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

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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 I²=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 I²=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 I²=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 2035¹. On the other hand, breast cancer is the most common malignancy in females and is the leading cause of cancer-related mortality in women². According to a recent study³, 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 factors²-⁴.

DM as a risk factor for developing breast cancer has been a subject of research for several studies⁵-⁷ published in the past decade, albeit with conflicting results. Some studies have reported a positive association between DM and subsequent risk of breast cancer⁷, while others have documented no compelling evidence⁵,⁶. Evidence from observational studies⁸-⁹, 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 DM⁹. The poorer outcomes have been attributed to the presence of insulin resistance and hyperinsulinemic states in these individuals¹⁰,¹¹ which has, in turn, led to research on the effect of different antidiabetic medications on the outcomes of cancer patients¹².

Evidence suggests that metformin, an antidiabetic drug, may have anticancer effects.
Studies\textsuperscript{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\textsuperscript{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\textsuperscript{16,17}. While several systematic reviews have assessed the relationship between metformin use and breast cancer survival\textsuperscript{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)\textsuperscript{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\textsuperscript{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
Impact of insulin use on outcomes of diabetic breast cancer patients

Table I. Search strategy.

<table>
<thead>
<tr>
<th>Search number</th>
<th>Query</th>
<th>Search Details</th>
</tr>
</thead>
</table>

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. 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. Five of the studies were carried out in North America, four in Asian counties, and two in Europe. There were some variations in the sample included in the studies. Only three studies included all breast cancer patients with DM. The other trials restricted the sample to either only surgical patients, 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
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, HER2 positive patients, Stage I/II patients, or only type 2 DM. 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 I²=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 I²=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 I²=0% *p*=0.003) (Figure 4). On the exclusion of the study
## Table II. Details of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Data source</th>
<th>Study duration</th>
<th>Study cohort</th>
<th>Total sample size</th>
<th>Mean age (years)</th>
<th>Patients on insulin</th>
<th>Factors adjusted for multivariate analysis</th>
<th>Outcomes assessed</th>
<th>Follow-up</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi 2021</td>
<td>Korea</td>
<td>Insurance database</td>
<td>2007-2015</td>
<td>Surgical breast cancer patients with DM</td>
<td>919</td>
<td>NR</td>
<td>27</td>
<td>Histologic types, TNM stage, ER status, PR status, age at diagnosis, and Charlson comorbidity index</td>
