**Association of metformin with breast cancer incidence and mortality in patients with type 2 diabetes: a GRADE assessed systematic review and meta-analysis**

**Supplementary Material**

Table 1. Summary of Study Characteristics for Breast Cancer Incidence

Table 2. Summary of Main Outcomes for Breast Cancer Incidence

Table 3. Summary of Study Characteristics for All-Cause Mortality

Table 4. Summary of Main Outcomes for All-Cause Mortality

Figure 1. Egger’s Funnel plot for metformin and incidence of breast cancer

Figure 2. Egger’s Funnel plot for metformin and all-cause mortality

**Table 1. Study Characteristics of the included studies for metformin and incidence of breast cancer**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study (Author, Year)** | **Location of Study** | **Study Design** | **Study duration; Follow up period (years)** | **Total Sample Size** | **Age (years)** | **Exposure ascertainment** | **Outcome Ascertainment; type of breast cancer** | **Inclusion Criteria** |
| Currie, 2009 | United Kingdom | Retrospective cohort; all cancers | ≥ 2002; 152,065 person-years | 62,809 | Mean, SD: 62, 14.6 | The Health Information Network Database | First record of any solid tumor in database; all | Age ≥40, had received six or more sequential prescriptions for oral hypoglycemic agents |
| Libby, 2009 | Scotland | Retrospective cohort; all cancers | 1994-2003; NR | 4085 | NR | Scottish Care Information Diabetes Collaboration database | ICD9 and ICD10 codes; all | Diagnosed with T2D, ≥ 35 years old, no previous diagnosis of cancer, no ADM previous use |
| Bosco, 2011 | Denmark | Nested case- control; breast cancer specific | 1989-2008; NR | 4323 | 50 to ≥ 80 | