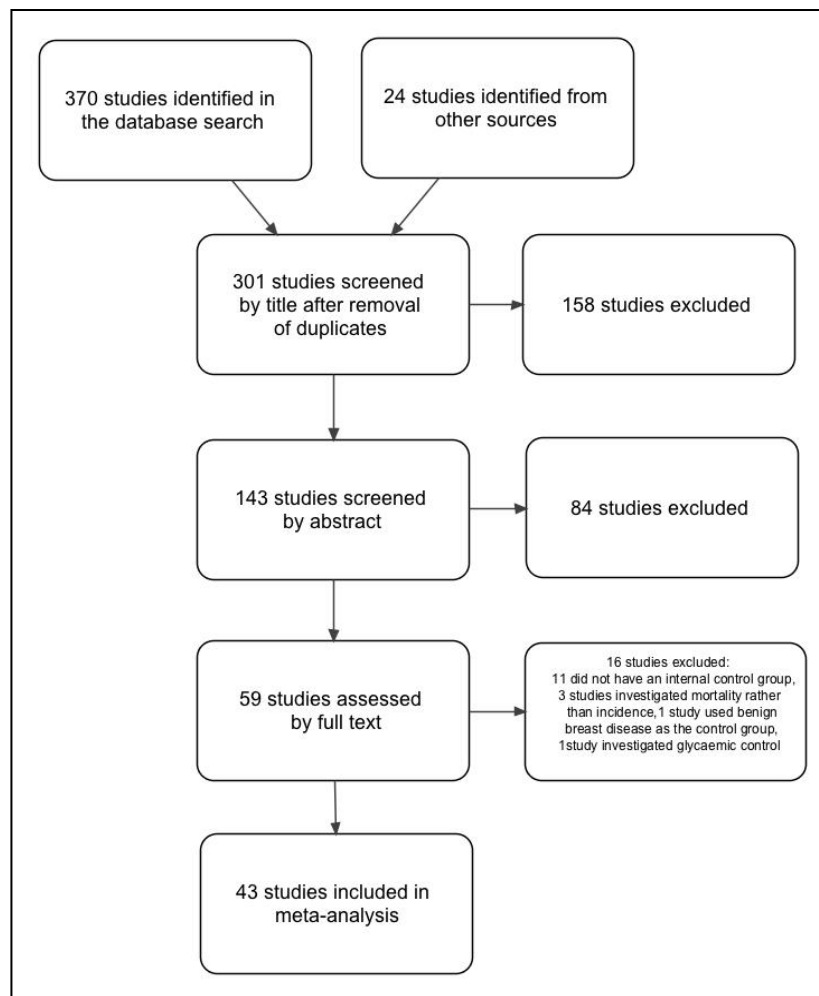


Figure 8. Results of the literature search into diabetes mellitus and breast cancer risk.

Non-Specific Diabetes Mellitus

40 studies were identified investigating diabetes and the risk of breast cancer in women. 14 studies reported a statistically significant increase in breast cancer risk in patients with diabetes mellitus[19, 94-98, 101, 102, 104, 112, 114, 119, 121, 122] while 24 studies reported results that did not reach statistical significance. Within these 24 studies, 17 studies had risk point estimates which favoured an increased risk of breast cancer[17, 18, 89, 90, 92, 99, 100, 103, 106, 109, 111, 115, 116, 118, 120, 123, 125] while six studies favoured a decreased risk[54, 88, 91, 107, 113, 117]. Three studies found no association between the two[52, 93, 108]. Quantitative analysis revealed a significant pooled risk point estimate of 1.20 (95% CI 1.13-1.29) (figure 9). Heterogeneity was high ($I^2=73.41$, $p< 0.001$) and there was evidence of publication bias ($n= 932$, eggers $p=0.01$). However, the funnel plot was found to be symmetrical using the Begg and Mazumdar rank correlation ($p=0.07$) (figure 10).

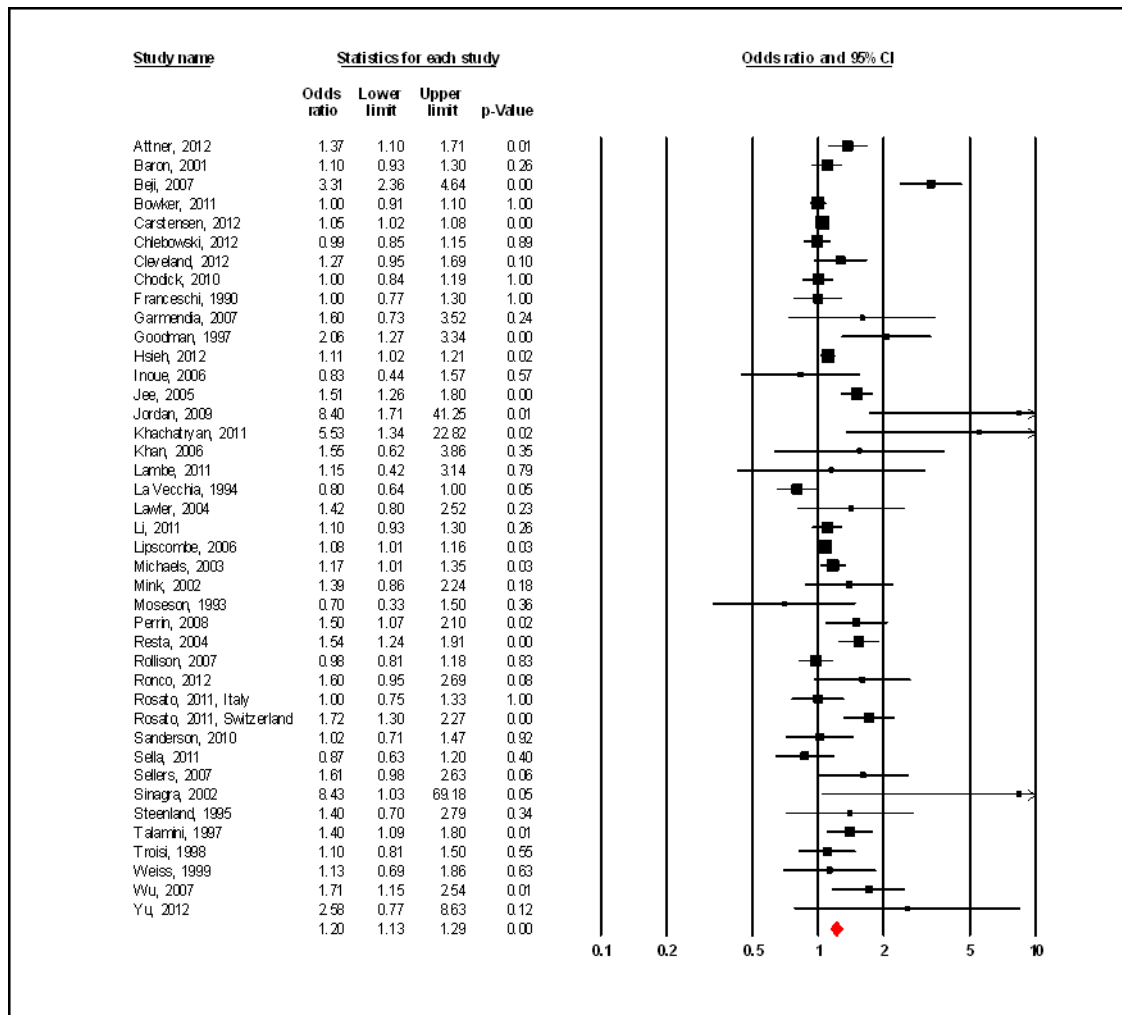


Figure 9. Non specific diabetes mellitus and breast cancer risk.

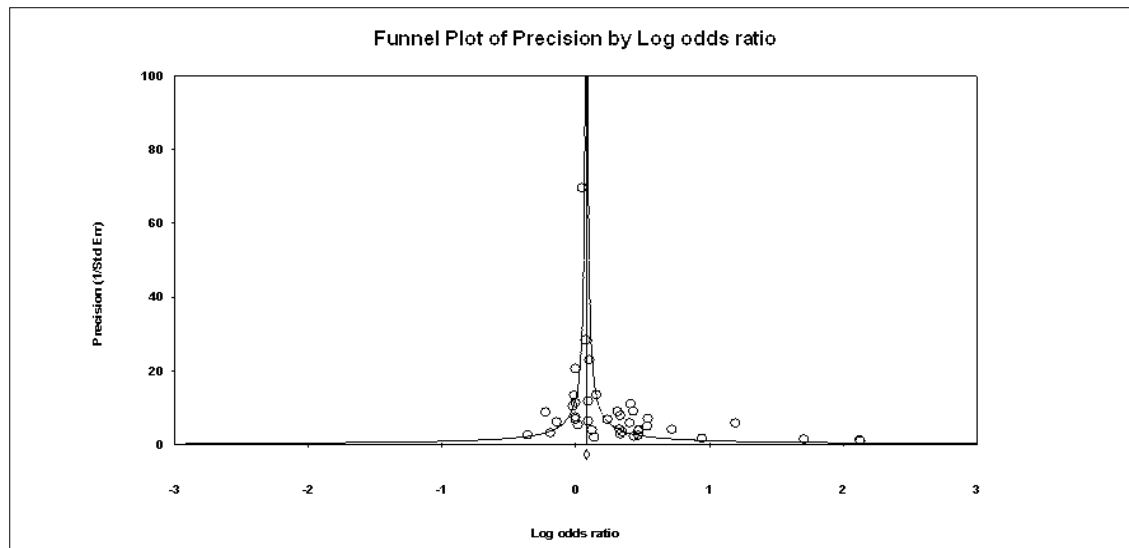


Figure 10. Funnel plot demonstrating publication bias.

