

Diabetes and breast cancer risk: a meta-analysis

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BACKGROUND: The potential of an increased risk of breast cancer in women with diabetes has been the subject of a great deal of recent research.

METHODS: A meta-analysis was undertaken using a random effects model to investigate the association between diabetes and breast cancer risk.

RESULTS: Thirty-nine independent risk estimates were available from observational epidemiological studies. The summary relative risk (SRR) for breast cancer in women with diabetes was 1.27 (95% confidence interval (CI), 1.16–1.39) with no evidence of publication bias. Prospective studies showed a lower risk (SRR 1.23 (95% CI, 1.12–1.35)) than retrospective studies (SRR 1.36 (95% CI, 1.13–1.63)). Type 1 diabetes, or diabetes in pre-menopausal women, were not associated with risk of breast cancer (SRR 1.00 (95% CI, 0.74–1.35) and SRR 0.86 (95% CI, 0.66–1.12), respectively). Studies adjusting for body mass index (BMI) showed lower estimates (SRR 1.16 (95% CI, 1.08–1.24)) as compared with those studies that were not adjusted for BMI (SRR 1.33 (95% CI, 1.18–1.51)).

CONCLUSION: The risk of breast cancer in women with type 2 diabetes is increased by 27%, a figure that decreased to 16% after adjustment for BMI. No increased risk was seen for women at pre-menopausal ages or with type 1 diabetes.

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Diabetes is one of the commonest chronic conditions in men and women. In 2010, it was estimated that there were approximately 285 million patients with diabetes, aged 20–79 years, around the world; this represents a prevalence of 6.4% (Sicree *et al*, 2006). Complications from diabetes, such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, amputations, renal failure and blindness are resulting in increasing disability, reduced life expectancy and enormous health costs for virtually every society. Diabetes and its complications contribute to a substantial proportion of causes of death in high-resource countries, and in many lower-resource regions, diabetes is rapidly increasing in incidence and prevalence. It is estimated that the global burden of diabetes will reach 439 million people (prevalence of 7.7%) by 2030 (Sicree *et al*, 2006).

Cancer is increasingly a global problem (Boyle, 2006), and breast cancer is not only the commonest incident form of cancer in women worldwide but is the first or second most common in all regions of the world, and is responsible for approximately 1.4 million new cases annually (Boyle and Levin, 2008). The incidence of breast cancer is increasing almost everywhere throughout the world, for example in Asia (Shin *et al*, 2010), although the mortality from breast cancer is declining in many high-income

countries (Autier *et al*, 2010). Notable exceptions to this increasing trend in incidence have taken place in the United States where there has been a sharp decrease in incidence from 2002–2003 that occurred in women 50–69 years old, who predominantly, but not exclusively, had oestrogen receptor positive tumours and may reflect the early benefit of the reduced use of hormone replacement therapy (Jemal *et al*, 2007).

The global burden of breast cancer doubled between 1975 and 2000. It seems certain to double again between now and 2030, and the great majority of this burden will fall on the low-income and lower middle-income countries where the resources to deal with the current situation, never mind the future increases, are absent to a great degree (Boyle and Howell, 2010). Focus on breast cancer up until now has almost entirely been on top of the situation in high-income countries. With growth and ageing of the world's population, notable increases in life expectancy in many countries and the sharp tendency towards adoption of a westernised lifestyle with lower fertility rates, cancer is a rapidly growing global problem (Boyle, 2006) and not one which the majority of the world is ready to cope with.

Initially hypothesised by Freund (1885), women with breast cancer have been described as having higher rates of diabetes than healthy women (Glicksman and Rawson, 1956). The potential of an increased risk of breast cancer in women with diabetes has been the subject of a great deal of recent research. Given how common both breast cancer and diabetes are in our ageing societies, this is an important issue for public health.

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Past meta-analysis have analysed the association between diabetes and breast cancer risk reported by observational studies (Wolf *et al*, 2005; Larsson *et al*, 2007; Liao *et al*, 2011), but it included a maximum of only 20 studies, which limited their statistical power and capacity to perform heterogeneity analysis.

The objective of the present study is to summarise results from observational studies on the association between breast cancer and diabetes, and to investigate source of heterogeneity in the estimated risks.

MATERIALS AND METHODS

Literature search, eligibility and data abstraction

A systematic literature search and quantitative analysis was conducted based on a protocol developed for this study, and is reported following the MOOSE guidelines regarding meta-analysis of observational studies (Stroup *et al*, 2000). Published reports in peer-reviewed journals were obtained from the following databases using validated search strategies: Ovid MEDLINE database, ISI Web of Science, Science Citation Index Expanded and PUBMED (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>). We used combinations of the following keywords and corresponding MeSH terms for the literature searches: 'Diabetes Mellitus', 'breast neoplasms', 'breast cancer'. Other sources were found in the reference lists of the retrieved articles and preceding reviews, including meta-analysis, on the topic. The literature search was conducted up to October 2011.

Studies eligible for this review had to meet the following criteria: (i) report data on incident invasive cases of breast cancer or on breast cancer deaths; (ii) report on whether women included in studies had diabetes or not; and (iii) have a cross-sectional, case-control, cohort, nested case-control design or a randomised trial including a control group of women in which the exposure of interest had been assessed in the same way as in breast cancer women. Control women had to have no history of breast cancer or of known benign breast tumour disease. For cohort studies, the control group could be external, like a cancer registry or a cause of death registry. Ecological studies, case reports, reviews and editorials were not considered eligible.

