European Review for Medical and Pharmacological Sciences 2021; 25: 3507-3518

Impact of insulin use on outcomes of diabetic breast cancer patients: a systematic review and meta-analysis

L. WANG[1], H.-J. ZHANG[1], Y.-F. LIU[2], G.-Y. CHEN[3]

[1]Department of Breast Surgery, The Fourth Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, P.R. China
[2]School of Nursing, Capital Medical University, Beijing, P.R. China
[3]Department of Cardiology, The Fourth Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, P.R. China

Abstract. – **OBJECTIVE:** The study aimed to assess the impact of insulin use on outcomes of breast cancer patients with diabetes mellitus (DM).

MATERIALS AND METHODS: Databases of PubMed, Embase, and CENTRAL were searched to identify all types of studies comparing mortality or recurrence between insulin and non-insulin DM patients with breast cancer. Adjusted hazard ratios (HR) were pooled for a meta-analysis.

RESULTS: Eleven studies were included. Meta-analysis indicated a statistically significant increased risk of all-cause mortality in insulin users as compared to non-users (HR: 1.52 95% CI: 1.23 to 1.86 I^2=83% p<0.0001). Our results also demonstrated a statistically significant increase in the risk of breast cancer mortality amongst insulin users as compared to non-users (HR: 1.33 95% CI: 1.08 to 1.63 I^2=43% p=0.007). Only four studies assessed the impact of insulin therapy on recurrence rates. Meta-analysis indicated a statistically significant increased risk of breast cancer recurrence in insulin users *vs.* non-users (HR: 1.43 95% CI: 1.13 to 1.80 I^2=0% p=0.003). Mortality results were stable on sensitivity analysis.

CONCLUSIONS: Diabetic breast cancer patients on insulin have increased mortality and recurrence rates as compared to insulin non-users. Owing to the several limitations of the review, results should be interpreted with caution. Future studies should assess the impact of timing, duration, dosage, and type of insulin therapy on clinical outcomes.

Key Words:
Breast cancer, Diabetes mellitus, Hyperglycaemia, Insulin, Mortality, Recurrence.

Introduction

Diabetes mellitus (DM) is a common metabolic disorder characterized by increased blood glucose, insulin resistance, and impaired insulin secretion. The disease has a high prevalence worldwide and estimates suggest around 592 million people shall have DM by 2035[1]. On the other hand, breast cancer is the most common malignancy in females and is the leading cause of cancer-related mortality in women[2]. According to a recent study[3], breast cancer was responsible for 626,679 deaths globally in 2018 with wide variations in mortality in different regions worldwide. The difference in the global mortality rates has been attributed to several factors like provisioning of cost-effective screening programs, availability of diagnostic and therapeutic services, awareness of breast cancer in the population, as well as mitigation of risk factors[2-4].

DM as a risk factor for developing breast cancer has been a subject of research for several studies[5-7] published in the past decade, albeit with conflicting results. Some studies have reported a positive association between DM and subsequent risk of breast cancer[7], while others have documented no compelling evidence[5,6]. Evidence from observational studies[8,9], however, suggests that DM is associated with poor outcomes in breast cancer patients. According to a systematic review and meta-analysis of 17 studies, diabetic breast cancer patients have a 51% increased risk of mortality and 28% increased risk of recurrence as compared to those without DM[10]. The poorer outcomes have been attributed to the presence of insulin resistance and hyperinsulinemic states in these individuals[11,12] which has, in turn, led to research on the effect of different antidiabetic medications on the outcomes of cancer patients[13].

Evidence suggests that metformin, an antidiabetic drug, may have anticancer effects.

Corresponding Author: Guiyuan Chen, MD; e-mail: Guiyuan1968115@163.com

Studies[13,14] have analyzed the effect of metformin on outcomes of several malignancies like colorectal, prostate, pancreatic, renal, cervical, endometrial, gastric, lung, breast, and ovarian cancer. A recent meta-analysis of 12 observational studies by Tang et al[15] has indicated that the use of metformin may improve overall survival in diabetic breast cancer patients. Contrastingly, insulin use has been associated with an increased risk of mortality in patients with colorectal, lung, gastric, pancreatic, and even breast cancer[16,17]. While several systematic reviews have assessed the relationship between metformin use and breast cancer survival[15,18,19], no study has focused on providing a pooled evidence on the association between insulin use and outcomes of breast cancer.

In clinical practice, nursing personnel is closely involved in the management of diabetic patients, as well as in the treatment process of breast cancer patients. Therefore, it shall be important for nursing personnel, as well as for treating physicians to know if any comorbidity and its related pharmacological management have adverse impact on outcomes. Therefore, the purpose of the current study was to assess the impact of insulin use on outcomes of breast cancer patients with DM via a systematic review and meta-analysis.

Materials and Methods

Inclusion Criteria

The review was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (**Prisma Statement-Supplementary**)[20]. The review was not pre-registered on PROSPERO.

Inclusion criteria for the review were as follows: (1) All types of studies conducted on breast cancer patients with DM. (2) Studies had to compare outcomes of insulin users *vs.* non-insulin users. (3) Outcomes of interest were mortality or recurrence of breast cancer. (4) Studies had to report adjusted hazard ratios (HR) of outcomes with 95% confidence intervals (CI). No restriction was placed on the type of diabetic drugs used in insulin non-users.

The following studies were excluded: (1) Studies comparing outcomes between DM and non-DM patients. (2) Studies not reporting separate data for breast cancer patients. (3) Studies not reporting separate data for insulin users. (4) Review articles and non-English language studies. For studies reporting duplicate or overlapping data, the study with the largest sample size was to be included.