Sub group analysis by study design identified a slightly increased risk of breast cancer in case control studies when compared with cohort studies evident in risk point estimates of 1.29 (95% CI 1.12-1.49) and 1.12 (95% CI 1.05-1.20) respectively. The pooled analysis for cross sectional studies was not significant despite an increased risk point estimate (OR 1.33, 95% CI 0.81-2.17).

To investigate the effect of confounders on breast cancer risk, a subgroup analysis was undertaken investigating only studies that adjusted for known risk factors of breast cancer. 21 studies adjusted for age and body mass index (BMI) with the pooled risk point estimate identifying a statistically significant increase in breast cancer risk (OR 1.12, 95% CI 1.04-1.21) with no evidence of heterogeneity ($I^2=30.78$, $p=0.09$). In a bid to further demonstrate causality, studies that adjusted for family history in addition to age and BMI were collated with the results continuing to favour an increased risk of breast cancer in patients with diabetes mellitus (OR 1.11, 95% CI 1.01-1.22, $I^2=25.02$, $p=0.23$).

Male Breast Cancer

Seven studies were identified investigating the association between breast cancer and diabetes mellitus in men [105, 106, 108, 110, 118, 124, 142]. Five studies were homogenous in their finding of an increased risk point estimate however only two studies reached statistical significance [105, 110]. The remaining two studies, despite not reaching statistical significance, favoured a protective effect associated with diabetes mellitus. The pooled odds ratio favoured an increased risk of breast cancer in males with diabetes mellitus (OR 1.29, 95% CI 0.99-1.67) (Figure 11). There was no evidence of heterogeneity ($I^2 = 32.83, p=0.18$).

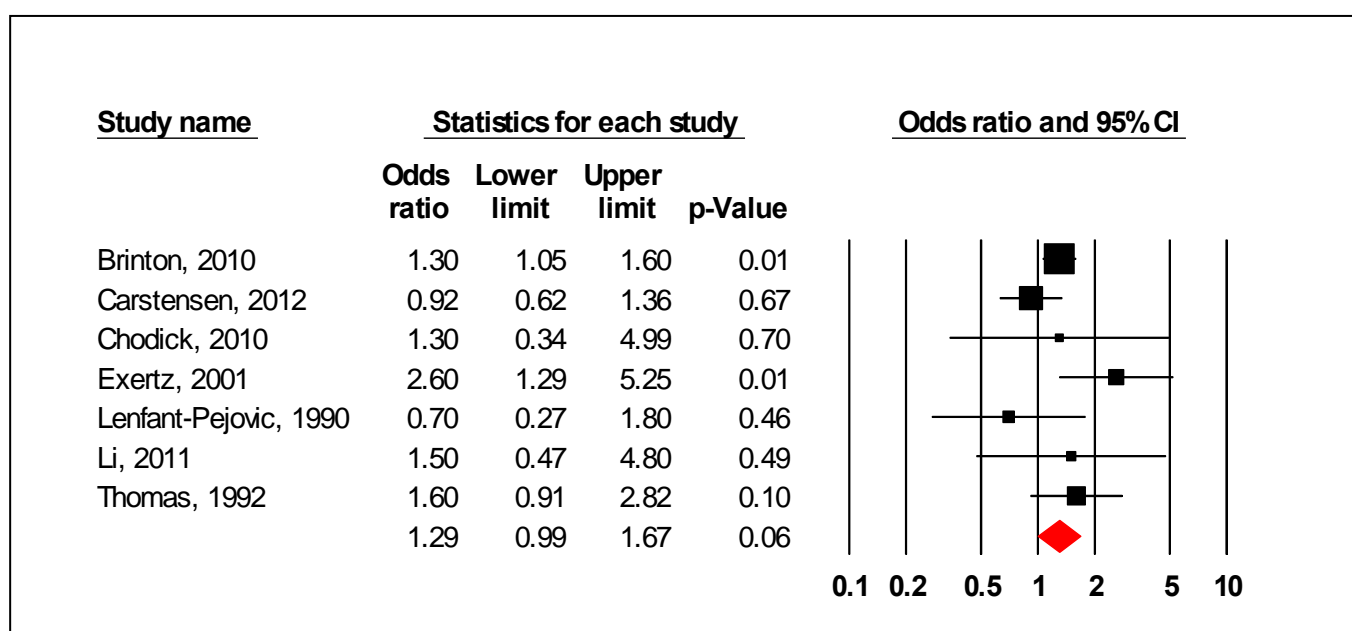


Figure 11. Diabetes mellitus and breast cancer in men.

Type 2 Diabetes Mellitus

Sub group analysis of non specific diabetes mellitus in women identified ten studies that specifically investigated type 2 diabetes mellitus [88, 93-101]. Eight studies reported a positive risk point estimate with six studies reaching statistical significance [94-98, 101]. The final two studies did not find any association between the two [93, 99]. The pooled odds ratio and 95% confidence interval supported an increased risk of breast cancer associated with type 2 diabetes mellitus (OR 1.22, 95% CI 1.07-1.40) (figure 12).

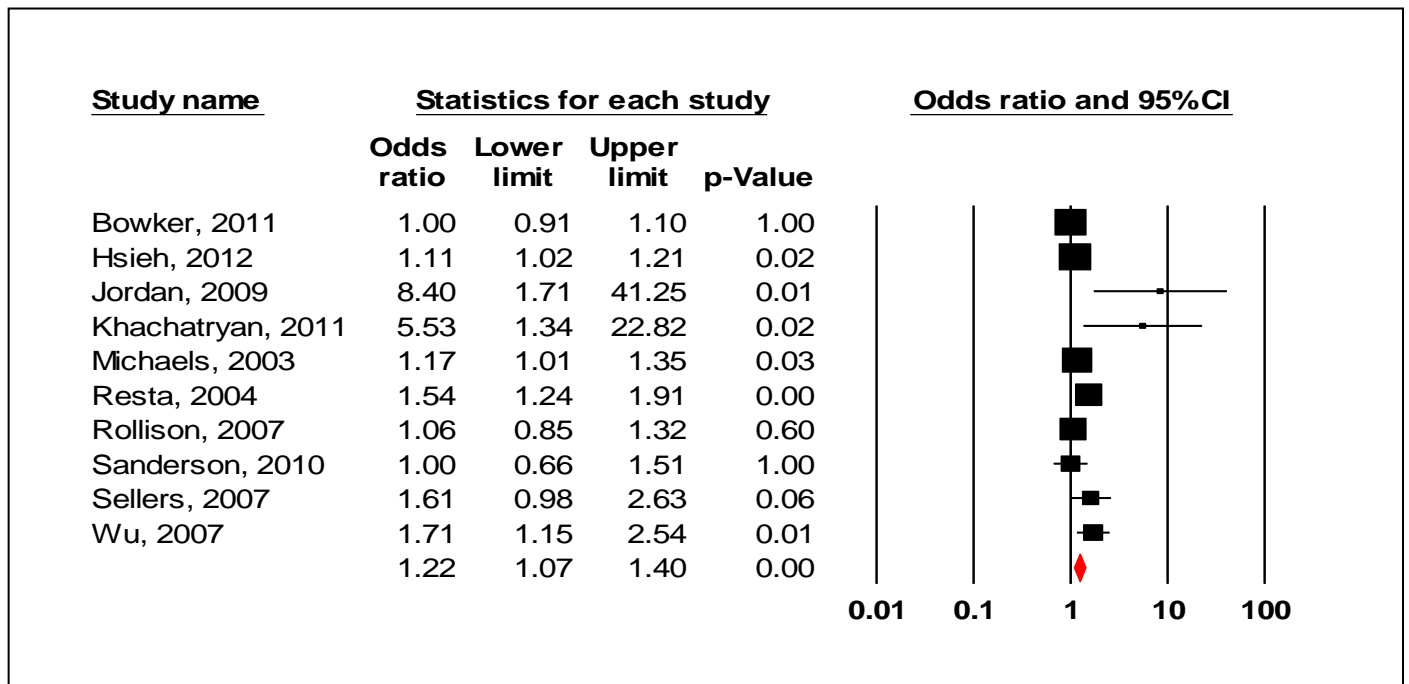


Figure 12. Type 2 diabetes mellitus and breast cancer risk.

Type 1 Diabetes Mellitus:

The literature search identified three studies investigating the effect of Type 1 diabetes mellitus on breast cancer risk. However, all three studies failed to meet the inclusion criteria with two studies failing to include an internal control

group[131, 135] while one study assumed a diagnosis of type 1 diabetes mellitus in all patients aged under 35 without confirmation [103]. Interestingly, the studies were homogenous in their finding of a protective risk point estimate despite none of the studies reaching statistical significance. Quantitative analysis was not undertaken on account of the studies failing to meet the inclusion criteria.

