

Diabetes increases the risk of breast cancer: a meta-analysis

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Abstract

The aim of this meta-analysis was to collate and analyse all primary observational studies investigating the risk of breast cancer (BC) associated with diabetes. In addition, we aimed to complete subgroup analyses by both type of diabetes and gender of study participants to further clarify the origin of any such association between the two. Studies were obtained from a database search of MEDLINE, EMBASE, PubMed, Current Contents Connect and Google Scholar with additional cross-checking of reference lists. Collated data were assessed for heterogeneity and a pooled odds ratio (OR) calculated. Forty-three studies were included in the meta-analysis with 40 studies investigating BC in women and six studies investigating BC in men. Overall, we found a significantly increased risk of BC associated with diabetes in women (OR 1.20, 95% confidence interval (CI) 1.13–1.29). After subgroup analysis by type of diabetes, the association was unchanged with type 2 diabetes (OR 1.22, 95% CI 1.07–1.40) and nullified with gestational diabetes (OR 1.06, 95% CI 0.79–1.40). There were insufficient studies to calculate a pooled OR of the risk of BC associated with type 1 diabetes. There was an increased risk of BC in males with diabetes mellitus; however, the results did not reach statistical significance (OR 1.29, 95% CI 0.99–1.67). In conclusion, diabetes increases the risk of BC in women. This association is confirmed in women with type 2 diabetes and supports the hypothesis that diabetes is an independent risk factor for BC.

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Introduction

The increased risk of breast cancer (BC) associated with lifestyle factors has been the subject of numerous observational studies. While there is significant evidence of an increased risk associated with obesity (Harvie *et al.* 2003), smoking (Khuder *et al.* 2001, Mucha *et al.* 2006) and alcohol intake (Key *et al.* 2006), 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 BC associated with non-specific diabetes mellitus; however, due to a lack of primary studies, there was no subgroup analysis by type of diabetes completed.

Liao *et al.* (2011) published another relevant study in 2011. This meta-analysis focused on studies published after 2000, investigating the association between diabetes and BC incidence with subgrouping by geographical location and menopausal status.

Interestingly, this study reported an increased BC risk in Europe and America with no increased risk identified in Asia. Furthermore, this study reported a significant association between BC and diabetes mellitus in only the postmenopausal age group.

In regard 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 (Rollison *et al.* 2008) while other studies reported an increased risk (Perrin *et al.* 2008) or no association between the two (Troisi *et al.* 1998, Lawlor *et al.* 2004, Sella *et al.* 2011). This discrepancy is also present within studies investigating type 2 diabetes mellitus and studies investigating the aetiology of BC in males.

While the exact mechanism behind any association between diabetes mellitus and BC has not yet been identified, the main hypothesis at this stage has focused on the hyperinsulinaemia 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 BC. Obesity is one such example.

The aim of this study was to quantify the risk of BC 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 effect of certain types of diabetes on the incidence of BC.

Materials and methods

Study protocol

One reviewer (P J H), following the meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup *et al.* 2000), 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 'BC' 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 that met the following inclusion criteria were included in the meta-analysis: i) the risk point estimate was reported as an odds ratio (OR) or the OR could be calculated from the presented data; ii) the 95% confidence interval (CI) was reported or the CI could be calculated from the presented data; and iii) 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 were extracted by a single reviewer (P J H) and entered into a standardised data spread sheet (Table 1). 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, CI and adjusted variables. Where applicable,

adjusted ORs were recorded. However, where no OR was given, an unadjusted OR and CI were calculated by the reviewer (P J H). Where multiple ORs were given within the same study, i.e. from two different geographical locations, the data were entered as two separate ORs. Studies that did not define the specific type of diabetes were analysed as 'non-specific diabetes'.

Statistical analysis

A random effects model was used to calculate a pooled OR for the effect of diabetes on the risk of developing BC. Heterogeneity was assessed using Cochran's Q statistic with a *P* value of <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. 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 <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 were analysed using Comprehensive Meta-analysis (version 2.0).

Results

The literature search identified 59 studies investigating the association between BC and diabetes, 16 studies were excluded from the meta-analysis for failing to meet the inclusion criteria (Fig. 1). Eleven studies were excluded for failing to include an internal control group (De Waard & Baanders Van Halewijn 1974, Ragozzino *et al.* 1982, Adami *et al.* 1991, Hjalgrim *et al.* 1997, Weiderpass *et al.* 1997, Wideroff *et al.* 1997, Kath *et al.* 2000, Zendeheh *et al.* 2003, Swerdlow *et al.* 2005, Hemminki *et al.* 2010, Shu *et al.* 2010), three studies were excluded for investigating mortality rather than incidence (Coughlin *et al.* 2004, Siegelmann-Danieli *et al.* 2006, Tseng *et al.* 2009), one study was excluded for using benign breast disease as a comparator (Muck *et al.* 1975) and the final study was excluded for investigating the effect of glycaemic control on BC incidence (Stefansdottir *et al.* 2011). The remaining 43 studies were included in the meta-analysis.

Table 1 Summary of included studies

Reference	Design	Cases	Controls	Type of diabetes	Summary of findings
Attner <i>et al.</i> (2012)	CC	19 756	147 324	Non-specific	Increased risk of BC in patients with DM
Baron <i>et al.</i> (2001)	CC	5564	5841	Non-specific	Increased risk of BC associated with late-onset DM, decreased risk of BC associated with early-onset DM
Beji & Reis (2007)	CC	405	1050	Non-specific	Increased risk of BC in patients with DM
Bowker <i>et al.</i> (2011)	CO	84 506	84 506	T2DM	No association between BC and DM
Brinton <i>et al.</i> (2010)	CO	111	4 501 578	Non-specific	Increased risk of BC in patients with DM
Carstensen <i>et al.</i> (2012)	CO	23 846	346 138	Non-specific	No association between BC and DM
Chlebowski <i>et al.</i> (2012)	CO	3401	64 618	Non-specific	No association between BC and DM
Chodick <i>et al.</i> (2010)	CO	16 721	83 874	Non-specific	No association between BC and DM
Cleveland <i>et al.</i> (2012)	CC	1447	1453	Non-specific	No significant association between BC and DM
Ewertz <i>et al.</i> (2001)	CC	156	468	Non-specific	Increased risk of BC in patients with DM
Franceschi <i>et al.</i> (1990)	CC	2663	2344	Non-specific	No association between BC and DM
Garmendia <i>et al.</i> (2007)	CC	170	170	Non-specific	No association between diabetes and BC
Goodman <i>et al.</i> (1997)	CO	161	22 039	Non-specific	Increased risk of BC in patients with diabetes
Hsieh <i>et al.</i> (2012)	CO	61 777	677 378	T2DM	Increased risk of BC associated with T2DM
Inoue <i>et al.</i> (2006)	CO	4668	93 103	Non-specific	No association between BC and DM
Jee <i>et al.</i> (2005)	CO	21 056	270 157	Non-specific	Increased risk of BC in patients with DM