Search Strategy

Two reviewers independently conducted the electronic search. With the help of a librarian, the databases of PubMed, Embase, and CENTRAL were searched to identify relevant publications. All databases were screened from inception to 10th January 2021. We used the following keywords for the literature search: "insulin", "diabetes", "medication", "breast cancer", and "mortality". Table I demonstrates the search strategy. Every search result was evaluated by the two reviewers independently, initially by their titles and abstracts and then by the full texts of relevant publications. All full-texts were reviewed based on the inclusion and exclusion criteria and the article satisfying all the criteria was finally selected for this review. Any disagreements were resolved by discussion. To avoid any missed studies, the bibliography of included studies was hand searched for any additional references.

Data Extraction and Risk of Bias Assessment

We prepared a data extraction form at the beginning of the review to extract relevant details from the studies. Details of the first author, publication year, study type, location, study cohort, sample size, mean age, number of insulin users, factors adjusted for multivariable analysis, outcomes assessed, and follow-up were extracted. The outcome of interest was all-cause mortality, breast cancer mortality, and recurrence.

The quality of included studies was assessed using the Newcastle-Ottawa scale[21]. Studies were awarded points for selection of study population, comparability, and outcomes. The maximum score which can be awarded is nine.

Statistical Analysis

"Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. Multivariable-adjusted HR of the outcomes were extracted and data were pooled using the generic inverse function of the meta-analysis software. A random-effects model was preferred for the meta-analysis. The I^2 statistic was used to assess inter-study heterogeneity. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial

Table I. Search strategy.

Search number	Query	Search Details
1	((insulin) AND (diabetes)) AND (breast cancer)	("insulin"[MeSH Terms] OR "insulin"[All Fields] OR "insulin s"[All Fields] OR "insuline"[All Fields] OR "insulinic"[All Fields] OR "insulinization" [All Fields] OR "insulinized"[All Fields] OR "insulins"[MeSH Terms] OR "insulins"[All Fields]) AND ("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields])
2	((insulin) AND (breast cancer)) AND (mortality)	("insulin"[MeSH Terms] OR "insulin"[All Fields] OR "insulin s"[All Fields] OR "insuline"[All Fields] OR "insulinic"[All Fields] OR "insulinization"[All Fields] OR "insulinized"[All Fields] OR "insulins"[MeSH Terms] OR "insulins" [All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading])
3	((diabetes) AND (medication)) AND (breast cancer)	("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields] OR "diabetic"[All Fields] OR "diabetics"[All Fields] OR "diabets"[All Fields]) AND ("medic"[All Fields] OR "medical"[All Fields] OR "medicalization"[MeSH Terms] OR "medicalization"[All Fields] OR "medicalizations"[All Fields] OR "medicalize"[All Fields] OR "medicalized"[All Fields] OR "medicalizes"[All Fields] OR "medicalizing"[All Fields] OR "medically"[All Fields] OR "medicals"[All Fields] OR "medicated"[All Fields] OR "medication s"[All Fields] OR "medics"[All Fields] OR "pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields] OR "medications"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[Al Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields])

heterogeneity. As less than 10 studies were included per meta-analysis, funnel plots were not used to assess publication bias. We also conducted a sensitivity analysis to assess the influence of each study on the overall effect size. Data of every study was sequentially excluded to recalculate the effect size and the results were presented in a tabular format.

Results

The initial search resulted in a total of 3822 records (Figure 1). After the exclusion of duplicates, 2842 articles were screened by their titles and abstracts. Twenty-four articles were selected for full-text analysis of which eleven studies fulfilled the inclusion criteria[16,22-31]. Details of included studies are presented in Table II.

All included studies were retrospective cohort studies, except for one which was a post-hoc analysis of a randomized controlled trial[23]. Five of the studies were carried out in North America[22,23,25,30,31], four in Asian counties[16,26,28,29] and two in Europe[24,27]. There were some variations in the sample included in the studies. Only three studies included all breast cancer patients with DM[16,26,29]. The other trials restricted the sample to either only surgical patients[28]metformin, and statin use with survival and whether the association was modified by the hormone receptor status of the tumor in patients with breast cancer.Materials and Methods We studied 7,452 patients who had undergone surgery for breast cancer at Seoul National University Hospital from 2008 to 2015 using the nationwide claims database. Exposure was