Gestational Diabetes:

Six studies were identified investigating the effect of gestational diabetes on breast cancer risk[88-92]. There was a degree of heterogeneity within the results with only one study reaching statistical significance [88]. This study found gestational diabetes to reduce the risk of breast cancer. The remaining four studies did not reach statistical significance with three studies finding an increased risk point estimate[89, 90, 92] and one study reporting a negative risk point estimate[91]. The pooled odds ratio did not find any association between gestational diabetes and breast cancer (OR 1.06, 95% CI 0.79-1.40) while significant heterogeneity was present ($I^2= 68.81$, $p= 0.01$).

3.4 Discussion

Our study identified a 20% increased risk of breast cancer in people with diabetes mellitus. This association was unchanged when considering only people with confirmed type 2 diabetes mellitus while there was no evidence of an increased risk associated with type 1 diabetes mellitus. These findings are consistent with the hyperinsulinemia hypothesis as a potential mechanism linking diabetes mellitus to breast cancer.

While type 1 diabetes mellitus is predominantly associated with insulin deficiency, type 2 diabetes is more readily known for its hyperinsulinemic state. This is particularly seen in the early stages of the disease where the pancreas is still able to compensate for the hyperglycemia. This increase in insulin is hypothesized to increase proliferation in two ways; activation of the insulin receptor substrate to increase mitosis at a cellular level [143] and causing an imbalance in sex steroids via a decrease in sex hormone binding globulin [144]. However, we cannot exclude an indirect relationship with potential confounders triggering a rise in plasma oestrogen. For example, obesity has also been shown to trigger a reduction in sex hormone binding globulin and consequentially an increase in the bioavailability of oestrogen. In addition, adipose tissue is known to generate an increase in plasma oestrogen via the aromatase enzyme thus providing an alternate mechanism linking diabetes to breast cancer [145, 146].

Another hypothesis centers on an iatrogenic link between breast cancer and diabetes mellitus. Insulin use has long been suspected of increasing the risk of

breast cancer and more recently the debate has focused on the use of insulin glargine. Jonasson et al. in a study published in 2009, found an increased risk of breast cancer associated with glargine use [147]. These results however, have not been replicated in other observational studies[148-150]. Additionally, while there has been a degree of heterogeneity in the results of broader studies investigating insulin use in general (rather than specifically glargine use), a recent Danish study did not find an association between the risk of breast cancer in people using insulin and people using other anti-glycemic agents[106].

Metformin use, on the other hand, has actually been shown to reduce the risk of breast cancer[151]. Hypothesised mechanisms explaining this protective effect include metformin's ability to reduce the hyperinsulinemia associated with type 2 diabetes and in vitro evidence of direct anticarcinogenic properties[152, 153]. While, a number of observational studies have confirmed this protective effect, a recent study specifically identified a 25% reduction in breast cancer risk associated with metformin use[107]. New evidence has also indicated that metformin use may improve prognosis[154].

Interestingly, our results did not identify an increased risk of breast cancer associated with gestational diabetes. Gestational diabetes occurs secondary to increased maternal adiposity and increased human placental lactogen (hPL) during pregnancy; both of which have been shown to promote insulin resistance[155, 156]However, our results do not support an increased risk of breast cancer associated with this period of hyperinsulinemia. This may be due to the short duration of hyperinsulinemia in this population, as opposed to the

decades of hyperinsulinemia associated with type 2 diabetes mellitus. In addition, western societies screen and closely manage gestational diabetes, further reducing the extent of hyperinsulinemia, to minimise both maternal and fetal complications. We hypothesise that these factors may explain the null findings in this study.

The vast majority of the included studies comprised broad, large scale observational studies, which took neither current nor past therapeutic regimes into account. For this reason, we were unable to adjust for metformin use and therefore, we could not exclude antiglycaemic therapy as a potential confounder. This constraint, in the context of new evidence potentially linking antiglycaemic agents to breast cancer risk, is a major limitation in our study. We recommend all future primary studies take both past and present therapy into account when considering aspects of study design. In addition, the effect of diabetes mellitus on different types of breast cancer has not been thoroughly assessed and it may be worthwhile for future studies to also take this into account.

The impact of genetics and family history is a further confounding factor that we could not exclude, particularly in the analysis of breast cancer risk in men. While in the analysis of breast cancer in women, the number and quality of included studies allowed an adjusted analysis to be completed; this was not possible in the analysis of breast cancer in men. The lack of primary studies and differences in variables adjusted for prevented further subgrouping of these results. This inability to exclude a genetic predisposition as a potential confounder is a limitation which should be considered when interpreting our results.

A further weakness in this study lay in our inability to differentiate between the different types of diabetes investigated. 34 studies were included in this analysis however only 13 of these studies specifically stated the type of diabetes investigated. While the vast majority of the studies had a mean age above 50, and thus a diagnosis of type 2 diabetes was most likely, we were unable to include the studies in our sub group analysis. For this reason, the power of the sub group analysis in type 2 diabetes mellitus was reduced. Furthermore, with only three studies investigating the association between type 1 diabetes mellitus and all three studies failing to meet the inclusion criteria we were unable to quantitatively analyse the results. For future research, we recommend further longitudinal studies of high quality be undertaken in this area.

Strengths of this study include a broad literature review, the use of precise inclusion criteria and comprehensive sub grouping to identify the differences between types of diabetes. We used five databases as well as reference list checking to identify relevant studies with double the number of studies identified compared with prior reviews[20, 87]. The increased number of studies allowed subgroup analysis by type of diabetes for the first time.

3.5 Conclusion

In patients with diabetes mellitus, we have found a 25% increase in the risk of breast cancer in women and 29% increase in men. This association was unchanged when the analysis was restricted to studies with a confirmed diagnosis of type 2 diabetes mellitus. These findings are consistent with the hyperinsulinemia theory in the aetiology of breast cancer.

4 Physical Activity, Weight Loss and Breast Cancer risk

4.1 Introduction

Breast cancer accounts for 28% of all cancer in women in Australia; a number which has steadily increased over the last 30 years[1]. Various lifestyle factors have been implicated in this rise in prevalence with evidence of an increase in breast cancer risk and worsened prognosis associated with both obesity and a sedentary lifestyle[78, 157, 158]. On the contrary, recent studies focusing on potentially beneficial lifestyle choices have found physical activity and weight loss to be protective in terms of breast cancer risk[159, 160]. However, with numerous studies investigating the timing and intensity of physical activity as well as the method and extent of weight loss, there is no real consensus on the most effective way to exercise in terms of breast cancer prevention[161].

Despite being the topic of a number of literature reviews, the effect of weight loss on breast cancer risk is yet to be quantified. While the primary studies predominantly identified a protective effect associated with weight loss, whether it be achieved conservatively[162, 163] or via bariatric surgery[164], a small number of studies failed to find an association between the two[165, 166]. Physical activity on the other hand, was investigated in a number of qualitative reviews[26, 167, 168] and a quantitative review published by Lagerros et al. in 2004[169]. This analysis however, limited its investigation to the effect of regular physical activity during adolescence and early adulthood.

Physical activity has been hypothesised to reduce breast cancer risk both directly and indirectly by a number of mechanisms. These include modulating

both the production and circulation of sex steroids[28] and indirectly suppressing proliferation via a reduction in hyperinsulinemia[27]. However, potential confounders may also play a part, with a number of other factors known to affect the levels of plasma sex steroids. Menopausal status is one such example.

The aim of this study was to collate and analyse all primary observational studies investigating the effect of either physical activity or weight loss on breast cancer risk. Specifically, we aimed to complete subgroup analyses investigating the effect of physical activity at different stages of life, different intensities, different types of breast cancer and in the high risk population. The high risk population included people with a family history of breast cancer, people with a BMI over 25 and people with a known BRCA1 or BRCA2 mutation. Additionally, we aimed to adjust for potential confounders allowing physical activity to be assessed as an independent modulator of breast cancer risk. Finally we aimed to investigate the effect of weight loss on breast cancer risk and more specifically, the best method of weight loss, comparing conservative and surgical weight loss and breast cancer risk.

4.2 Methods

Study Protocol

One reviewer (PH) following the Preferred Reporting Items for Systematic Review and Meta-Analyses Guidelines (PRISMA)[170] completed a database search. The databases, MEDLINE (from 1950), EMBASE (from 1949), PubMed (from 1946), Current Contents Connect (from 1998) and Google Scholar (from 1992), were searched using medical subject headings, text word and keyword searches wherever possible (figure 12). The search terms used were “Exercise” or “physical activity” or “weight loss” AND “breast carcinoma”, or “breast cancer” or “breast neoplasm”. Reference lists were checked for missing studies (included under “other sources” in figure 13) however we did not search for unpublished literature.