The search was restricted to articles published in English language. There was no restriction on geographical location of studies. We screened titles and looked at abstracts when the title suggested a study possibly meeting the main criteria. If the abstract content was relevant, full copies of articles were retrieved and fully read by at least two co-authors. Articles reporting on prognosis after breast cancer diagnosis were excluded. Review articles not reporting original data were also excluded, but checked for references.

A standard data extraction form was used for abstracting data from eligible publications. This data extraction was conducted by two co-authors, and when necessary, a third co-author analysed discrepancies. We extracted any measure of association of the risk of breast cancer associated with diabetes, taking the most adjusted risk. We did not differentiate between odds ratios, relative risks and standardised incidence ratios, and we considered that each was an estimate of relative risk, later referred as RR. We also extracted the 95% confidence interval (95% CI) around the RR.

Note that two studies (de Waard and Baanders-van Halewijn, 1974; O'Mara *et al*, 1985) did not calculate any measure of dispersion (95% CI, variance, etc.) for their RR. For these articles, variances were taken as the average variance of all other studies. In addition, the standardised incidence ratio (SIR) reported by Wideroff *et al* (1997) has only one decimal and a very narrow CI, being presented as SIR = 1.1 (95% CI, 1.1–1.2). To improve the variance estimate, which could be underestimated by using these original values, the CI was re-estimated based on the variance of

the crude rate and the point estimate and 95% CI compatible with the rounding performed in the original article. The SIR included in our analysis was therefore 1.14 (95% CI, 1.06–1.22).

We also extracted the type of study separating prospective studies from others (mainly case-control studies) and the various adjustment factors used. We extracted whether the study was restricted to type 1 diabetes, type 2 diabetes, or included both types of diabetes and when the type of diabetes was not reported. We attempted to identify studies whose primary objective was the investigation of the association between diabetes and breast cancer. However, in most articles, the diabetes-breast cancer association was just one of the many exposure-breast cancer relationships that were explored. We therefore examined whether the diabetes has been self-declared or obtained from medical records or prescription databases, because studies recording diabetes from medical records or prescription database probably had a greater focus on diabetes than studies with diabetes as an item in a questionnaire.

When data were available, stratified by menopausal status, specific RR and 95% CI were gathered. In a heterogeneity analysis, we additionally extracted RR adjusted and not adjusted for body mass index (BMI), and both RRs were provided by a study.

Statistical analysis

The various estimates of RR and their CIs were transformed into log (RR) and the corresponding variance was calculated. Where no estimates were reported, the crude estimates and 95% CI were calculated from tabular data. From the transformed data, maximum likelihood summary relative risks (SRR) were calculated using a random effects model including two sources of variation (between study variance and, when applicable, within study variance; van Houwelingen *et al*, 2002). The meta-analysis was carried out in programming language R (version 2.13.1, GNU General Public Licence, 2011) and package *metafor* (Viechtbauer, 2010). Heterogeneity across studies was evaluated by I^2 , which represents the percentage of total variation across studies that is attributable to heterogeneity rather than to chance (Higgins and Thompson, 2002). Sensitivity analyses were carried out to evaluate the influence of each study on the overall estimate from the meta-analysis.

Statistically significant results are more likely to be easily and quickly published in international peer-reviewed journals. Null or

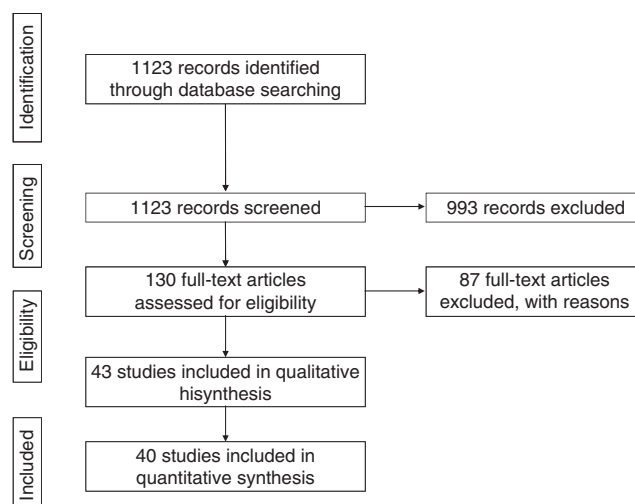


Figure 1 Flow chart of the literature search strategy to identify observational studies on breast cancer risk and diabetes.