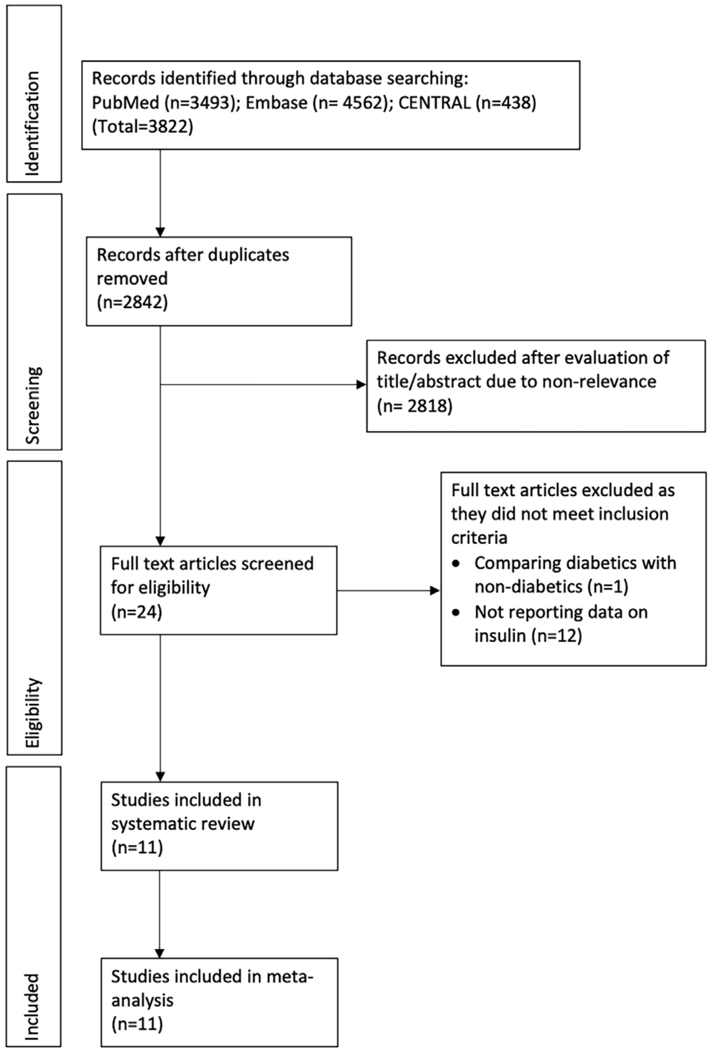

Figure 1. Study flow-chart.

defined as a recorded prescription of each drug within 12 months before the diagnosis of breast cancer.Results Patients with prior insulin or statin use were more likely to be older than 50 years at diagnosis and had a higher comorbidity index than those without it ($p < 0.01$ for both, age <64/66 years[22,31], HER2 positive patients[23], Stage I/II patients[25,30], or only type 2 DM[24,27]. There was wide variation in the sample size ranging from 190 patients to 48880 patients. Similarly, the included studies also differed in the factors adjusted for the multivariable analysis and follow-up period. The quality of studies was high on the Newcastle-Ottawa scale.

Outcomes

Data on all-cause mortality were reported by eight studies. Meta-analysis indicated a statistically significant increased risk of all-cause mortality in insulin users as compared to non-users (HR: 1.52 95% CI: 1.23 to 1.86 I^2=83% p<0.0001) (Figure 2). On sensitivity analysis, the result was statistically significant after exclusion of any of the included studies (Table III). Data on breast cancer mortality were reported by nine studies. On pooled analysis, our results demonstrated a statistically significant increase in the risk of breast cancer mortality amongst insulin users as compared to non-users (HR: 1.33 95% CI: 1.08 to 1.63 I^2=43% p=0.007) (Figure 3). On the sequential exclusion of one study at a time, there was no change in the significance of the results (Table III). Only four studies assessed the impact of insulin therapy on recurrence rates. Meta-analysis indicated a statistically significant increased risk of breast cancer recurrence in insulin users *vs.* non-users (HR: 1.43 95% CI: 1.13 to 1.80 I^2=0% p=0.003) (Figure 4). On the exclusion of the study

Table II. Details of included studies.

Study	Location	Data source	Study duration	Study cohort	Total sample size	Mean age (years)	Patients on insulin	Factors adjusted for multivariate analysis	Outcomes assessed	Follow-up	NOS score
Choi 2021[28]	Korea	Insurance database	2007-2015	Surgical breast cancer patients with DM	919	NR	27	Histologic types, TNM stage, ER status, PR status, age at diagnosis, and Charlson comorbidity index	All-cause mortality	5 years	8
Lawrence 202031	USA	Insurance database	2004-2016	Breast cancer patients aged < 64 years with DM	1477	54.7	NR	Race/ethnicity, estimated menopausal status, age at breast cancer diagnosis, breast cancer date of diagnosis, marital status at diagnosis, obesity, coronary heart disease, stroke, chronic kidney disease, molecular subtype, chemotherapy, surgery, hormone therapy, SEER Summary Staging, days between first type 2 diabetes mellitus diagnosis claim and breast cancer date of diagnosis	All-cause mortality, breast cancer mortality	12 years	8
Hosio 2020[24]	Finland	National registry	1998-2011	All breast cancer patients with type-2 DM	3533	NR	686	Calendar year, age, duration of DM and stage of breast cancer	All-cause mortality, breast cancer mortality	Median 4.6 years	8
Baglia 2019[16]	China	Regional registry	2004-2014	All breast cancer patients with DM	190	NR	NR	Education, body mass index, smoking status, regular exercise, comorbidity, TNM stage of cancer, chemotherapy, radiotherapy, and surgery; other diabetic medication	All-cause mortality, breast cancer mortality	Median 3.4 years	9
Sonnenblick 2017[23]	USA	Post-hoc analysis of RCT	NR	HER2 positive primary BC with DM	446	NR	80	Timing of chemotherapy, central hormone receptor status, and lymph node status), treatment arm, tumor size, and body mass index status	Breast cancer mortality, recurrence	Median 4.5 years	8
Chen 2017[30]	USA	Insurance database	2007-2011	Stage I/II breast cancer with DM	4544	NR	1051	Age at diagnosis, year of diagnosis, AJCC stage, ER/PR status, receipt of complete first course treatment (yes *vs.* no), receipt of any chemotherapy (yes *vs.* no), use of adjuvant hormone therapy (time-varying) and hypertension	Breast cancer mortality, recurrence	Median 3 years	8

Continued

Table II ***(Continued).*** Details of included studies.