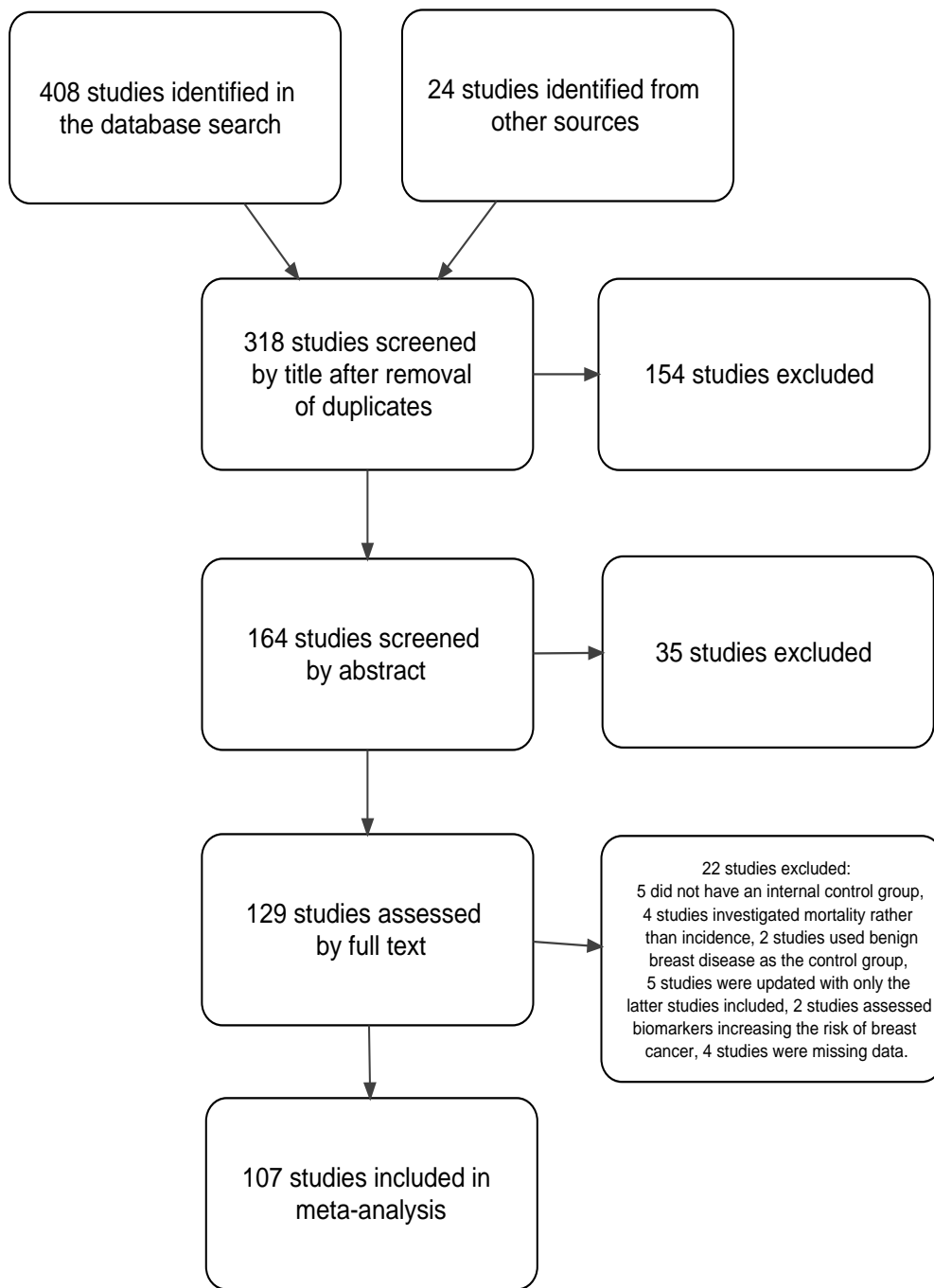


Figure 13. Results of the literature search.

Study Selection

Studies which met the following inclusion criteria were included in the meta-analysis: (1) Cases included in the physical activity analysis must have completed physical activity whether it be incidental, occupational or intentional; (2) Cases included in the weight loss analysis had to have lost weight during the study period, with only those studies using a minimum cut off of 5kg weight loss included in the sub group analyses; (3) the risk point estimate was reported as an odds ratio (OR), Relative risk (RR) or Hazard Ratio (HR) or the OR could be calculated from the presented data; (4) the 95% confidence interval (CI) was reported or the CI could be calculated from the presented data; (5) an internal control group was used to calculate the OR and the internal control group had not been diagnosed with breast disease; (6) the study had a sample size greater than 50. Any study that did not meet the above criteria was excluded from the meta-analysis.

Data Extraction

Data was extracted by a single reviewer (P.H) and entered into a standardised data spread sheet. For each article, data collected included publication date, time frame for data collection, study type (cross section, Cohort or case control), sample size, mean age, country (geographical and economic status), odds ratio, confidence interval and adjusted variables. Where applicable, adjusted odds ratios were recorded. However, where no odds ratio was given, an unadjusted odds ratio and confidence interval was calculated by the reviewer (P.H). Where multiple odds ratios were given within the same study, i.e. from two different populations[171], the data was entered as two separate odds ratios. Studies that

did not define the timing, intensity or duration of physical activity were analysed as “non-specific physical activity”.

Statistical Analysis

A random effects model was used to calculate a pooled odds ratio for the effect of physical activity and weight loss on the risk of developing breast cancer. Heterogeneity was assessed using Cochran’s Q statistic with a p value of less than 0.10 indicating significant heterogeneity. The extent of heterogeneity was further quantified using the I^2 statistic with results of 25%, 50% and 75% correlating with low, moderate and high levels of heterogeneity respectively. The Begg and Mazumdar Rank Correlation was used to assess publication bias with a p value of less than 0.05 considered an asymmetrical funnel plot. Data was analysed using Comprehensive Meta-analysis (version 2.0).

4.3 Results

408 studies were identified in the literature review of which 129 were assessed by full text and 107 included in the meta-analysis resulting in a pooled population of 128,945 women and 1,862,970 controls. Of the 22 studies excluded from the meta-analysis, four studies were excluded for investigating mortality rather than incidence[172-175], two studies were excluded for assessing biomarkers of breast cancer risk rather than breast cancer risk per se [176, 177], five studies did not include an internal control group[178-182], five studies were early analyses of a cohort later updated, the updated versions were included in this analysis[183-187], four studies were missing data [188-191] and two studies did not include a control group without breast disease[192, 193]. Ten studies were later updated however; the latter studies did not report data on all aspects of physical activity or weight loss assessed in this analysis. For this reason, these studies were included in the quantitative review however, where two or more studies presented data on the same population or subgroup, only the latter study was included in the sub group analyses[194-203].

Physical Activity

Overall Physical Activity

89 studies were identified investigating the effect of physical activity on breast cancer. 34 studies found physical activity to be protective[159, 160, 171, 197, 199, 202, 204-231] while the remaining 55 studies did not reach statistical significance. 41 of the 55 studies favoured a protective effect[158, 165, 196, 232-269] while the remaining 14 studies favoured an increased risk of breast cancer

associated with physical activity[270-283]. The pooled risk point estimate demonstrated a statistically significant reduction in breast cancer risk (OR 0.81, 95% CI 0.78-0.84). While there was significant heterogeneity ($I^2 = 79.95$, $p < 0.01$), there was no evidence of publication bias ($p=0.70$) (figure 14). Subgroup analyses by study design identified an increased protective effect in case control studies, relative to cohort studies however the results were significant in both groups (case control OR 0.76 (95% CI 0.73-0.80), cohort OR 0.89 (95% CI 0.85-0.93)). Further analysis by year of publication did not identify a trend in results while analysis of studies by geographical location is shown in table 4. Analysis by economical status, ie. Developing countries vs developed countries did not identify any significant change although the size of the risk reduction was greater in developed countries compared with developing countries (OR 0.78 (95% CI 0.75-0.82) and 0.94 (95% CI 0.90-0.99) respectively).

Table 4. Analysis of studies investigating physical activity and breast cancer by geographical location

Country	Pooled odd's ratio	95% confidence interval
America	0.79	0.74-0.84
Canada	0.74	0.51-1.05
China	0.79	0.69-0.90
Germany	0.76	0.66-0.88
India	1.77	0.17-18.07
Italy	0.71	0.58-0.86
Japan	0.74	0.59-0.94

Mexico	0.96	0.93-0.98
Netherlands	0.73	0.62-0.85
Sweden	0.57	0.71-1.07
Turkey	1.03	0.65-1.63