Jordan <i>et al.</i> (2009)	CC	43	860	T2DM	Increased risk of BC in patients with DM
Khachatryan <i>et al.</i> (2011)	CC	150	152	T2DM	Increased risk of BC associated with T2DM
Khan <i>et al.</i> (2006)	CO	1554	31 949	Non-specific	No association between BC and DM
Lambe <i>et al.</i> (2011)	CO	5615	218 279	Non-specific	Increased risk of BC in postmenopausal women with DM
La Vecchia <i>et al.</i> (1994)	CC	9991	7834	Non-specific	No association between BC and DM
Lawlor <i>et al.</i> (2004)	CS	147	3690	Non-specific, gestational	No significant association between DM and BC
Li <i>et al.</i> (2011)	CS	48 418	349 365	Non-specific	Increased risk of BC associated with DM
Lipscombe <i>et al.</i> (2006)	CO	73 796	391 714	Non-specific	Increased risk of BC associated with DM
Michels <i>et al.</i> (2003)	CO	6220	116 488	T2DM	Increased risk of BC associated with T2DM
Mink <i>et al.</i> (2002)	CO	26	7894	Non-specific	No association between BC and DM
Moseson <i>et al.</i> (1993)	CC	354	747	Non-specific	No significant association between BC and DM
Perrin <i>et al.</i> (2008)	CO	410	37 516	Gestational	Increased risk of BC associated with gestational diabetes
Resta <i>et al.</i> (2004)	CC	1663	4702	T2DM	Increased risk of BC associated with T2DM
Ronco <i>et al.</i> (2012)	CC	367	545	Non-specific	Increased risk of BC associated with DM
Rollison <i>et al.</i> (2008)	CC	2324	2523	Non-specific, gestational, T2DM	Gestational diabetes reduces risk of BC, no association between T2DM and non-specific DM
Rosato <i>et al.</i> (2011)	CC	3869	4082	Non-specific	Increased risk of BC associated with DM
Sanderson <i>et al.</i> (2010)	CC	190	979	T2DM, gestational	No association between DM and BC
Sella <i>et al.</i> (2011)	CO	11 624	174 051	Gestational	No association between gestational diabetes and BC
Sellers <i>et al.</i> (2007)	CO	403	5727	T2DM	No significant risk of BC associated with DM
Sinagra <i>et al.</i> (2002)	CS	50	25	Non-specific	Increased risk of BC associated with DM
Steenland <i>et al.</i> (1995)	CC	1250	11 804	Non-specific	No significant increased risk of BC associated with DM
Talamini <i>et al.</i> (1997)	CC	2769	2588	Non-specific	Increased risk of BC in postmenopausal women with DM
Thomas <i>et al.</i> (1992)	CC	227	300	Non-specific	No significant increase in risk of BC in males with DM
Troisi <i>et al.</i> (1998)	CC	1239	1166	Gestational	No association between gestational diabetes and BC
Weiss <i>et al.</i> (1999)	CC	2173	1990	Non-specific	No association between BC and DM
Wu <i>et al.</i> (2007)	CC	1248	1148	T2DM	Increased risk of BC associated with T2DM
Yu <i>et al.</i> (2012)	CC	103	309	Non-specific	No significant increased risk of BC associated with DM

Non-specific diabetes mellitus

Forty studies were identified investigating diabetes and the risk of BC in women. Fourteen studies reported a statistically significant increase in BC incidence in patients with diabetes mellitus (Goodman *et al.* 1997, Sinagra *et al.* 2002, Michels *et al.* 2003, Resta *et al.* 2004, Jee *et al.* 2005, Lipscombe *et al.* 2006, Beji &

Reis 2007, Wu *et al.* 2007, Jordan *et al.* 2009, Khachatryan *et al.* 2011, Rosato *et al.* 2011, Attner *et al.* 2012, Hsieh *et al.* 2012, Ronco *et al.* 2012) while 24 studies reported results that did not reach statistical significance. Within these 24 studies, 17 studies had risk point estimates that favoured an increased risk of BC (Steenland *et al.* 1995, Talamini *et al.* 1997,

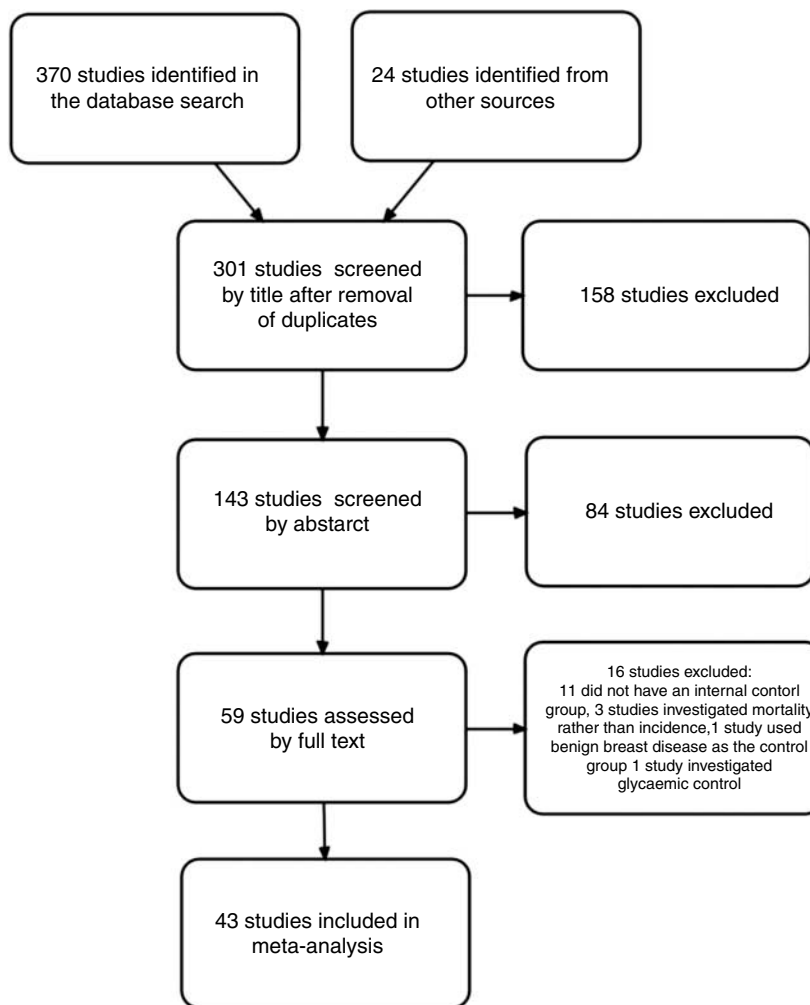


Figure 1 Results of the literature search.

Troisi *et al.* 1998, Weiss *et al.* 1999, Baron *et al.* 2001, Mink *et al.* 2002, Lawlor *et al.* 2004, Khan *et al.* 2006, Garmendia *et al.* 2007, Sellers *et al.* 2007, Perrin *et al.* 2008, Sanderson *et al.* 2010, Lambe *et al.* 2011, Li *et al.* 2011, Carstensen *et al.* 2012, Cleveland *et al.* 2012, Yu *et al.* 2012) while six studies favoured a decreased risk (Moseson *et al.* 1993, Inoue *et al.* 2006, Rollison *et al.* 2008, La Vecchia *et al.* 1994, Sella *et al.* 2011, Chlebowski *et al.* 2012). Three studies found no association between the two (Franceschi *et al.* 1990, Chodick *et al.* 2010, Bowker *et al.* 2011). Quantitative analysis revealed a significant pooled risk point estimate of 1.20 (95% CI 1.13–1.29) (Fig. 2). Heterogeneity was high ($I^2=73.41$, $P<0.001$) and there was evidence of publication bias ($n=932$, Egger's $P=0.01$). However, the funnel plot was found to be symmetrical using the Begg and Mazumdar rank correlation ($P=0.07$; Fig. 3).

Subgroup analysis by study design identified a slightly increased risk of BC in CC studies when compared with CO 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 BC incidence, a subgroup analysis was undertaken investigating only studies that adjusted for known risk factors of BC. Twenty-one studies adjusted for age and BMI with the pooled risk point estimate identifying a statistically significant increase in BC 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