Study	Location	Data source	Study duration	Study cohort	Total sample size	Mean age (years)	Patients on insulin	Factors adjusted for multivariate analysis	Outcomes assessed	Follow-up	NOS score
Mu 2016[29]	China	Single centre cohort	2005-2010	All breast cancer patients with DM	462	NR	219	Age, body mass index, tumour size, lymph node status, pathological subtype, histological grade, ER/PR and human epidermal growth factor receptor-2 expression, chemotherapy, hormone therapy and serum glucose.	Breast cancer mortality, recurrence	5 year	9
Vissers 2015[27]	UK	National registry	1998-2010	All breast cancer patients with type-2 DM	1057	70.6	220	Age at diagnosis, diabetes duration, year of breast cancer diagnosis, cancer treatment (surgery, radiotherapy, chemotherapy and hormone therapy within 6 months of diagnosis), hormone replacement therapy prior to cancer diagnosis and comorbidity (stroke, chronic pulmonary disease, congestive heart disease, diabetes with complications, myocardial infarction, peptic ulcer disease, peripheral vascular disease and renal disease) prior to cancer diagnosis.	All-cause mortality, breast cancer mortality	Mean 4.4 years	8
Tseng 2015[26]	Taiwan	Insurance database	1995-2006	All breast cancer patients with DM	48880	62.5	5184	Age, diabetes type, diabetes duration, body mass index, smoking, and area of residence	All-cause mortality, breast cancer mortality	12 years	9

Continued

Table II ***(Continued).*** Details of included studies.

Study	Location	Data source	Study duration	Study cohort	Total sample size	Mean age (years)	Patients on insulin	Factors adjusted for multivariate analysis	Outcomes assessed	Follow-up	NOS score
Calip 2015[25]	USA	Insurance database	1990-2008	Stage I/II breast cancer with DM	610	67	246	Age at diagnosis, diagnosis year, AJCC stage, ER/PR status, primary treatment for breast cancer (mastectomy, breast-conserving surgery with radiation, breast-conserving surgery without radiation), endocrine therapy, body mass index at diagnosis, smoking status, menopausal status, Charlson comorbidity score, statin use, prescription nonsteroidal anti-inflammatory medication use, Cox-2 inhibitors, and aspirin, and receipt of screening mammogram in the 12 months prior to events.	All-cause mortality, recurrence	Median 6.3 years	8
Lega 2013[22]	Canada	Regional registry	1997-2008	Breast cancer patients aged < 66 years with DM	2361	NR	NR	Adjusted for diabetic medication, age, duration of diabetes before cancer, comorbidity score, cancer treatments within 1 year of diagnosis (surgery, radiotherapy, chemotherapy, aromatase inhibitor, tamoxifen), and exposure to glucose-lowering drugs before cancer	All-cause breast cancer mortality	Mean 4.5 years	8

DM, diabetes mellitus; ER, estrogen receptor; PR, progesterone receptor; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results program; NR, not reported; RCT, randomised controlled trial; TNM, tumor, node and metastasis; NOS, Newcastle-Ottawa scale.

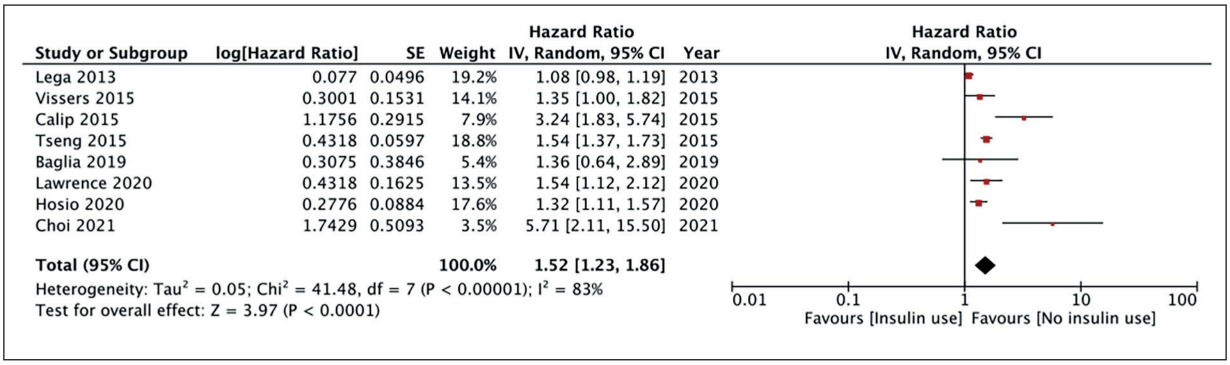

Figure 2. Meta-analysis of all-cause mortality between insulin users *vs.* non-users.

of Mu et al[29] the results were non-significant but with a tendency of increased mortality amongst insulin users (HR: 1.40 95% CI: 0.99 to 1.97 I^2=18% p=0.06) (Table III). The results were, however, still statistically significant after the exclusion of the remaining studies.

Discussion

Our study is the first systematic review and meta-analysis to assess the impact of insulin use on outcomes of breast cancer. Pooled analysis of data from 64,479 diabetic breast cancer patients demonstrated that insulin users had a 52% increased risk of all-cause mortality and 33% increased risk of breast cancer mortality as compared to insulin non-users. Analysis of a limited number of studies indicated that insulin use is associated with a 43% increased risk of recurrence as compared to no insulin use.

The effect of prior DM on the incidence of cancer and cancer-related mortality has been a subject of intense research in the past two

Table III. Results of sensitivity analysis.