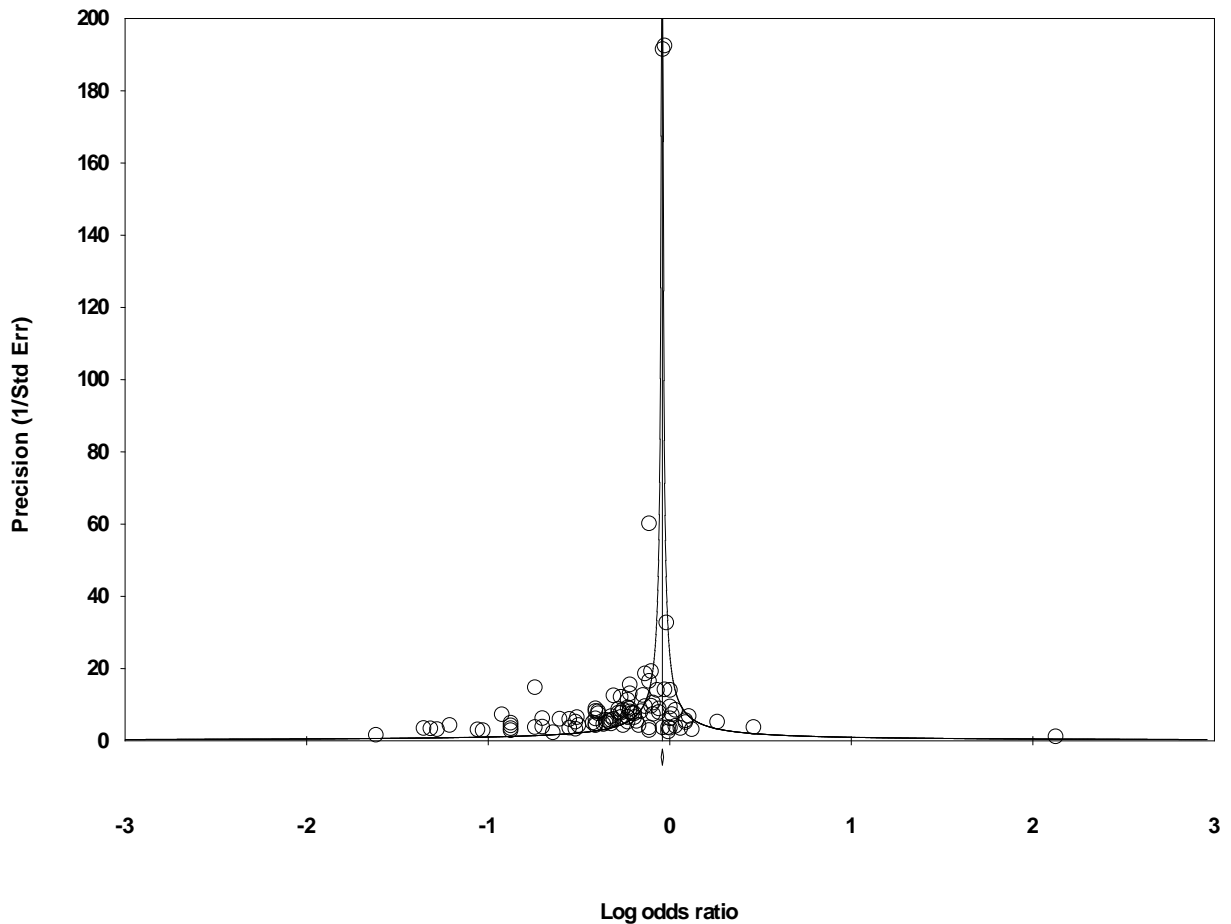


Figure 14. Funnel plot of publication bias in studies assessing physical activity and breast cancer risk.

To investigate the effect of confounders on breast cancer risk, a subgroup analysis was undertaken investigating only studies that adjusted for known risk factors of breast cancer. The five confounders that were addressed include age, body mass index, family history of breast cancer, age at menarche and age at menopause. The results of this subgroup analysis are shown in table 5.

Table 5. Pooled risk point estimates in studies that adjusted for common confounders.

Confounders	Pooled Risk Point Estimate (95% confidence interval)	Heterogeneity	Number of studies
Age, BMI	0.84 (0.81-0.87)	I ² = 82.04, p<0.001	45 [158-160, 196, 199, 205-209, 211, 212, 214, 216, 219, 220, 222, 227, 233, 235, 236, 238-244, 246, 247, 249, 251, 255, 258, 260-262, 265, 266, 269, 272, 276, 279, 282, 283]
Age, BMI, family history of breast cancer	0.90 (0.87-0.93)	I ² =64.49, p<0.001	29 [159, 160, 196, 207-209, 211, 212, 214, 219, 220, 233, 236, 238-242, 244, 247, 249, 251, 254, 260, 262, 265, 266, 272, 276]
Age, BMI, family history of breast cancer, age at menarche, age at menopause	0.84 (0.79-0.89)	I ² = 33.32, p=0.07	21 [159, 196, 209, 211, 219, 220, 233, 236, 238, 240, 242, 244, 247, 249, 251, 254, 260, 262, 265, 266, 276]

Exercise and Menopausal status

60 studies were identified in the literature review investigating the effect of physical activity on either premenopausal or postmenopausal breast cancer[158-160, 171, 196-199, 202, 204, 206, 208-212, 214, 222, 224, 225, 227-230, 233, 235, 236, 238-243, 246, 247, 249-251, 254, 258-266, 268, 269, 272, 277-279, 281-286]. 40 studies identified the effect of physical activity on premenopausal breast cancer of which nine studies reported a statistically significant reduced risk of breast cancer[159, 160, 171, 222, 228-230, 238, 266]. The remaining 31 studies did not reach statistical significance despite 21 studies

favouring a protective effect [196, 198, 204, 206, 212, 214, 218, 225, 242, 244, 250, 258-261, 263-265, 268, 269, 283] and ten studies favouring an increased risk of premenopausal breast cancer associated with physical activity [197, 240, 241, 243, 246, 249, 258, 272, 278, 279]. The pooled risk point estimate favoured physical activity evident in a statistically significant reduction in breast cancer risk (OR 0.80 95% CI 0.73-0.87) (figure 15). The heterogeneity was moderate ($I^2 = 62.79$) and significant ($p < 0.001$).

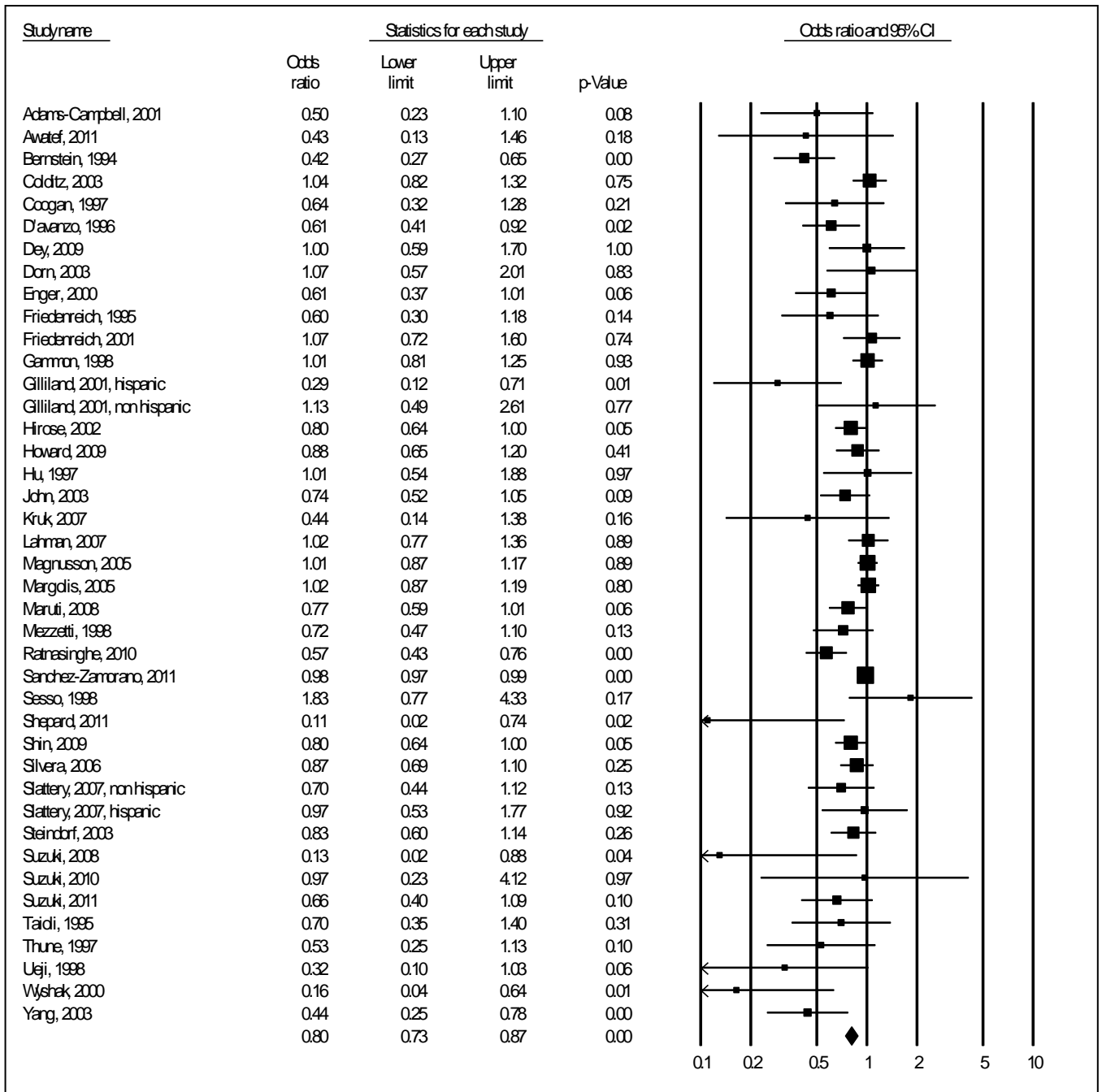


Figure 15. Physical activity and premenopausal breast cancer risk.

55 studies investigated the effect of physical activity on the risk of postmenopausal breast cancer. 51 studies favoured a reduced risk of breast cancer[158-160, 171, 195-199, 202, 204, 206, 209-212, 214, 218, 222, 224, 225,

227, 229, 233, 235, 236, 238-244, 246, 247, 249, 251, 254, 258, 259, 261, 262, 264-266, 268, 269, 276-278, 286] however only 22 studies reached statistical significance[159, 160, 171, 197-199, 202, 206, 208-212, 222, 224, 227, 229, 238, 258, 264, 266, 286]. The remaining four studies favoured an increased risk of postmenopausal breast cancer associated with physical activity despite not reaching statistical significance[260, 281-283]. The pooled risk point estimate favoured physical activity (OR 0.75 95% CI 0.70-0.80) (figure 16). However, the heterogeneity was high ($I^2 = 77.12$) and significant ($p < 0.001$).