<td>All-cause mortality</td>
<td>5 years</td>
<td>8</td>
</tr>
<tr>
<td>Lawrence 2020</td>
<td>USA</td>
<td>Insurance database</td>
<td>2004-2016</td>
<td>Breast cancer patients aged &lt; 64 years with DM</td>
<td>1477</td>
<td>54.7</td>
<td>NR</td>
<td>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</td>
<td>All-cause mortality, breast cancer mortality</td>
<td>12 years</td>
<td>8</td>
</tr>
<tr>
<td>Hosio 2020</td>
<td>Finland</td>
<td>National registry</td>
<td>1998-2011</td>
<td>All breast cancer patients with type-2 DM</td>
<td>3533</td>
<td>NR</td>
<td>686</td>
<td>Calendar year, age, duration of DM and stage of breast cancer</td>
<td>All-cause mortality, breast cancer mortality</td>
<td>Median 4.6 years</td>
<td>8</td>
</tr>
<tr>
<td>Baglia 2019</td>
<td>China</td>
<td>Regional registry</td>
<td>2004-2014</td>
<td>All breast cancer patients with DM</td>
<td>190</td>
<td>NR</td>
<td>NR</td>
<td>Education, body mass index, smoking status, regular exercise, comorbidity, TNM stage of cancer, chemotherapy, radiotherapy, and surgery; other diabetic medication</td>
<td>All-cause mortality, breast cancer mortality</td>
<td>Median 3.4 years</td>
<td>9</td>
</tr>
<tr>
<td>Sonnenblick 2017</td>
<td>USA</td>
<td>Post-hoc analysis of RCT</td>
<td>NR</td>
<td>HER2 positive primary BC with DM</td>
<td>446</td>
<td>NR</td>
<td>80</td>
<td>Timing of chemotherapy, central hormone receptor status, and lymph node status), treatment arm, tumor size, and body mass index status</td>
<td>Breast cancer mortality, recurrence</td>
<td>Median 4.5 years</td>
<td>8</td>
</tr>
<tr>
<td>Chen 2017</td>
<td>USA</td>
<td>Insurance database</td>
<td>2007-2011</td>
<td>Stage I/II breast cancer with DM</td>
<td>4544</td>
<td>NR</td>
<td>1051</td>
<td>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</td>
<td>Breast cancer mortality, recurrence</td>
<td>Median 3 years</td>
<td>8</td>
</tr>
</tbody>
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### Table II (Continued). Details of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Data source</th>
<th>Study duration</th>
<th>Study cohort</th>
<th>Total sample size</th>
<th>Mean age (years)</th>
<th>Patients on insulin</th>
<th>Factors adjusted for multivariate analysis</th>
<th>Outcomes assessed</th>
<th>Follow-up</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu 2016(^{20})</td>
<td>China</td>
<td>Single centre cohort</td>
<td>2005-2010</td>
<td>All breast cancer patients with DM</td>
<td>462</td>
<td>NR</td>
<td>219</td>
<td>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. 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. Age, diabetes type, diabetes duration, body mass index, smoking, and area of residence</td>
<td>Breast cancer mortality, recurrence, All-cause mortality, breast cancer mortality</td>
<td>Mean 4.4 years</td>
<td>8</td>
</tr>
<tr>
<td>Vissers 2015(^{27})</td>
<td>UK</td>
<td>National registry</td>
<td>1998-2010</td>
<td>All breast cancer patients with type-2 DM</td>
<td>1057</td>
<td>70.6</td>
<td>220</td>
<td>All-cause mortality, breast cancer mortality</td>
<td></td>
<td>5 year</td>
<td>9</td>
</tr>
<tr>
<td>Tseng 2015(^{26})</td>
<td>Taiwan</td>
<td>Insurance database</td>
<td>1995-2006</td>
<td>All breast cancer patients with DM</td>
<td>48880</td>
<td>62.5</td>
<td>5184</td>
<td>All-cause mortality, breast cancer mortality</td>
<td></td>
<td>12 years</td>
<td>9</td>
</tr>
</tbody>
</table>
### Table II (Continued). Details of included studies.