Excluded study	Resultant effect size (Hazard ratios)
All-cause mortality	
Lega 2013[22]	1.60 (95% CI 1.32, 1.94 I^2 = 64% p < 0.00001)
Vissers 2015[27]	1.56 (95% CI 1.24, 1.96 I^2 = 86% p = 0.0002)
Calip 2015[25]	1.14 (95% CI 1.16, 1.70 I^2 = 81% p = 0.0005)
Tseng 2015[26]	1.54 (95% CI 1.20, 1.97 I^2 = 80% p = 0.0007)
Baglia 2019[16]	1.53 (95% CI 1.23, 1.90 I^2 = 86% p = 0.0001)
Lawrence 2020[31]	1.52 (95% CI 1.21, 1.91 I^2 = 85% p = 0.0003)
Hosio 2020[24]	1.59 (95% CI 1.24, 2.05 I^2 = 86% p = 0.0003)
Choi 2021[28]	1.43 (95% CI 1.18, 1.73 I^2 = 82% p = 0.0002)
Breast cancer mortality	
Lega 2013[22]	1.41 (95% CI 1.18, 1.70 I^2 = 16% p = 0.0002)
Tseng 2015[26]	1.33 (95% CI 1.06, 1.67 I^2 = 50% p = 0.01)
Vissers 2015[27]	1.33 (95% CI 1.05, 1.68 I^2 = 49% p = 0.02)
Mu 2016[29]	1.30 (95% CI 1.04, 1.62 I^2 = 46% p = 0.02)
Chen 2017[30]	1.20 (95% CI 1.03, 1.39 I^2 = 0% p = 0.02)
Sonnenblick 2017[23]	1.30 (95% CI 1.05, 1.62 I^2 = 47% p = 0.02)
Baglia 2019[16]	1.35 (95% CI 1.09, 1.67 I^2 = 48% p = 0.006)
Lawrence 2020[31]	1.35 (95% CI 1.06, 1.71 I^2 = 50% p = 0.01)
Hosio 2020[24]	1.37 (95% CI 1.08, 1.75 I^2 = 48% p = 0.01)
Recurrence	
Calip 2015[25]	1.38 (95% CI 1.09, 1.75 I^2 = 0% p = 0.008)
Mu 2016[29]	1.40 (95% CI 0.99, 1.97 I^2 = 18% p = 0.06)
Chen 2017[30]	1.58 (95% CI 1.15, 2.16 I^2 = 0% p = 0.005)
Sonnenblick 2017[23]	1.48 (95% CI 1.07, 2.06 I^2 = 26% p = 0.02)

CI, confidence intervals.

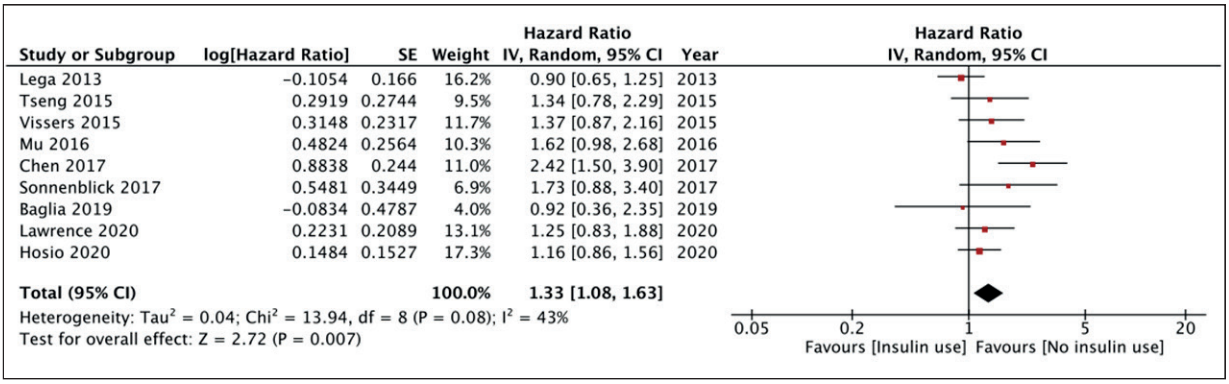

Figure 3. Meta-analysis of breast cancer mortality between insulin users *vs.* non-users.

decades[10,13,32-34]. A recent systematic review and meta-analysis of 151 cohorts comprising of 32 million individuals has demonstrated an increased risk of liver, pancreatic and endometrial cancer with type 2 DM[32]. Similarly, several meta-analyses of a large number of observational studies[33,34] have indicated a heightened risk of breast cancer amongst diabetic females. It is postulated that activation of insulin and insulin-like-growth-factor pathways, dysregulation of sex hormones, high blood glucose levels, and chronic inflammation seen in DM contribute to the increased risk of cancer in these patients[35,36]. Since antidiabetic medications can influence several of these pathophysiological processes there is a growing interest in the influence of specific antidiabetic medications on cancer risk and mortality[35]. The effect of antidiabetic drugs like metformin and insulin on the incidence of breast cancer has been well-researched with systematic reviews indicating no association between these drugs and the risk of breast cancer[15,37]. Regarding breast cancer outcomes, Tang et al[15] have indicated improved survival with metformin use but a similar study on the impact of insulin use is lacking so far.