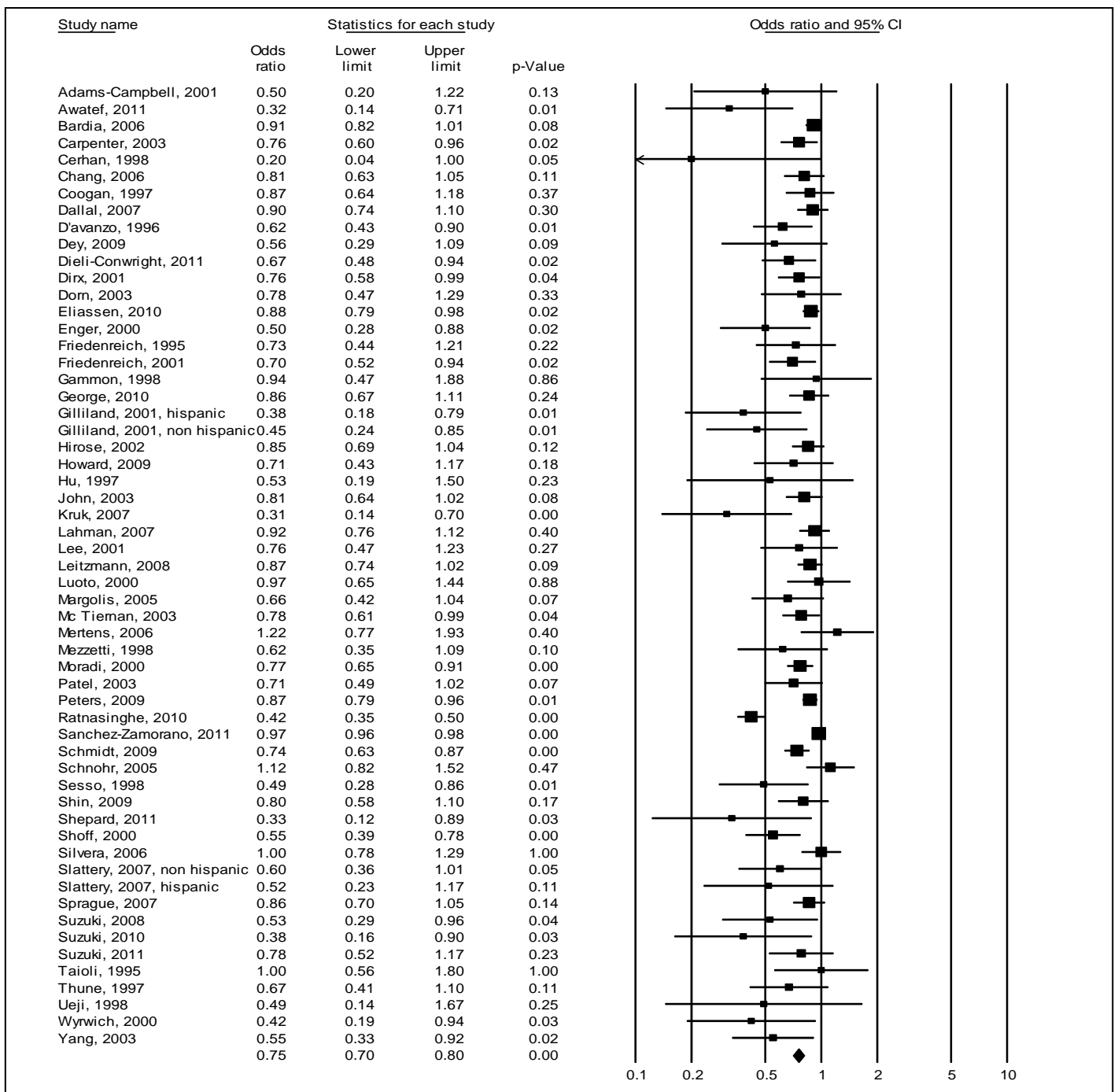


Figure 16. Physical activity and postmenopausal breast cancer risk.

Intensity of the Physical Activity

36 studies were identified investigating the effect of the intensity of exercise on breast cancer risk[159, 171, 186, 197, 204, 210, 211, 216, 219, 220, 223, 226,

229, 233, 237, 239, 242, 244, 247, 249-251, 256, 259-261, 263, 264, 266, 267, 272, 274, 277, 280, 282, 287]. 31 studies investigated the effect of high intensity exercise (exercise likely to cause sweating i.e. Running, competitive sports) of which 9 studies found physical activity to be protective in regards to breast cancer risk [159, 171, 186, 204, 216, 220, 223, 239, 267]. Despite the remaining studies not reaching statistical significance, 17 studies favoured a protective effect [210, 211, 219, 233, 237, 242, 244, 247, 250, 251, 260, 261, 263, 268, 272, 277, 280] while five studies favoured an increased risk of breast cancer [197, 226, 249, 264, 282]. The pooled risk point estimate demonstrated a protective effect associated with vigorous exercise evident in a statistically significant risk point estimate (OR 0.78, 95% CI 0.71- 0.86). However, the heterogeneity was moderate ($I^2= 65.35$) and significant ($p<0.001$).

27 studies were identified investigating the effect of low-moderate intensity exercise on breast cancer risk. Low –moderate intensity activities included walking, dancing and gardening. Seven studies reported a statistically significant protective effect [197, 216, 219, 223, 229, 244, 251] while 15 studies favoured a protective effect despite not reaching statistical significance [159, 210, 220, 226, 239, 242, 250, 256, 259, 263, 264, 266-268, 287]. The remaining five studies favoured an increased risk of breast cancer associated with low intensity exercise despite not reaching statistical significance [247, 249, 272, 274, 282]. The pooled risk point estimate favoured a decreased risk of breast cancer associated with low-moderate intensity exercise (OR 0.82, 95% CI 0.76-0.90). The heterogeneity was moderate ($I^2= 61.71$) and significant ($p<0.001$).

Physical activity at different stages of life

36 studies were identified in the literature review investigating the effect of the timing of the physical activity on breast cancer risk in relation to different stages of life[195, 197-200, 202, 204, 208, 210, 211, 214, 217, 219, 220, 223, 224, 226, 230, 235, 237, 238, 241, 243, 248-251, 254, 261-264, 276, 277, 279, 280, 282].

30 studies investigated the effect of physical activity during adolescence of which nine studies found a significantly reduced risk of breast cancer[198, 214, 217, 219, 223, 224, 241, 250, 264]. The remaining 21 studies did not reach statistical significance despite 14 studies favouring a protective effect[195, 197, 226, 230, 238, 243, 248, 251, 261-263, 276, 277, 279]. The remaining seven studies favoured an increased risk of breast cancer associated with physical activity during adolescence despite not reaching statistical significance.[199, 200, 204, 210, 237, 249, 251]. The pooled risk point estimate found physical activity during adolescence to be protective in terms of breast cancer risk (OR 0.84, 95% CI 0.78-0.90). The heterogeneity was moderate ($I^2= 68.18$) and significant ($p<0.001$).

26 studies were identified which investigated the effect of physical activity during adulthood (20-50 years) on breast cancer risk. 21 studies favoured a reduction in breast cancer risk associated with physical exercise during adulthood [197, 200, 202, 204, 214, 217, 220, 223, 226, 230, 237, 238, 250, 251, 254, 261-264, 277, 280] however only seven studies reached statistical significance[202, 204, 217, 220, 223, 230, 251]. The remaining five studies favoured an increased risk of breast cancer associated with physical activity

during adulthood however none of the studies reached statistical significance[198, 210, 249, 276, 279]. The pooled risk point estimate favoured physical activity evident in a reduction in breast cancer risk associated with exercise during the reproductive years (OR 0.85, 95% CI 0.79-0.92). The heterogeneity was moderate ($I^2 = 54.67$) and significant ($p < 0.001$).

23 studies investigated the effect of exercise in later life (post menopausal or age >50). 21 studies reported a favourable association [197, 198, 200, 202, 204, 208, 210, 211, 214, 217, 220, 224, 235, 238, 241, 245, 251, 254, 261, 262, 280] however only six studies reached statistical significance[197, 200, 202, 217, 224, 245]. The final two studies reported an increased risk of breast cancer associated with postmenopausal exercise however neither study reached statistical significance[277, 282]. The pooled risk point estimate demonstrated a significantly reduced risk of breast cancer associated with postmenopausal physical activity (OR 0.83, 95% CI 0.76-0.89). The heterogeneity was moderate ($I^2 = 51.41$) and significant ($p = 0.002$).

Physical Activity and Risk of Breast Cancer in the High Risk Population

A subgroup analysis was completed looking at studies assessing physical activity in high risk populations including those with a BMI greater than 25, a positive family history of breast cancer or a known genetic predisposition. 30 studies investigated the effect of physical activity on breast cancer risk in a population already at an increased risk[165, 197, 202, 207, 208, 210, 214, 220, 222, 226, 234, 238, 239, 247, 250, 251, 253-255, 260, 262, 264, 265, 267, 269, 270, 272, 276, 278, 279]. 22 studies focused on an overweight population (BMI >25) with

four studies reporting a significantly reduced risk of breast cancer associated with physical activity in this population [220, 222, 238, 265]. The remaining 18 studies did not reach statistical significance despite 13 studies favouring a protective effect[165, 197, 202, 210, 214, 239, 250, 251, 254, 260, 264, 267, 278] and five studies favouring an increased risk of breast cancer associated with physical activity in the overweight population[247, 253, 269, 272, 284]. The pooled risk point estimate demonstrated a statistically significant reduction in breast cancer risk in the overweight population when comparing those who undertake physical activity with those who do not (OR 0.79 95% CI 0.70-0.89). There was moderate heterogeneity ($I^2 = 50.35$), which was significant ($p < 0.001$).