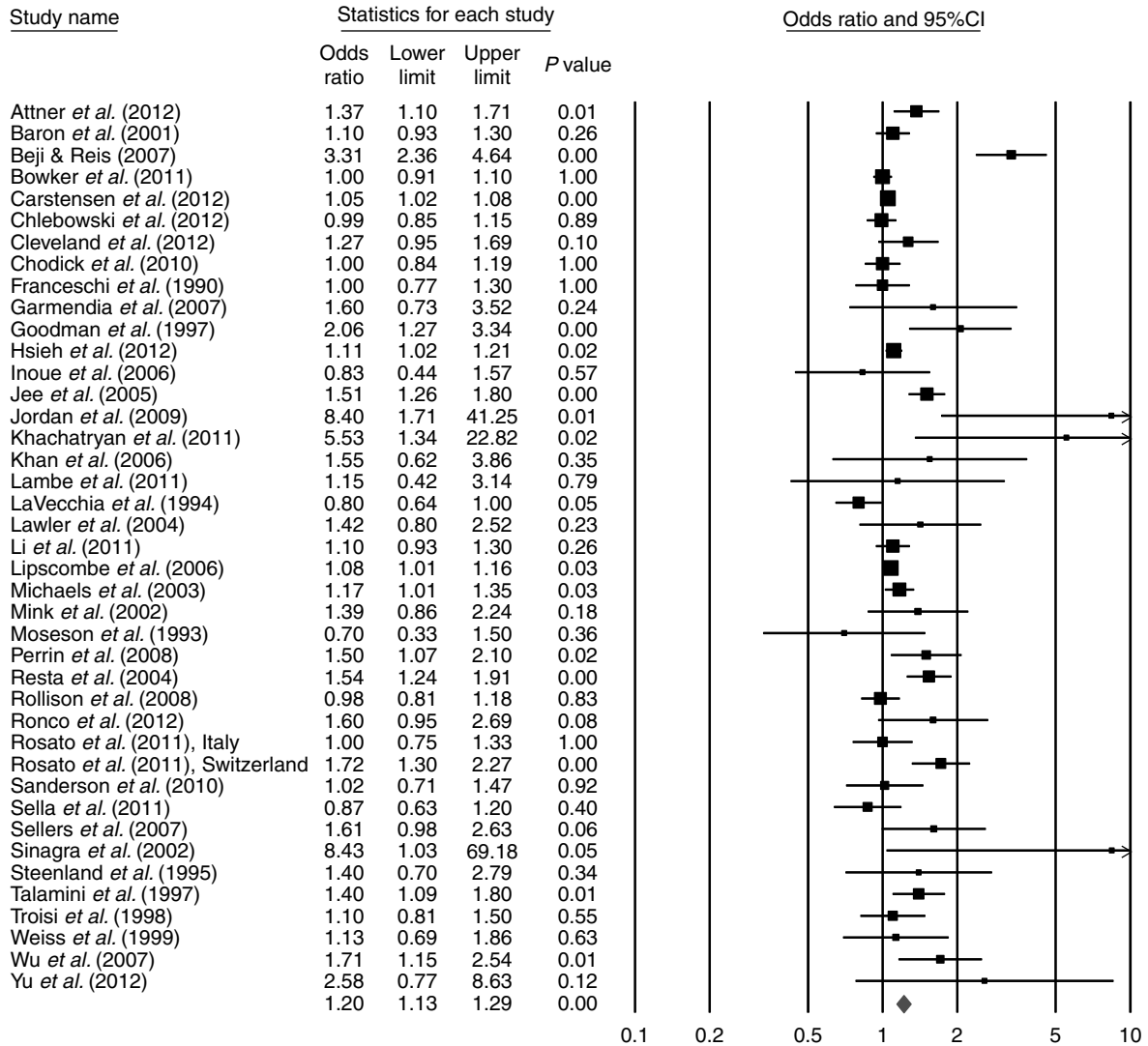


Figure 2 Diabetes and breast cancer incidence in women.

the results continuing to favour an increased risk of BC in patients with diabetes mellitus (OR 1.11, 95% CI 1.01–1.22, $I^2 = 25.02$, $P = 0.23$).

Male BC

Seven studies were identified investigating the association between BC and diabetes mellitus in men (Lenfant-Pejovic *et al.* 1990, Thomas *et al.* 1992, Ewertz *et al.* 2001, Brinton *et al.* 2010, Chodick *et al.* 2010, Li *et al.* 2011, Carstensen *et al.* 2012). Five studies were homogenous in their finding of an increased risk point estimate; however, only two studies reached statistical significance (Ewertz *et al.* 2001, Brinton *et al.* 2010). The remaining two studies, despite not reaching statistical significance, favoured

a protective effect associated with diabetes mellitus. The pooled OR favoured an increased risk of BC in males with diabetes mellitus (OR 1.29, 95% CI 0.99–1.67) (Fig. 4). There was no evidence of heterogeneity ($I^2 = 32.83$, $P = 0.18$).

Type 2 diabetes mellitus

Subgroup analysis of non-specific diabetes mellitus in women identified ten studies that specifically investigated type 2 diabetes mellitus (Michels *et al.* 2003, Resta *et al.* 2004, Sellers *et al.* 2007, Wu *et al.* 2007, Rollison *et al.* 2008, Jordan *et al.* 2009, Sanderson *et al.* 2010, Bowker *et al.* 2011, Khachatryan *et al.* 2011, Hsieh *et al.* 2012). Eight studies reported a positive risk point estimate with six studies reaching