On meta-analysis of multivariable-adjusted HR from individual studies, our review demonstrated a significantly increased risk of all-cause mortality, breast cancer mortality, as well as breast cancer recurrence in DM patients using insulin as compared to those on other antidiabetic drugs. The risk of all-cause mortality was higher as compared to cancer-related mortality in our analysis (52% *vs.* 33%). It is important to note that non-specific mortality data would have included a large portion of cardiovascular mortality as well. Death due to cardiovascular causes is common in breast cancer patients[38]. Furthermore, insulin use is more common in patients with poorly controlled DM who are older and have increased comorbidities which further increases the risk of cardiovascular mortality[28]. Holden et al[39] have also indicated that the use of exogenous insulin itself may increase all-cause and cardiovascular mortality in DM patients. This may explain the larger effect size of all-cause mortality as compared to breast cancer mortality in our review. Amongst the included studies, only Lawrence et al[31] reported separate data on cardiovascular mortality amongst insulin users *vs.* non-users. Their study indicated a tendency of increased cardio-

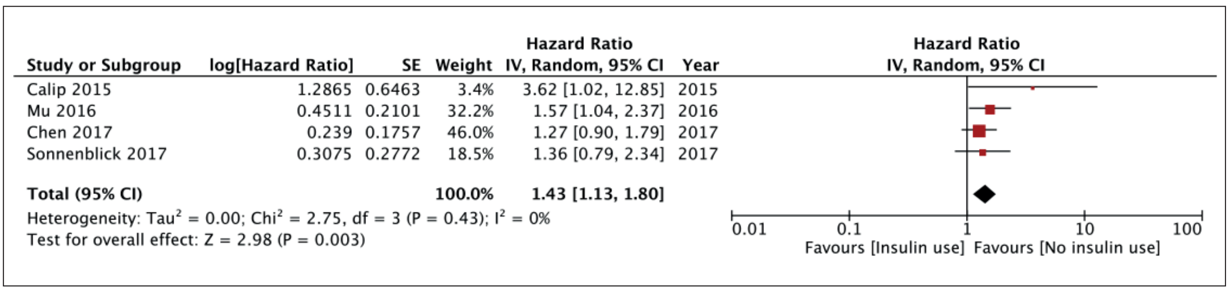

Figure 4. Meta-analysis of breast cancer recurrence between insulin users *vs.* non-users.

vascular mortality in insulin users but it did not reach statistical significance probably due to the limited sample size of their cohort (HR: 2.00 95% CI: 0.98 to 4.09).

The effect of insulin on breast cancer mortality and recurrence may be explained by its direct mitogenic action[40]. Studies[36,41] have reported that insulin via its receptor action and insulin-like growth factors increases malignant cell proliferation and suppresses apoptosis through the phosphoinositide 3-kinase/Akt and mitogen-activated protein kinase pathways. Its amplificatory effect on endogenous sex hormone levels and suppression of serum sex hormone-binding globulin has also been implicated in breast cancer progression[42]. Indeed, Ferroni et al[43] have indicated that pre-treatment insulin levels may be an important indicator for adverse outcomes even in nondiabetic females with breast cancer. Goodwin et al[44] in a prospective study of 512 non-diabetic women with early-stage breast cancer have demonstrated that high fasting insulin levels are associated with a significantly increased risk of mortality and distant recurrence. The improved survival of breast cancer patients on metformin has also been explained partly in context to its effect on insulin. Metformin is known to enhance insulin sensitivity thereby decreasing blood glucose and insulin levels. Thus, tumor proliferation may be reduced by its indirect action on insulin[44,45].

An important point of consideration while assessing the impact of insulin use on breast cancer outcomes is the duration of therapy. Since most of the studies extracted data from patient registries or insurance databases, information on the duration of insulin use was not available in most studies. Hence, our review was unable to discern how much insulin use is detrimental to breast cancer patients. Some patients may have used it only once during the course of the follow-up while others may have been chronic insulin users. Secondly, it was also unclear as to how the timing of insulin concerning breast cancer diagnosis impacts outcomes. The duration of insulin use before breast cancer diagnosis and post-diagnosis may also be important factors that need to be assessed in future studies. In one of the included studies of our review, Vissers et al[27] found no significant association between duration of insulin use and breast cancer mortality (ever *vs.* never, per year use, <2 years *vs.* none, ≥2 years *vs.* none). Similar non-significant results were obtained by Tseng et al[26] comparing breast cancer mortality in <5 years insulin users *vs.* non-users and >5years insulin users.

Our study has some limitations. Foremost, the majority of the studies did not include the entire cohort of breast cancer patients with DM with restrictions placed either on age, type of DM, receptor status, cancer staging, or treatment type. The St. Gallen International Expert Consensus has classified breast cancer into four subtypes for treatment purpose[46]. Thus, it is not clear from our review how does insulin use impact the prognosis of different cancer sub-types and our results may not apply to all types of breast cancer patients with DM. Secondly, the factors adjusted for the multivariable analysis differed across studies. The type of treatment i.e., surgery/chemotherapy was not uniformly included in the adjusted analysis of the included studies. Such known and unknown confounding factors that were missed in the analysis could have influenced results. Thirdly, there was a wide variation in the sample size across studies. The largest study of Tseng[17] had a sample greater than all of the other studies combined. Fourthly, as mentioned earlier, limited information was available from included studies regarding the timing, duration, dosage, and type of insulin therapy. All these factors could have influenced results. Many patients would have been on multiple diabetic medications and our review was unable to distinguish the effect of insulin monotherapy on clinical outcomes. Also, the studies compared insulin users with a broad group of non-users which would have significantly differed in the type of oral antidiabetic medication. The better outcomes in the non-insulin users could have been due to the use of metformin in this group.