14 studies investigated the effect of physical activity in people with a family history of breast cancer. Nine studies reported physical activity to be favourable[202, 208, 214, 222, 226, 234, 255, 267, 279] however only three studies reached statistical significance[202, 222, 226]. The remaining five studies favoured an increased risk of breast cancer associated with exercise in people with a positive family history of breast cancer[207, 220, 239, 262, 270]. The pooled risk point estimate favoured a beneficial effect however the odd's ratio did not reach statistical significance (OR 0.84, 95% CI 0.67-1.05). The heterogeneity was moderate ($I^2 = 69.68$) and significant ($p < 0.001$).

Two studies investigated the effect of physical activity on breast cancer risk in women who carry a gene mutation predisposing to breast cancer (BRCA1 or BRCA2). While we did not quantitatively analyse these two studies due to the small number, it should be noted that both studies favoured a protective effect

associated with physical activity despite not reaching statistical significance.
[234, 255]

Oestrogen and Progesterone Receptor Status

16 studies investigated the effect of physical activity on the risk of developing breast cancer by hormonal status[194, 201, 202, 207, 211, 212, 220, 233, 239, 240, 247, 250, 264, 265, 277, 286]. 14 studies investigated the risk of developing an oestrogen receptor positive breast cancer[194, 201, 202, 207, 212, 220, 233, 239, 240, 247, 250, 264, 265, 286] while five studies investigated the risk of developing a progesterone positive breast cancer[194, 202, 220, 233, 247] and ten studies investigated the risk of developing a dual oestrogen/progesterone receptor positive breast cancer[194, 202, 211, 212, 233, 247, 250, 264, 265, 277]. The results of the quantitative analysis by receptor status are shown in table 2. There were insufficient studies to assess the risk of being diagnosed with triple negative or HER2 positive breast cancer at this stage.

Weight Loss

18 studies were identified in the literature review investigating the effect of weight loss on breast cancer risk[162-165, 203, 224, 288-299]. 13 studies favoured a protective effect whereby weight loss reduced the risk of breast cancer[162-164, 224, 290-294, 296-299] however only four studies reached statistical significance[162-164, 291]. The remaining five studies favoured an increased risk of breast cancer associated with weight loss[165, 203, 288, 289, 295] with two studies reaching statistical significance[165, 289]. The pooled risk point estimate favoured weight loss (OR 0.81, 95% CI 0.67-0.97) (figure 17)

however, there was significant heterogeneity ($I^2= 77.61$, $p<0.001$). There was no evidence of publication bias ($p=0.83$). When the studies were restricted to only studies which used a cut off of 5kg weight loss during the study period the pooled odds ratio was nullified (OR 0.97, 95% CI 0.71-1.33) however only five studies met this criteria.

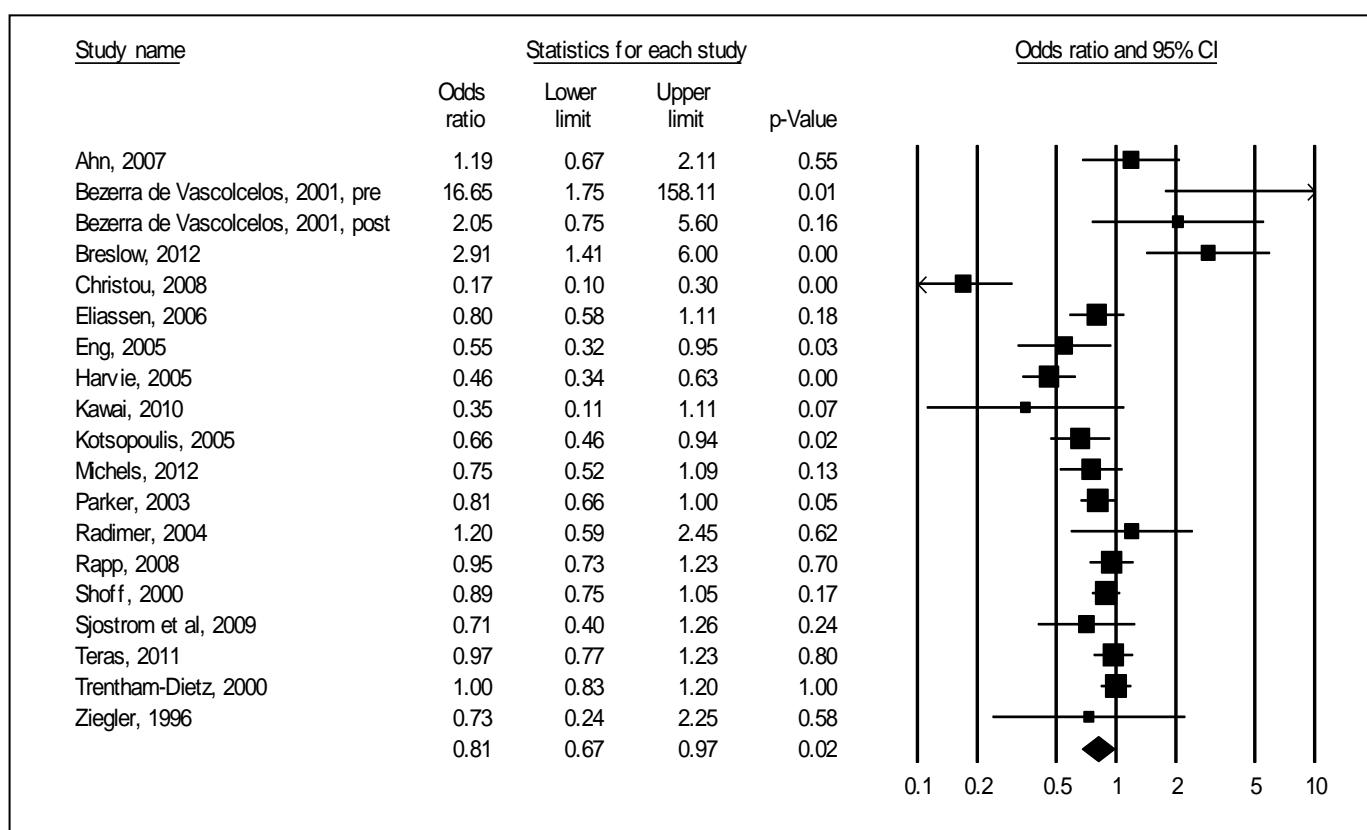


Figure 17. Weight loss and breast cancer risk.

Bariatric Surgery

The studies investigating weight loss were sub grouped by method of weight loss. Three studies investigated the effect of bariatric surgery[164, 294, 299]. Despite all three studies favouring a protective effect associated with weight loss, only the study by Christou et al.[164] reached statistical significance. The

pooled risk point estimate strongly favoured a protective effect associated with weight loss however the odds ratio did not reach statistical significance (OR 0.47, 95% CI 0.19-1.17). However, the heterogeneity was high ($I^2= 91.96$) and significant ($p<0.001$).

Conservative Weight Loss

15 studies identified in the literature review investigated the effect of conservative weight loss on breast cancer risk. Conservative weight loss was defined as weight loss using any means which did not include surgery, thus diet, exercise and pharmacological therapies were all included in this group. Ten studies favoured a protective effect associated with physical activity[162, 163, 224, 290-293, 296-298] however only three studies reached statistical significance[162, 163, 291]. The remaining five studies favoured an increased risk of breast cancer associated with weight loss[165, 203, 288, 289, 295] with two studies reaching statistical significance[165, 289]. The pooled risk point estimate favoured a protective effect however the results were not statistically significant (OR 0.88, 95% CI 0.73-1.05). There was moderate heterogeneity amongst the 15 studies ($I^2=60.77$, $p<0.001$).

4.4 Discussion

This study has demonstrated a significant reduction in breast cancer risk associated with physical activity. However, the timing and intensity of the exercise did not significantly alter the protective effect with only a slight increase in the protective effect when limited to high intensity exercise. In addition, weight loss was shown to significantly reduce the risk of breast cancer although more studies are required to investigate the best method of weight loss. These results are in keeping with the healthy lifestyle approach, whereby maintaining regular exercise, weight loss, smoking cessation[10, 82], avoidance of hormonal therapy[79, 85] and a reduction in alcohol consumption[10, 84] are likely to reduce the risk of breast cancer without the need to focus on the specific timing or intensity of the physical activity.

Physical activity is hypothesised to reduce breast cancer risk by a number of mechanisms. These include increasing the plasma levels of sex hormone binding globulin (SHBG) and inhibiting the hyperinsulinemia pathway[28, 300]. SHBG is a glycoprotein produced by the liver that binds free plasma sex hormones. Both physical activity and intentional weight loss have been shown to increase the plasma SHBG concentration and consequentially reduce free oestradiol[28, 301]. In addition, physical activity has been shown to prevent the onset of hyperinsulinemia and reduce established hyperinsulinemia. As a result, physical activity is hypothesised to indirectly reduce breast cancer risk via inhibition of the hyperinsulinemia pathway: a pathway known to increase the risk of breast cancer[300, 302].