Table 1 Main characteristics of studies included in the meta-analysis, ranked by year of publication

First author (year)	Country	Study design	Number of cases			Follow-up (years) in cohorts	Age groups
			All women	Pre-menopause	Post-menopause		
Li <i>et al</i> (2011)	USA	CS	7830	NR	NR	—	18–99
Lambe <i>et al</i> (2011)	Sweden	CS	5967	1425	4272	—	>25
Rosato <i>et al</i> (2011)	Italy	CC	3869	NR	3869	—	33–80
Hemminki <i>et al</i> (2010)	Sweden	CH	844	NR	NR	15	>39
Sanderson <i>et al</i> (2010)	USA	CC	190	NR	NR	—	30–79
Jordan <i>et al</i> (2009)	Thailand	CC	43	NR	NR	—	NR
Tseng <i>et al</i> (2009)	Taiwan	CH	482	NR	NR	10	>25
Rollison <i>et al</i> (2008)	USA	CC	2324	871	1448	—	Mean age 55.5
Beji and Reis (2007)	Turkey	CC	405	NR	NR	—	28–72
Garmendia <i>et al</i> (2007)	Chile	CC	170	NR	122	—	33–86
Wu <i>et al</i> (2007)	USA	CC	1224	547	677	—	25–74
Inoue <i>et al</i> (2006)	Japan	CH	451	NR	NR	10.7	40–69
Khan <i>et al</i> (2006)	Japan	CH	120	NR	NR	8	40–79
Lipscombe <i>et al</i> (2006)	Canada	CH	6107	NR	6107	4.5	55–79
Jee <i>et al</i> (2005)	Korea	CH	289 ^a	NR	NR	10 (max)	30–95
Rapp <i>et al</i> (2006)	Austria	CH	50	NR	NR	8.6	35–54
Swerdlow <i>et al</i> (2005)	UK	CH	75 cases / 27 deaths	NR	NR	18	<49
Coughlin <i>et al</i> (2004)	USA	CH	4346	NR	NR	16 (max)	>30
Lawlor <i>et al</i> (2004)	UK	CS	147	NR	NR	—	60–79
Resta <i>et al</i> (2004)	Italy	CC	1663	NR	NR	—	24–85
Michels <i>et al</i> (2003)	USA	CH	5605	1469	3562	22 (max)	30–55
Verlato <i>et al</i> (2003)	Italy	CH	57	NR	NR	10 (max)	Mean age 69.2
Zendehdel <i>et al</i> (2003)	Sweden	CH	69	69	NR	14.4	0–30
Sinagra <i>et al</i> (2002)	Italy	CC	50	NR	NR	—	Mean age 49.4
Mink <i>et al</i> (2002)	USA	CH	187	NR	NR	7.1	45–64
Baron <i>et al</i> (2001)	USA	CC	5564	NR	NR	—	50–75
Weiss <i>et al</i> (1999)	USA	CC	2158	NR	NR	—	20–54
Goodman <i>et al</i> (1997)	Japan	CH	161	NR	NR	8.31	All ages
Hjalgrim <i>et al</i> (1997)	Denmark	CH	11	NR	NR	12.9	All ages
Weiderpass <i>et al</i> (1997)	Sweden	CH	1145	NR	NR	6.7	Mean age 64.2
Wideroff <i>et al</i> (1997)	Denmark	CH	777	NR	NR	5.7	All ages
Steenland <i>et al</i> (1995)	USA	CH	163	NR	NR	7.7	25–74
Sellers <i>et al</i> (1994)	USA	CH	611	NR	611	5 (max)	55–69
Moseson <i>et al</i> (1993)	USA	CC	354	90	264	—	22–86
Adami <i>et al</i> (1991)	Sweden	CH	240	NR	NR	5.2	All ages
O'Mara <i>et al</i> (1985) ^b	USA	CC	1883	NR	NR	—	30–89
Ragozzino <i>et al</i> (1982)	USA	CH	14	NR	NR	8.6	All ages
Adami and Rimsten (1978)	Sweden	CC	179	30	149	—	Mean age 63
Muck <i>et al</i> (1975)	Germany	CC	217	NR	NR	—	All ages
de Waard and Baanders-van Halewijn (1974) ^b	The Netherlands	CH	70	NR	70	5.4	55–75

Abbreviations: CC = case-control; CH = cohort; CS = cross-sectional; NCC = nested case-control in a cohort; NR = not reported. The control group consisted in a 511 high-risk group of women receiving a diagnostic mammogram either due to inconclusive or abnormal results, and in 468 low-risk group of women with no family history of BC, no history of breast biopsy and negative mammograms for the past 2 years. ^aNot reported but computed from incidence rate and sample size in Table 5 from Jee *et al* (2005). ^bDid not report confidence intervals. Variance was taken as the average variance of all other studies.

non-significant results are harder to publish. This has to be taken into account in meta-analyses, because this may introduce publication bias. Publication bias was graphically assessed using a funnel-plot-based approach; the regression of log (OR) on the sample size, weighted by the inverse of the variance (Macaskill test) was calculated (Macaskill *et al*, 2001). To complete this visual analysis, the three main publication bias tests were computed, namely Begg's test (rank correlation test; Begg and Mazumdar, 1994), Egger's test (weighted linear regression test for funnel plot symmetry; Egger *et al*, 1997) and Macaskill's test (Macaskill *et al*, 2001).

As sensitivity analysis for assessing the relative weight of each study on the SRR, the meta-analysis was run again, systematically omitting each study (leave-one-out analysis).

To investigate sources of heterogeneity, separate analyses were performed for type 1 and type 2 diabetes, for pre-menopausal and post-menopausal women, for BMI-adjusted risk estimates vs not BMI-adjusted risk estimates, for studies on breast cancer

mortality vs studies on incident cases, and for self-declared and medically reviewed diabetes. To test for differences between subgroups, we conducted a meta-regression in a random-effect model, with subgroup variable as a fixed parameter. An analysis was also conducted for cohort studies and case-control studies separately.