Nevertheless, our review has some novelties. Our study presents the first aggregated evidence on the impact of insulin use on breast cancer outcomes. We used only multivariable-adjusted HR in our analysis to present optimal evidence. A sensitivity analysis was performed for all outcomes to assess if any study had an undue impact on the effect size. The stability of our results on sensitivity analysis lends support to the study conclusions.

Conclusions

Diabetic breast cancer patients on insulin have increased mortality and recurrence rates as compared to insulin non-users. Results should be interpreted with caution due to the several limitations of the review. Future studies should assess the impact of timing, duration, dosage, and type of insulin therapy on clinical outcomes. Nursing staff should record in detail the duration, dose and type of medications, and the impact of patient compliance on clinical effects, and provide standardized health guidance and regular follow-ups to obtain more accurate information.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

LW designed the project; HZ and YL were involved in data collection and data analysis; LW prepared the manuscript; GC edit the manuscript; all authors read and approved the final manuscript.

References

1) Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014; 103: 137-149.
2) Li T, Mello-Thoms C, Brennan PC. Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence. Breast Cancer Res Treat 2016; 159: 395-406.
3) Sharma R. Global, regional, national burden of breast cancer in 185 countries: evidence from GLOBOCAN 2018. Breast Cancer Res Treat. 2021 Jan 30. doi: 10.1007/s10549-020-06083-6. Epub ahead of print.
4) Youlden DR, Cramb SM, Dunn NA, Muller JM, Pyke CM, Baade PD. The descriptive epidemiology of female breast cancer: an international comparison of screening, incidence, survival and mortality. Cancer Epidemiol 2012; 36: 237-248.
5) Sanderson M, Lipworth L, Shrubsole MJ, Andersen SW, Shu XO, Zheng W, Hargreaves MK, Blot WJ. Diabetes, obesity, and subsequent risk of postmenopausal breast cancer among white and black women in the Southern Community Cohort Study. Cancer Causes Control 2019; 30: 425-433.
6) Au Yeung SL, Schooling CM. Impact of glycemic traits, type 2 diabetes and metformin use on breast and prostate cancer risk: a Mendelian randomization study. BMJ Open Diabetes Res Care 2019; 7: e000872.
7) Anothaisintawee T, Wiratkapun C, Lerdsitthichai P, et al. Risk factors of breast cancer: A systematic review and meta-analysis. Asia-Pacific J Public Heal 2013; 25: 368-387.
8) Kang C, LeRoith D, Gallagher EJ. Diabetes, obesity, and breast cancer. Endocrinology 2018; 159: 3801-3812.
9) Lee KN, Torres MA, Troeschel AN, He J, Gogineni K, McCullough LE. Type 2 diabetes, breast cancer specific and overall mortality: Associations by metformin use and modification by race, body mass, and estrogen receptor status. PLoS One 2020; 15: e0232581.
10) Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2016; 95: e5602.
11) Duggan C, Irwin ML, Xiao L, Henderson KD, Smith AW, Baumgartner RN, Baumgartner KB, Bernstein L, Ballard-Barbash R, McTiernan A. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. J Clin Oncol 2011; 29: 32-39.
12) Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Taylor SK, Hood N. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. J Clin Oncol 2012; 30: 164-171.
13) Shlomai G, Neel B, LeRoith D, Gallagher EJ. type 2 diabetes mellitus and cancer: the role of pharmacotherapy. J Clin Oncol 2016; 34: 4261-4269.
14) Kheirandish M, Mahboobi H, Yazdanparast M, Kamal W, Kamal MA. Anti-cancer effects of metformin: recent evidences for its role in prevention and treatment of cancer. Curr Drug Metab 2018; 19: 793-797.
15) Tang GH, Satkunam M, Pond GR, Steinberg GR, Blandino G, Schünemann HJ, Muti P. Association of metformin with breast cancer incidence and mortality in patients with type ii diabetes: a grade-assessed systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2018; 27: 627-635.
16) Baglia ML, Cui Y, Zheng T, Yang G, Li H, You M, Xu L, Murff H, Gao YT, Zheng W, Xiang YB, Shu XO. Diabetes medication use in association with survival among patients of breast, colorectal, lung, or gastric cancer. Cancer Res Treat 2019; 51: 538-546.
17) Tseng CH. Diabetes, insulin use, smoking, and pancreatic cancer mortality in Taiwan. Acta Diabetol 2013; 50: 879-886.
18) Xu H, Chen K, Jia X, Tian Y, Dai Y, Li D, Xie J, Tao M, Mao Y. Metformin use is associated with better survival of breast cancer patients with diabetes: a meta-analysis. Oncologist. 2015; 20: 1236-1244.
19) Zhang ZJ, Yuan J, Bi Y, Wang C, Liu Y. The effect of metformin on biomarkers and survivals for breast cancer- a systematic review and meta-analysis of randomized clinical trials. Pharmacol Res 2019; 141: 551-555.
20) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med 2009; 6: e1000097.
21) Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed October 30, 2020.
22) Lega IC, Austin PC, Gruneir A, Goodwin PJ, Rochon PA, Lipscombe LL. Association between metformin therapy and mortality after breast cancer: A population-based study. Diabetes Care; 36: 3018-3026.
23) Sonnenblick A, Agbor-Tarh D, Bradbury I, Di Cosimo S, Azim HA Jr, Fumagalli D, Sarp S, Wolff AC,

Andersson M, Kroep J, Cufer T, Simon SD, Salman P, Toi M, Harris L, Gralow J, Keane M, Moreno-Aspitia A, Piccart-Gebhart M, de Azambuja E. Impact of diabetes, insulin, and metformin use on the outcome of patients with human epidermal growth factor receptor 2-positive primary breast cancer: analysis from the ALTTO phase III randomized trial. J Clin Oncol 2017; 35: 1421-1429.