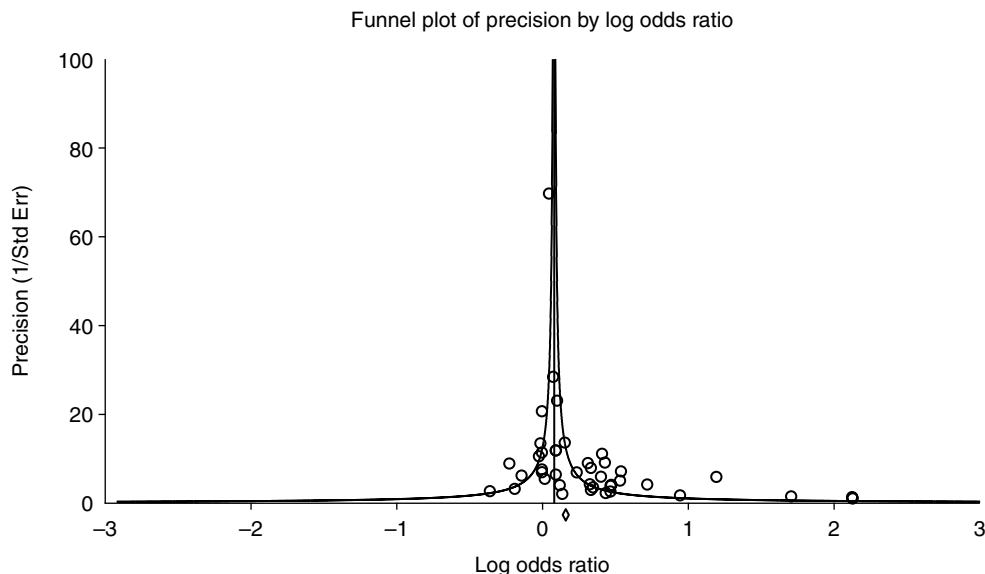


Figure 3 Funnel plot assessing publication bias.

statistical significance (Michels *et al.* 2003, Resta *et al.* 2004, Wu *et al.* 2007, Jordan *et al.* 2009, Khachatryan *et al.* 2011, Hsieh *et al.* 2012). The final two studies did not find any association between the two (Sanderson *et al.* 2010, Bowker *et al.* 2011). The pooled OR and 95% CI supported an increased risk of BC associated with type 2 diabetes mellitus (OR 1.22, 95% CI 1.07–1.40) (Fig. 5).

Type 1 diabetes mellitus

The literature search identified three studies investigating the effect of type 1 diabetes mellitus on BC incidence. However, all three studies failed to meet the inclusion criteria with two studies failing to include an internal control group (Zendehel *et al.* 2003, Shu *et al.* 2010) while one study assumed a diagnosis of type 1 diabetes mellitus in all patients aged under

35 years without confirmation (Baron *et al.* 2001). 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 BC incidence (Troisi *et al.* 1998, Lawlor *et al.* 2004, Perrin *et al.* 2008, Rollison *et al.* 2008, Sella *et al.* 2011). There was a degree of heterogeneity within the results with only one study reaching statistical significance (Rollison *et al.* 2008). This study found gestational diabetes to reduce the risk of BC. The remaining four studies did not reach statistical significance with three studies finding an

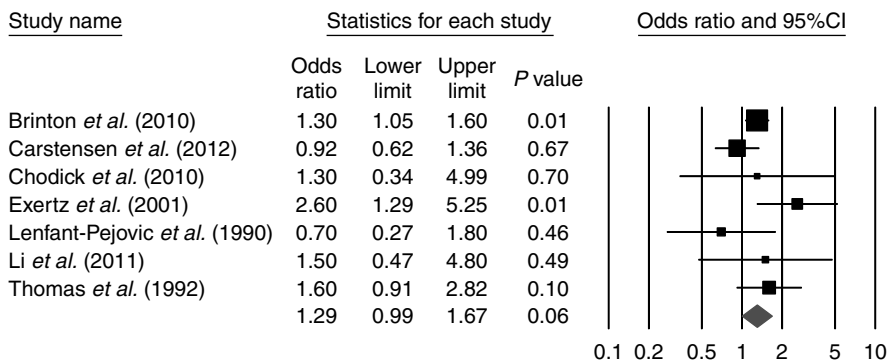


Figure 4 Diabetes and breast cancer incidence in men.