RESULTS

Figure 1 summarises the process of literature search of the present meta-analysis. Overall, 43 studies have been identified from the literature search. Three studies were excluded (Franceschi *et al*, 1990; La Vecchia *et al*, 1994; Talamini *et al*, 1997), because they were included in Rosato *et al*, 2011.

The meta-analysis included 40 independent risk estimates reported in 40 articles (Table 1). Of these, 18 were retrospective (15 case-control, 3 cross-sectional) studies and 22 were prospective

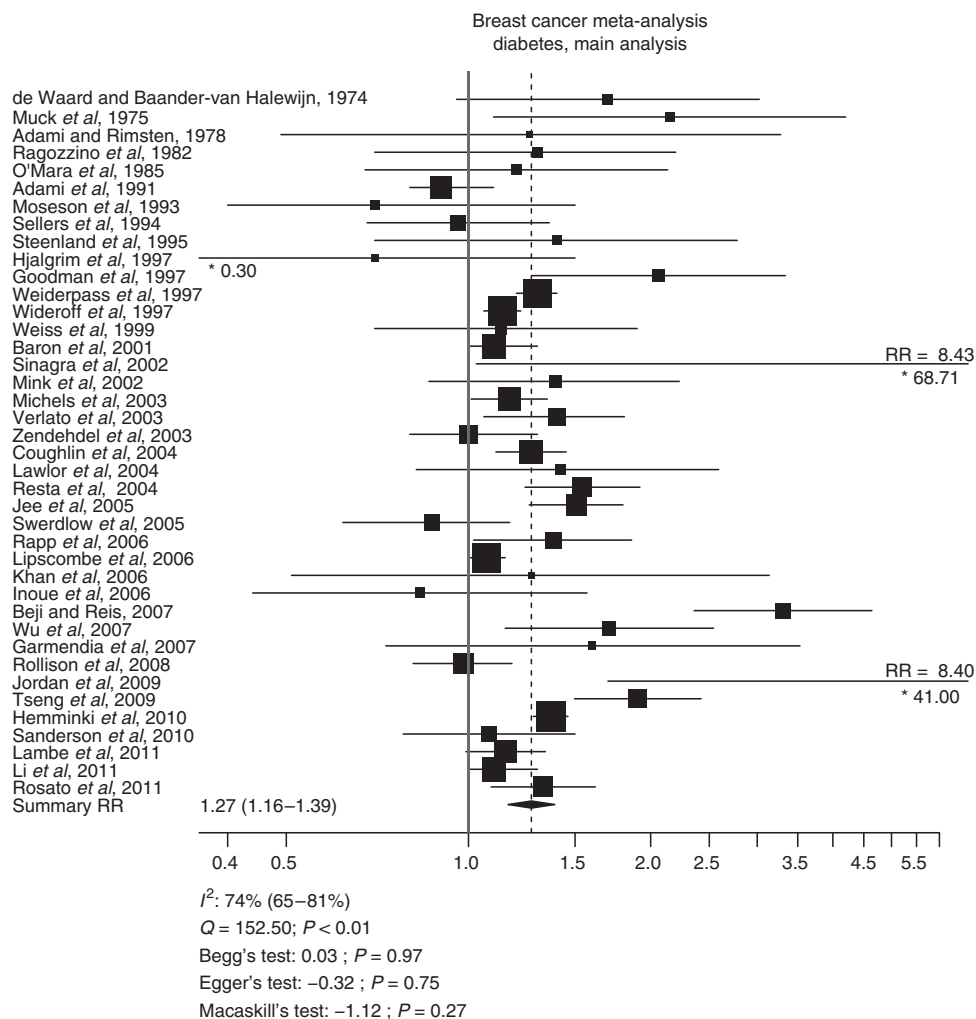


Figure 2 Forest plot of meta-analysis of breast cancer in women with diabetes. Individual studies represented by relative risk (RR) and 95% confidence interval (CI).

studies. Fifteen studies were conducted in Northern America, 1 in South America, 18 in Europe and 6 in Asia. Studies included a total of 56 111 breast cancer cases. Study size ranged from 11 to 7830 breast cancer cases, with a median of 322. The majority of cases (38 560) were recruited in the northern American studies.

Figure 2 presents the meta-analysis of all 40 studies combined. The SRR of breast cancer in diabetic women was 1.27 (95% CI, 1.16–1.39) with $I^2 = 74%$ (95% CI, 65–81%), the percentage of heterogeneity which could not be explained by chance. The Begg's test (0.03, $P = 0.97$), the Egger's test (-0.32 , $P = 0.75$) and the Macaskill's test (-1.12 , $P = 0.27$) were non-significant, indicating that publication bias was unlikely.

The sensitivity analysis (leaving one out at a time) produced no statistically significantly increased or decreased summary odds ratio, although the findings from Beji and Reis (2007) were quite influential (Figure 3).

When the meta-analysis was restricted to the 22 prospective studies, the SRR was about the same as for all studies combined (SRR = 1.23 (95% CI, 1.12–1.35); Table 2), with substantial heterogeneity and no publication bias. Restricting the analysis to the 18 retrospective (mainly case-control) studies also leads to significantly elevated SRR that was higher than for cohort studies (SRR 1.36 (95% CI, 1.13–1.63)) with similar heterogeneity and no publication bias. No significant difference was evidenced from meta-regression ($P = 0.37$).