<table>
<thead>
<tr>
<th>Study</th>
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<th>Data source</th>
<th>Study duration</th>
<th>Study cohort</th>
<th>Total sample size</th>
<th>Mean age (years)</th>
<th>Patients on insulin</th>
<th>Factors adjusted for multivariate analysis</th>
<th>Outcomes assessed</th>
<th>Follow-up</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calip 2015&lt;sup&gt;25&lt;/sup&gt;</td>
<td>USA</td>
<td>Insurance database</td>
<td>1990-2008</td>
<td>Stage I/II breast cancer with DM</td>
<td>610</td>
<td>67</td>
<td>246</td>
<td>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. 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</td>
<td>All-cause mortality, recurrence</td>
<td>Median 6.3 years</td>
<td>8</td>
</tr>
<tr>
<td>Lega 2013&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Canada</td>
<td>Regional registry</td>
<td>1997-2008</td>
<td>Breast cancer patients aged &lt; 66 years with DM</td>
<td>2361</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>All-cause breast cancer mortality</td>
<td>Mean 4.5 years</td>
<td>8</td>
</tr>
</tbody>
</table>

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.
of Mu et al\textsuperscript{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.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lega 2013</td>
<td>0.077</td>
<td>0.0496</td>
<td>19.2%</td>
<td>1.08 (0.98, 1.19) 2013</td>
</tr>
<tr>
<td>Vissers 2015</td>
<td>0.3001</td>
<td>0.1531</td>
<td>14.1%</td>
<td>1.35 (1.00, 1.82) 2015</td>
</tr>
<tr>
<td>Calip 2015</td>
<td>1.1756</td>
<td>0.2915</td>
<td>7.9%</td>
<td>3.24 (1.83, 5.74) 2015</td>
</tr>
<tr>
<td>Tseng 2015</td>
<td>0.4318</td>
<td>0.0597</td>
<td>18.8%</td>
<td>1.54 (1.37, 1.73) 2015</td>
</tr>
<tr>
<td>Baglia 2019</td>
<td>0.3075</td>
<td>0.3846</td>
<td>5.4%</td>
<td>1.36 (0.64, 2.89) 2019</td>
</tr>
<tr>
<td>Lawrence 2020</td>
<td>0.4318</td>
<td>0.1625</td>
<td>13.5%</td>
<td>1.54 (1.12, 2.12) 2020</td>
</tr>
<tr>
<td>Hosio 2020</td>
<td>0.2776</td>
<td>0.0884</td>
<td>17.6%</td>
<td>1.32 (1.11, 1.57) 2020</td>
</tr>
<tr>
<td>Choi 2021</td>
<td>1.7429</td>
<td>0.5093</td>
<td>3.5%</td>
<td>5.71 (2.11, 15.50) 2021</td>
</tr>
</tbody>
</table>

**Figure 2.** Meta-analysis of all-cause mortality between insulin users vs. non-users.
Impact of insulin use on outcomes of diabetic breast cancer patients

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. Similarly, several meta-analyses of a large number of observational studies 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.

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. 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. Regarding breast cancer outcomes, Tang et al. 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. 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. Holden et al. 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. reported separate data on cardiovascular mortality amongst insulin users vs. non-users. Their study indicated a tendency of increased cardio-

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Lega 2013</td>
<td>-0.3054</td>
<td>0.166</td>
<td>16.2%</td>
<td>0.90 [0.65, 1.25]</td>
<td>2013</td>
</tr>
<tr>
<td>Tseng 2015</td>
<td>0.2919</td>
<td>0.2744</td>
<td>9.5%</td>
<td>1.34 [0.78, 2.29]</td>
<td>2015</td>
</tr>
<tr>
<td>Vissers 2015</td>
<td>0.3146</td>
<td>0.2317</td>
<td>11.7%</td>
<td>1.37 [0.87, 2.16]</td>
<td>2015</td>
</tr>
<tr>
<td>Mu 2016</td>
<td>0.4824</td>
<td>0.2564</td>
<td>10.3%</td>
<td>1.62 [0.98, 2.68]</td>
<td>2016</td>
</tr>
<tr>
<td>Chen 2017</td>
<td>0.8838</td>
<td>0.2441</td>
<td>11.0%</td>
<td>2.42 [1.50, 3.90]</td>
<td>2017</td>
</tr>
<tr>
<td>Sonnenblick 2017</td>
<td>0.5481</td>
<td>0.3449</td>
<td>6.9%</td>
<td>1.73 [0.88, 3.40]</td>
<td>2017</td>
</tr>
<tr>
<td>Baglia 2019</td>
<td>-0.0834</td>
<td>0.4787</td>
<td>4.0%</td>
<td>0.92 [0.36, 2.35]</td>
<td>2019</td>
</tr>
<tr>
<td>Lawrence 2020</td>
<td>0.2231</td>
<td>0.2089</td>
<td>13.1%</td>
<td>1.25 [0.83, 1.88]</td>
<td>2020</td>
</tr>
<tr>
<td>Hosio 2020</td>
<td>0.1484</td>
<td>0.1527</td>
<td>17.3%</td>
<td>1.16 [0.86, 1.56]</td>
<td>2020</td>
</tr>
</tbody>
</table>

Total (95% CI) 1.33 [1.08, 1.63] 100.0%

Heterogeneity: $\tau^2 = 0.04; \chi^2 = 13.94, df = 8 (P = 0.08); I^2 = 43%$
Test for overall effect: $Z = 2.72 (P = 0.007)$

![Figure 3. Meta-analysis of breast cancer mortality between insulin users vs. non-users.](image)

![Figure 4. Meta-analysis of breast cancer recurrence between insulin users vs. non-users.](image)
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. Studies 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. Indeed, Ferroni et al have indicated that pre-treatment insulin reduced by its indirect action 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.

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 impacted breast cancer progression. Indeed, our review 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. 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 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 stan-
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dardized 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