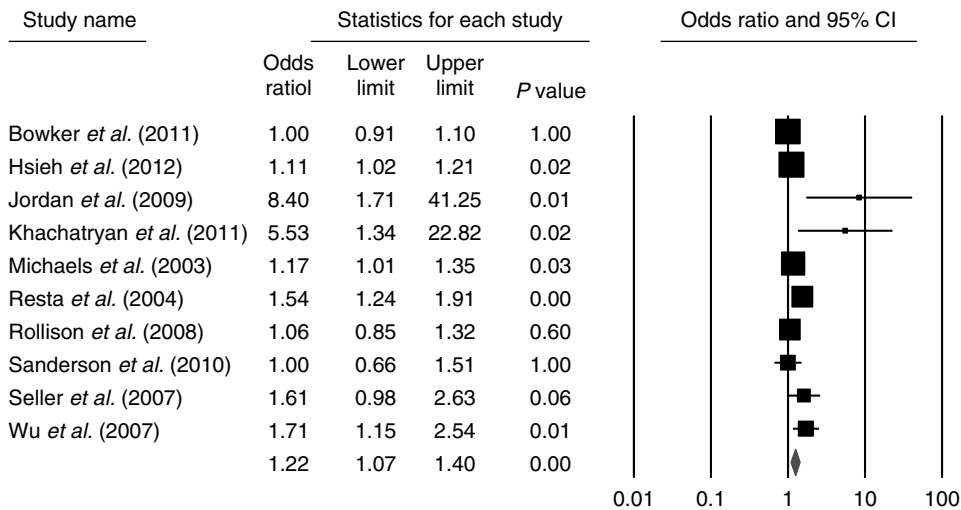


Figure 5 Type 2 diabetes and breast cancer incidence.

increased risk point estimate (Troisi *et al.* 1998, Lawlor *et al.* 2004, Perrin *et al.* 2008) and one study reporting a negative risk point estimate (Sella *et al.* 2011). The pooled OR did not find any association between gestational diabetes and BC (OR 1.06, 95% CI 0.79–1.40) while significant heterogeneity was present ($I^2 = 68.81$, $P = 0.01$).

Discussion

Our study identified a 20% increased risk of BC 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 hyperinsulinaemia hypothesis as a potential mechanism linking diabetes mellitus to BC.

While type 1 diabetes mellitus is predominantly associated with insulin deficiency, type 2 diabetes is more readily known for its hyperinsulinaemic state. This is particularly seen in the early stages of the disease where the pancreas is still able to compensate for the hyperglycaemia. This increase in insulin is hypothesised to increase proliferation in two ways; activation of the insulin receptor substrate to increase mitosis at a cellular level (Chan & Lee 2008) and causing an imbalance in sex steroids via a decrease in sex hormone binding globulin (Nestler 2000). 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 BC (Ballard-Barbash *et al.* 1990, Carmichael & Bates 2004).

Another hypothesis centres on an iatrogenic link between BC and diabetes mellitus. Insulin use has long been suspected of increasing the risk of BC and more recently the debate has focused on the use of insulin glargine. Jonasson *et al.* (2009) in a study published in 2009 found an increased risk of BC associated with glargine use. These results, however, have not been replicated in other observational studies (Colhoun & Group 2009, Currie *et al.* 2009, Home & Lagarenne 2009). 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 BC in people using insulin and people using other antiglycaemic agents (Carstensen *et al.* 2012).

Metformin use, on the other hand, has actually been shown to reduce the risk of BC (Bodmer *et al.* 2010). Hypothesised mechanisms explaining this protective effect include metformin's ability to reduce the hyperinsulinaemia associated with type 2 diabetes and *in vitro* evidence of direct anticarcinogenic properties (Martin-Castillo *et al.* 2010, Belda-Iniesta *et al.* 2011). While a number of observational studies have confirmed this protective effect, a recent study specifically identified a 25% reduction in BC incidence associated with metformin use (Chlebowski *et al.* 2012). New evidence has also indicated that metformin use may improve prognosis (Jiralerspong *et al.* 2009).

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 exclude antiglycaemic therapy as a potential confounder. This constraint, in the context of new evidence potentially linking antiglycaemic agents to BC incidence, is a major limitation in our study. We recommend that 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 BC has not been thoroughly assessed and it may be worthwhile for future studies to also take this into account.

A further weakness in this study lay in our inability to differentiate between the different types of diabetes investigated. Thirty-four 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 years, and thus a diagnosis of type 2 diabetes was most likely, we were unable to include the studies in our subgroup analysis. For this reason, the power of the subgroup 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 subgrouping 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 previous reviews (Larsson *et al.* 2007, Liao *et al.* 2011). The increased number of studies allowed subgroup analysis by type of diabetes for the first time.

In conclusion, in patients with diabetes mellitus, we have found a 20% increase in the incidence of BC 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 hyperinsulinaemia theory in the aetiology of BC.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

All authors contributed to the conception, design and interpretation of the data; the preparation of the manuscript; and the final editing and approval of the manuscript.

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