24) Hosio M, Urpilainen E, Hautakoski A, Marttila M, Arffman M, Sund R, Ahtikoski A, Puistola U, Karihtala P, Jukkola A, Läärä E. Survival after breast cancer in women with type 2 diabetes using antidiabetic medication and statins: a retrospective cohort study. Acta Oncol 2020; 59: 1110-1117.

25) Calip GS, Yu O, Hoskins KF, Boudreau DM. Associations between diabetes medication use and risk of second breast cancer events and mortality. Cancer Causes Control 2015; 26: 1065-1077.

26) Tseng CH. Use of insulin and mortality from breast cancer among taiwanese women with diabetes. J Diabetes Res 2015; 2015: 678756.

27) Vissers PA, Cardwell CR, van de Poll-Franse LV, Young IS, Pouwer F, Murray LJ. The association between glucose-lowering drug use and mortality among breast cancer patients with type 2 diabetes. Breast Cancer Res Treat 2015; 150: 427-437.

28) Choi M, Han J, Yang BR, Jang MJ, Kim M, Lee DW, Kim TY, Im SA, Lee HB, Moon HG, Han W, Noh DY, Lee KH. Association of insulin, metformin, and statin with mortality in breast cancer Patients. Cancer Res Treat 2021; 53: 65-76.

29) Mu L, Zhu N, Zhang J, Xing F, Li D, Wang X. Type 2 diabetes, insulin treatment and prognosis of breast cancer. Diabetes Metab Res Rev 2017; 33.

30) Chen L, Chubak J, Boudreau DM, Barlow WE, Weiss NS, Li CI. Diabetes treatments and risks of adverse breast cancer outcomes among early-stage breast cancer patients: a SEER-medicare analysis. Cancer Res 2017; 77: 6033-6041.

31) Lawrence WR, Hosler AS, Gates Kuliszewski M, Leinung MC, Zhang X, Schymura MJ, Boscoe FP. Impact of preexisting type 2 diabetes mellitus and antidiabetic drugs on all-cause and cause-specific mortality among Medicaid-insured women diagnosed with breast cancer. Cancer Epidemiol 2020; 66: 101710.

32) Ling S, Brown K, Miksza JK, Howells L, Morrison A, Issa E, Yates T, Khunti K, Davies MJ, Zaccardi F. Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People. Diabetes Care 2020; 43: 2313-2322.

33) Boyle P, Boniol M, Koechlin A, Robertson C, Valentini F, Coppens K, Fairley LL, Boniol M, Pasterk M, Smaus M, Curado MP, Mullie P, Gandini S, Bota M, Autier P. Diabetes and breast cancer risk: A meta-analysis. Br J Cancer 2012; 107: 1608-1617.

34) Hardefeldt PJ, Edirimanne S, Eslick GD. Diabetes increases the risk of breast cancer: a meta-analysis. Endocr Relat Cancer 2012; 19: 793-803.

35) Cohen DH, LeRoith D. Obesity, type 2 diabetes, and cancer: the insulin and IGF connection. Endocr Relat Cancer 2012; 19: F27-45.

36) Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. Diabetes Care 2010; 33: 1674-1685.

37) Bronsveld HK, ter Braak B, Karlstad Ø, Vestergaard P, Starup-Linde J, Bazelier MT, De Bruin ML, de Boer A, Siezen CL, van de Water B, van der Laan JW, Schmidt MK. Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence. Breast Cancer Res 2015; 17: 100.

38) Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, Fung K, Anderson GM. A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA Cardiol 2017; 2: 88-93. Erratum in: JAMA Cardiol 2017; 2: 821.

39) Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events and cancer. Diabetes Obes Metab 2015; 17: 350-362.

40) Rosenfeld RG. Insulin-like growth factors and the basis of growth. N Engl J Med 2003; 349: 2184-2186.

41) Feng YH, Velazquez-Torres G, Gully C, Chen J, Lee MH, Yeung SC. The impact of type 2 diabetes and antidiabetic drugs on cancer cell growth. J Cell Mol Med 2011; 15: 825-836.

42) Novosyadlyy R, LeRoith D. Hyperinsulinemia and type 2 diabetes: impact on cancer. Cell Cycle 2010; 9: 1449-1450.

43) Ferroni P, Riondino S, Laudisi A, Portarena I, Formica V, Alessandroni J, D'Alessandro R, Orlandi A, Costarelli L, Cavaliere F, Guadagni F, Roselli M. Pretreatment insulin levels as a prognostic factor for breast cancer progression. Oncologist 2016; 21: 1041-1049.

44) Goodwin PJ, Pritchard KI, Ennis M, Clemons M, Graham M, Fantus IG. Insulin-lowering effects of metformin in women with early breast cancer. Clin Breast Cancer 2008; 8: 501-505.

45) Dowling RJ, Niraula S, Chang MC, Done SJ, Ennis M, McCready DR, Leong WL, Escallon JM, Reedijk M, Goodwin PJ, Stambolic V. Changes in insulin receptor signaling underlie neoadjuvant metformin administration in breast cancer: a prospective window of opportunity neoadjuvant study. Breast Cancer Res 2015; 17: 32.

46) Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ. Strategies for subtypes-dealing with the diversity of breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011; 22: 1736-1747.