A clear difference was identified according to whether studies adjusted or not for BMI; the SRR for BMI-adjusted studies was 1.16 (95% CI, 1.08–1.24) with an I^2 of 11% (Figure 4), whereas in studies not adjusted for BMI, the SRR was 1.33 (95% CI, 1.18–1.51) with an I^2 of 89% (Figure 5). These unadjusted studies contributed strongly to the heterogeneity, as the heterogeneity in adjusted studies was only 11%. However, the adjusted and unadjusted SRRs were not significantly different in meta-regression ($P = 0.34$). The analysis restricted to studies that reported both RRs adjusted and not adjusted for BMI showed similar differences in SRRs (Table 2).

Four studies presented results for type 1 diabetes on its own. The SRR was 1 (95% CI, 0.74–1.35) with an I^2 of 0% (i.e., no heterogeneity that could not be explained by chance alone) and no evidence of publication bias. On the contrary, women with type 2 diabetes had an increased risk of breast cancer (SRR 1.16 (95% CI, 1.04–1.29)) based on 14 studies. The meta-regression did not show significant differences ($P = 0.25$). The majority of studies did not report the type of diabetes; in these 25 studies, the SRR was 1.37 (95% CI, 1.20–1.56).

The SRR was different according to menopausal status. From the five original studies, which presented information about breast cancer diagnosed before the menopause, the SRR was 0.86 (95% CI, 0.66–1.12) with an I^2 of 0%. In the 10 studies on breast cancer diagnosed after the menopause, the SRR was 1.15 (95% CI, 1.07–1.24) with an I^2 of 47%. The difference between pre-menopausal and post-menopausal women was statistically

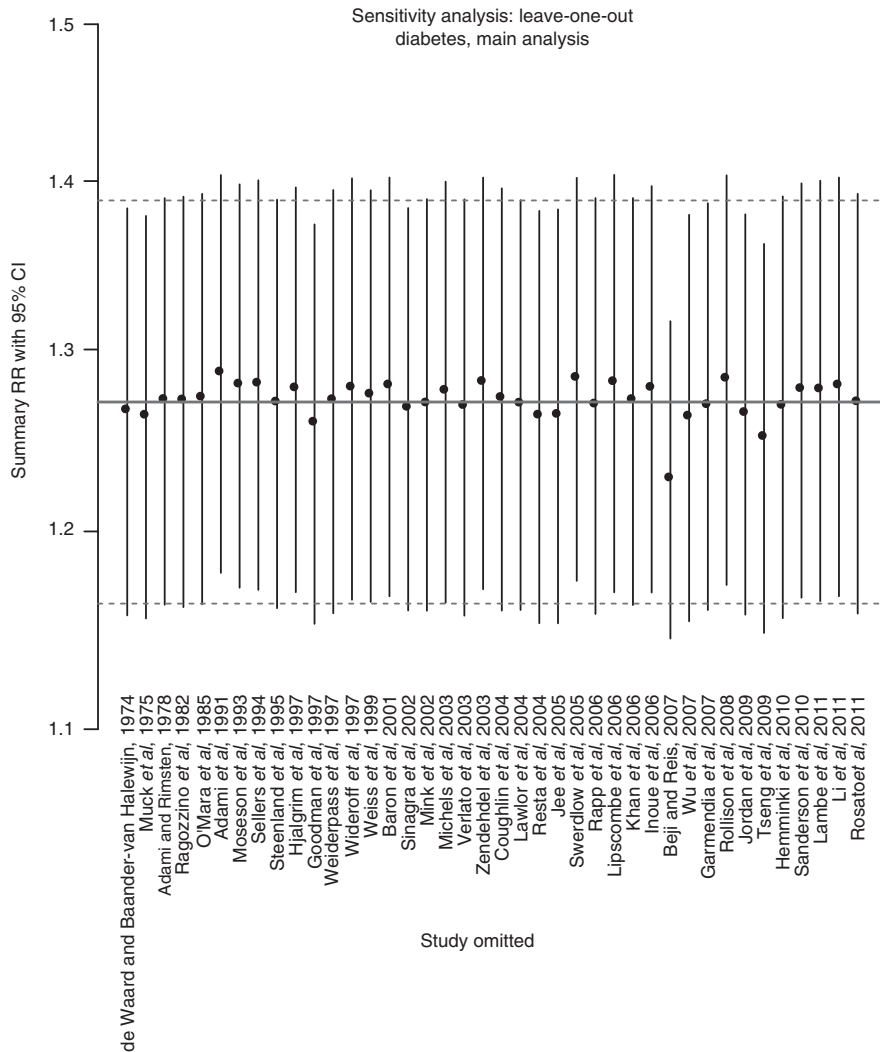


Figure 3 Sensitivity analysis (leave-one-out) of meta-analysis of risk of breast cancer women with diabetes.

significant in meta-regression ($P=0.004$). The result in post-menopausal ages did not change significantly when restricted to studies on type 2 diabetes.