The main limitation in this study lay in the subjective nature of the underlying data and the heterogeneity between the studies. There was a reliance on self-reporting to assess both physical activity and weight loss amongst the primary studies that has the potential to affect the quantitative analysis. Studies have revealed a discrepancy between both the intensity and duration of self reported physical activity when compared with an objective measure. Typically, participants have tended to overestimate physical activity when responding to subjective questionnaires [303, 304]. However, with the large number of included studies and the prospective nature of a number of the included studies, this potential overestimation of physical activity is unlikely to nullify the results. There was, however, significant heterogeneity between the studies in a number of the subgroups analysed. We were unable to find a specific cause for the heterogeneity with no significant change in results when analyzing by study design, year of publication or study population characteristics including geographical location and economic status. In addition, analysis of studies which adjusted for potential confounders did not significantly alter the protective effect.

A Further limitation lay in our inability to complete subgroup analyses into all the breast cancer subgroups. While we were able to assess the association between physical activity and both oestrogen receptor and progesterone receptor positive breast cancer, there were insufficient studies to adequately assess the relationship between HER2 positive breast cancer or triple negative breast cancer.

A final limitation lay in our inability to exclude physical activity as a confounder when assessing the association between weight loss and breast cancer risk. As the primary studies did not adjust for the change in diet or increased physical activity used to achieve the weight loss, we were unable to take this into consideration when completing the quantitative analysis. For this reason, we cannot exclude physical activity as a potential confounder.

Strengths of this study included a broad literature review with over 100 primary observational studies included resulting in a pooled population of over 1 million people. In addition, subgrouping by intensity, timing and menopausal status allowed a thorough investigation into the risk of breast cancer associated with physical activity. Finally, this meta-analysis investigated both the effect of weight loss on breast cancer risk in addition to the association between physical activity and hormone receptor positive breast cancer for the first time; exploring the protective effects associated with positive lifestyle choices and breast cancer risk.

4.4 Conclusion

This quantitative analysis has identified a statistically significant reduction in breast cancer risk associated with physical activity and weight loss. The timing and intensity of the physical activity do not appear to significantly alter this protective effect nor menopausal status at the time of breast cancer diagnosis. Ongoing studies investigating the effect of bariatric surgery on breast cancer risk and further investigation into the association between physical activity and hormone receptor status are recommended to clarify the association and build on the positive results of early studies.

5. Summary

The results of this study identified a reduced risk of breast cancer associated with physical activity and weight loss and an increased risk of breast associated with diabetes mellitus. These results support the significance of lifestyle factors on breast cancer risk whereby a sedentary lifestyle, weight gain and diabetes mellitus have been shown to increase the risk of breast cancer. This increase in breast cancer risk is hypothesised to occur secondary to an increase in one of a number of proliferative hormones including insulin[90], oestrogen[305] and, to a lesser extent, thyroxin[42].

Oestrogen is the most well-known of these hormones, with an increase in lifetime exposure known to increase the risk of breast cancer[305]. While age at menarche and menopause directly affect lifetime oestrogen exposure, a number of other risk factors modulate the oestrogen pathway via a reduction in sex hormone binding globulin (SHBG). SHBG is a glycoprotein produced by the liver that binds free oestrogen circulating in plasma. The amount of SHBG circulating can be affected by the four risk factors investigated in this study: physical activity, diabetes mellitus, weight loss and benign thyroid diseases. Both physical activity and weight loss are known to increase the SHBG concentration, thus reducing the amount of free oestrogen circulating in the blood [306, 307]. Type 2 diabetes mellitus, on the other hand, is known to reduce the concentration of SHBG during the hyperinsulinemia stage whereby the endogenous increase in insulin production has been shown to directly correlate with a reduction in SHBG concentration[308].

Hyperinsulinemia, rather than exogenous insulin use, has also been shown to promote proliferation and increase the risk of breast cancer[302]. This again links in with the "lifestyle" approach to breast cancer risk with weight gain and type 2 diabetes mellitus known to increase insulin production while weight loss and physical activity have been shown to reduce hyperinsulinemia. Furthermore, these features have been shown to effect prognosis in addition to breast cancer risk. Weight loss as an adjuvant treatment has demonstrated survival benefit[309] while physical activity has been shown to improve prognosis in addition to improving quality of life[310, 311]. Diabetes Mellitus, on the other hand, adversely effects breast cancer prognosis, with one study identifying a 40% increase in 5 year mortality when comparing breast cancer prognosis in patients with and without diabetes mellitus[312].

The difficulty in excluding confounders was the major limitation across all three studies. Obesity is one such confounder with the potential to affect the results of each of the three studies. Obesity is a known risk factor or breast cancer, with one study identifying a two fold increase in breast cancer risk when comparing the highest verses the lowest quartile of body mass index (BMI) in postmenopausal women[313] In addition, obesity has a strong association with both type 2 diabetes mellitus and autoimmune thyroiditis making its exclusion as a confounder vital in demonstrating causality. While there were sufficient studies investigating diabetes mellitus and breast cancer that adjusted for BMI to run an adjusted analysis, the same was not possible for benign thyroid disease. For this reason, in addition to the lack of longitudinal studies, we could not prove

causality despite demonstrating a strong association between autoimmune thyroiditis and breast cancer.

There were further limitations in the methodology used to complete the quantitative analysis. This was a study level meta-analysis without acquiring and analyzing the data at an individual level. In addition, only one reviewer was used to assess studies against the inclusion criteria, opening the study up to potential bias in the studies included or excluded. This was minimized, however, through the application of clear and strict inclusion criteria such that the process to include and eliminate studies was as objective as possible.

The methodology behind completing the meta-analysis had its own strengths and limitations. Limitations included the potential for publication bias, with null studies less likely to be published and therefore, potentially missing from the meta-analysis. This limitation can be minimized by assessing the distribution of studies around the effect line. Egger's regression and the Begg and Mazumdar rank correlation were the two methods used throughout this analysis to assess publication bias. Egger's regression is perhaps the more accepted method, having been shown to have greater power to identify publication bias than the other main methods and thus, this was the primary method we used to assess publication bias[314]. However, Begg and Mazumdar's rank correlation was also used to assess the symmetry of the studies around the effect line, offering an alternate approach to the assessment of the publication bias.

A random effects model was used in this analysis as it was felt that the degree of variation in the methodology of the primary studies would better suit a random effects model than fixed effects. While using a random effects model does have its limitations, predominantly larger variance, standard error and confidence intervals when compared with a fixed effect model, it allows for variance in the effect size due to differences in the methodology of the primary studies (ie. differences in study population, study size, geographical location etc) [315]. In addition, this acceptance of variance in the methodology of the primary studies allows extrapolation of the data when generalizing back to the population as a whole [315].

Strengths of this study included the investigation of three new topics for the first time and subgrouping of the included studies wherever possible. The investigations into benign thyroid disease, physical activity and weight loss were completed for the first time, offering new data to generate a consensus on the affect each of these risk factors has on breast cancer risk. Diabetes mellitus, on the other hand, was updated in the general analysis and sub grouped for the first time to gain further insight into the impact specific types of diabetes mellitus have on breast cancer risk. The knowledge that it is type 2 diabetes mellitus that increases the risk of breast cancer allows further research investigating both the mechanism behind this association and strategies to address this association to be specifically targeted at this type rather than type 1 diabetes mellitus or gestational diabetes.

Recommendations

This study has identified a number of areas requiring further investigation as well as a number of areas offering promise for the future. The lack of longitudinal studies investigating benign thyroid diseases and their effect on breast cancer risk resulted in an inability to prove causality despite the results showing a significant association between the two. For this reason, further high quality prospective longitudinal studies are required to definitively exclude reverse causality and further isolate any adverse effect on breast cancer risk associated with thyroid disease.

On the other hand, the results demonstrating a reduced risk of breast cancer associated with bariatric surgery offer significant promise for the future. Despite lacking the power to reach statistical significance, the results of the primary studies all support a reduced breast cancer risk associated with bariatric surgery with one study identifying a five fold reduction in breast cancer risk[164]. These results are in keeping with other studies investigating bariatric surgery and cancer risk in women[316] and show enough potential to initiate further studies. Future studies should aim, wherever possible, to be prospective in nature and of significant size such that they have the necessary power to generate significant results.

Finally, the literature search into diabetes mellitus and breast cancer lacked sufficient primary studies investigating type 1 diabetes mellitus. Furthermore, the small number of studies that were available lacked sufficient quality to reach the inclusion criteria. In order to accurately investigate the effect of type 1

diabetes mellitus on breast cancer risk further longitudinal studies are required of high enough quality such that they have sufficient power to identify any association and are able to account for potential confounders.

The reduced risk of breast cancer associated with exercise and weight loss are promising in terms of reversing the current rise in breast cancer incidence. However, before any change in public health policy can even be contemplated, a number of further studies need to be completed including cost- benefit analyses and investigations of the risks associated with any potential policy change. In addition, as the majority of these studies were observational, randomized controlled trials may need to be completed prior to any direct change in policy.

Conclusion

The results of this study have identified a statistically significant reduction in breast cancer risk associated with both physical activity and weight loss. Diabetes mellitus, however, was found to adversely affect breast cancer risk with this increased risk quantified at 20%. Benign thyroid diseases, on the other hand, were not found to adversely affect breast cancer risk with the exception of autoimmune thyroiditis which was strongly associated with breast cancer despite lacking the longitudinal studies to definitively prove causality.

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