The stratified analysis on how the diabetes status was ascertained showed no difference between studies with self-declared diabetes or diabetes from medical records, the meta-regression also showed no significant difference ($P=0.66$).

Four studies (Verlato *et al*, 2003; Coughlin *et al*, 2004; Jee *et al*, 2005; Tseng *et al*, 2009) were conducted on breast cancer mortality, and the study of Swerdlow *et al* (2005) also reported risk for breast cancer mortality. When stratifying studies on mortality or incidence, considering the wide CI for mortality, we conclude that similar relationships with similar heterogeneity were found.

Figure 6 presents a cumulative meta-analysis, and it is apparent that the increased risk of breast cancer in women with diabetes was statistically significant in publications up until and including 1997, and has remained statistically elevated subsequently. The meta-regression did not find significant impact of publication year ($P=0.76$).

DISCUSSION

For the 40 independent risk estimates combined, compared with women without a diagnosis of breast cancer, the risk of breast cancer

in women was significantly associated with diabetes. Type 1 diabetes and diabetes in pre-menopausal women were not associated with significant increase risk of breast cancer. Adjustment for BMI in the original studies made an important difference in terms of risk with an higher risk in unadjusted studies (SRR = 1.33) than in BMI-adjusted studies (SRR = 1.16). Although this difference was not significant in meta-regression, the unadjusted studies had an important role in the heterogeneity, because unadjusted studies yielded highly variable and conflicting results. The findings were unchanged when the diagnosis of diabetes was self-reported or confirmed from review of medical records. When analysis was restricted to those studies where risk estimates of breast cancer could be obtained for post-menopausal women with type 2 diabetes, the risk of breast cancer was elevated (SRR 1.12 (95% CI, 1.03–1.21)). The risk of breast cancer in studies with type not reported is slightly higher than the main analysis. This observation could be an artefact from inclusion of few studies adjusted on BMI (only five were adjusted) and several studies with retrospective design (12 studies). The risk did not substantially differ between studies on mortality and studies on incidental breast cancer. Of note is the Swerdlow *et al* (2005) study, which reported both outcomes had very close estimate: 0.86 for mortality and 0.87 for incidence. The largest study on diabetes and breast cancer mortality by Coughlin *et al* (2004) found an RR of 1.27, quite close to the summary estimate of the present meta-analysis. All these

Table 2 Summary of results of meta-analyses of breast cancer and diabetes

Analysis	Number of studies	Summary estimate	95% CI		I ² (95% CI)	Publication bias (P-value)		
						Begg's test	Egger's test	Macaskill's test
All studies	40	1.27	1.16	1.39	74% (65–81)	0.97	0.75	0.27
Heterogeneity analysis								
<i>Study design</i>								
Cohort studies	22	1.23	1.12	1.35	75% (63–84)	0.91	0.88	0.39
Case-control studies	18	1.36	1.13	1.63	75% (60–84)	0.88	0.03	0.33
<i>Adjustment for BMI</i>								
Adjusted for BMI	13	1.16	1.08	1.24	11% (0–50)	0.71	0.72	0.24
Not adjusted for BMI	35	1.33	1.18	1.51	89% (86–92)	0.94	0.84	0.62
<i>Analysis of studies that reported with both RRs adjusted and not adjusted for BMI</i>								
Adjusted for BMI	8	1.13	1.02	1.24	22% (0–64)	0.62	0.78	0.83
Not adjusted for BMI	8	1.28	0.98	1.67	93% (88–95)	0.62	0.02	0.01
<i>Type of diabetes</i>								
Type 1	4	1.00	0.74	1.35	0% (0–83)	0.50	0.85	0.44
Type 2	14	1.16	1.04	1.29	72% (52–84)	1.00	0.51	0.09
Type not reported	25	1.37	1.20	1.56	77% (66–84)	0.98	0.39	0.92
<i>Breast cancer cases or deaths</i>								
Mortality	5	1.48	1.07	2.06	76% (43–90)	1.00	0.24	0.47
Incidence	36	1.24	1.12	1.36	73% (63–81)	0.96	0.36	0.12
<i>Diabetes ascertainment</i>								
Self-declared	26	1.23	1.14	1.33	47% (16–66)	0.93	0.17	0.71
Chart review	13	1.21	1.05	1.39	83% (73–90)	0.95	0.70	0.30
<i>Menopausal status</i>								
Pre-menopausal	5	0.86	0.66	1.12	0% (0–72)	0.33	0.96	0.24
Post-menopausal	10	1.15	1.07	1.24	47% (0–75)	0.93	0.20	0.13
Post-menopausal women with type 2 diabetes	6	1.12	1.03	1.21	51% (0–81)	0.57	0.64	0.39

Abbreviations: BMI = body mass index; CI = confidence interval; RR = relative risk.

elements suggest that the increase of breast cancer with diabetes is similar for both incidence and mortality. When meta-analysis was conducted on a temporal basis, the SRR became significant in 1997 and remained fairly constant (and statistically significantly increased), with addition of subsequent studies according to recency of publication.

The mechanisms by which type 2 diabetes might increase the risk of breast cancer are not known. Hyperinsulinaemia, a marker of insulin resistance in obesity and type 2 diabetes, has been advocated as potential factor (Plymate *et al*, 1990; Rosner, 1990; Singh *et al*, 1990; Kaaks, 1996). In addition, obesity is associated with type 2 diabetes and leads to a rise in endogenous oestrogen levels. Insulin inhibits the production of sex hormone-binding globulin (Barker *et al*, 1964; Van der Burg *et al*, 1988), which results in an increase in free steroid hormones, free oestrogens in particular, because testosterone successfully competes with oestrogen for the sex hormone-binding globulin (Conover *et al*, 1992). Hyperinsulinaemia may also have joint effects with the insulin growth factor I that could be involved in breast carcinogenic processes (Novosyadlyy *et al*, 2010).

In vitro insulin is also a growth-promoting hormone with mitogenic effects in both normal and malignant breast tissues (Lippman and Bolan, 1975; Cannata *et al*, 2010).

Another mechanism could be chronic hyperglycaemia that could increase the breast cancer risk, for instance, via the Warburg effect (Warburg, 1930; Brown and Simpson, 2010), that is, the

mechanism by which cancer cells predominantly produce energy by a high rate of glycolysis in the cytosol rather than by glycolysis followed by the oxygen-dependent Krebs cycle in mitochondria. But reviews of randomised trials showed no reduction in the risk of cancer with more intense glycaemic control of type 2 diabetes patients (Johnson and Bowker, 2011).

In summary, this meta-analysis found a significant increased risk of breast cancer among women with diabetes. The association between diabetes and breast cancer risk seemed to be restricted to post-menopausal women. The main factor influencing SRR is adiposity (as measured by the BMI). Studies that adjusted for BMI found lower SRRs than studies that did not adjust for this factor. The meta-regression analysis did not find that the difference in SRR between BMI-adjusted and non-adjusted studies was significant. However, because of considerable heterogeneity of results of studies that did not adjust, the meta-regression analysis is of limited power. Most studies adjusted for BMI by introducing the variable BMI as a continuous variable, which assumes a linear effect between BMI and breast cancer risk. However, there is no evidence that the assumption of a simple linear or a log-linear relationship between BMI and breast cancer risk is real, in particular when BMI is less than 25 (IARC, 2002).

It is also worth considering the hypothesis by which type 2 diabetes would be a marker of the adiposity-breast cancer association rather than being a genuine causation of this cancer. The risk of breast cancer is increased in obese post-menopausal

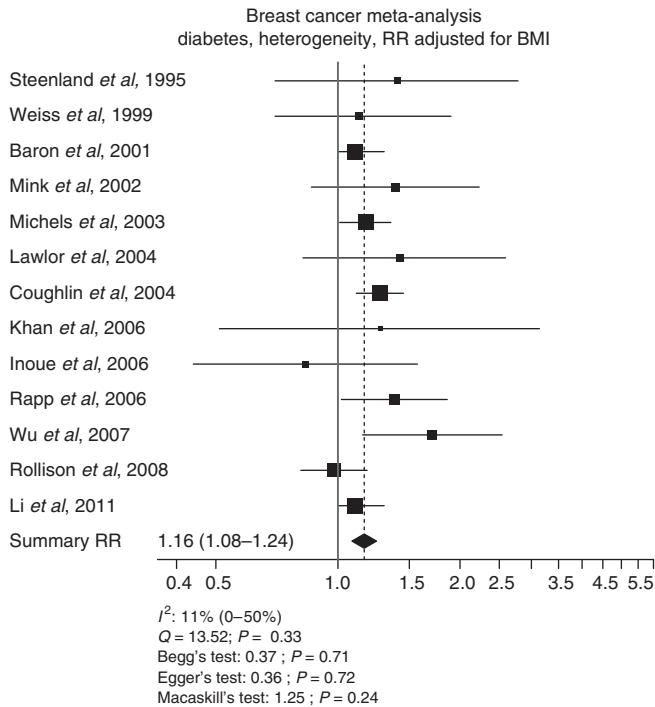


Figure 4 Forest plot of meta-analysis of breast cancer and diabetes in studies with relative risk (RR) adjusted for BMI. Individual studies represented by RR and 95% confidence interval (CI).

women by around 50%, whereas it is marginally reduced in premenopausal obese women (IARC, 2002). This risk pattern is similar to that obtained by our meta-analysis observed for diabetes and breast cancer. Hence, BMI could be acting like a classic confounder being related to both the exposure (diabetes) and the outcome (breast cancer).

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Conflict of interest

The authors declare no conflict of interest.

Author Contributions

PB contributed to discussion and wrote the manuscript; MB and AK researched data, conducted the statistical analysis, contributed to discussion and reviewed/edited the manuscript; CR, MP and SG contributed to discussion and reviewed/edited the manuscript; FV researched data and reviewed/edited manuscript; KC, Magali B, TZ and YZ researched data; L-LF, MS, MPC, PM and M Bota reviewed/edited the manuscript; GB and JR contributed to discussion; PA researched data, contributed to discussion and reviewed/edited the manuscript.

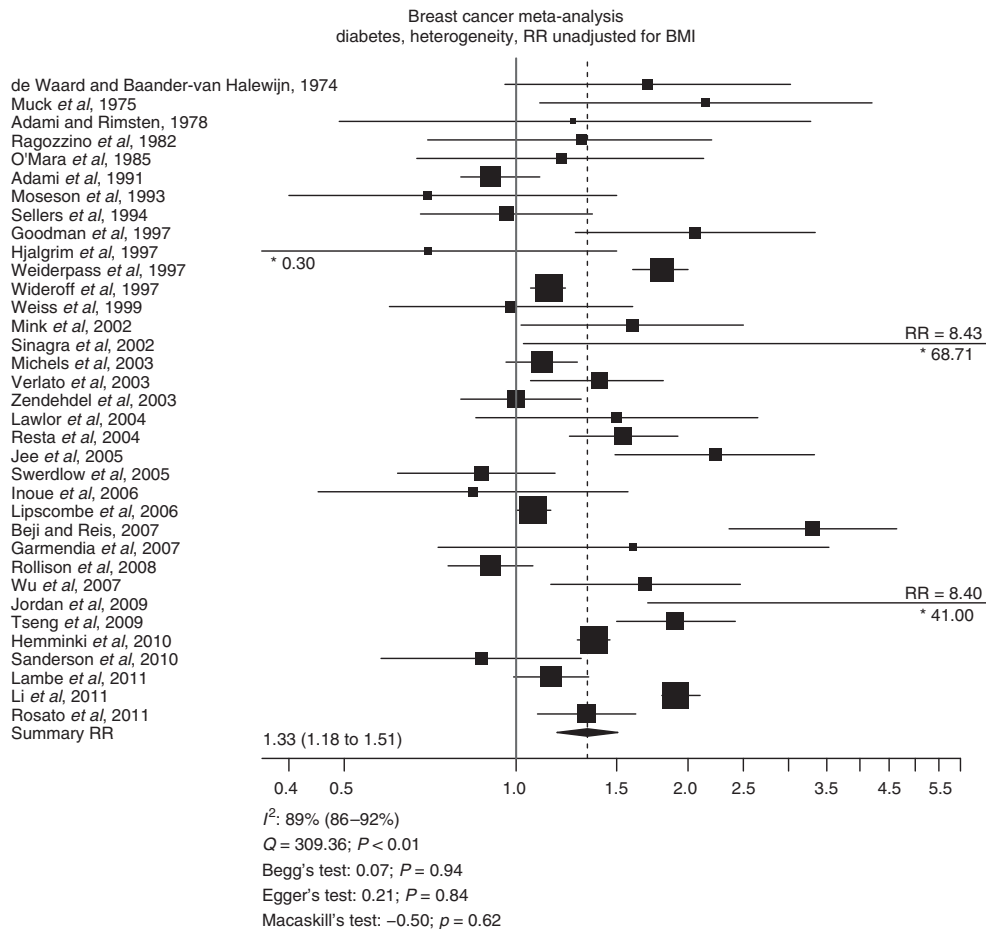


Figure 5 Forest plot of meta-analysis of breast cancer and diabetes in studies with relative risk (RR) not adjusted for BMI. Individual studies represented by RR and 95% confidence interval (CI).

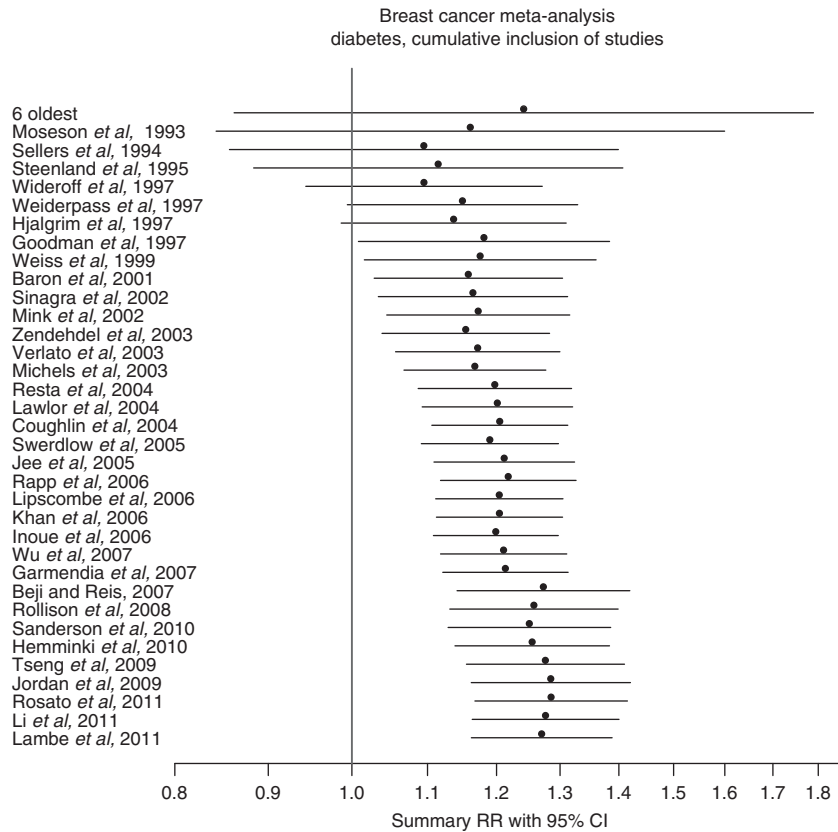


Figure 6 Cumulative temporal meta-analysis of breast cancer risk in diabetic women.

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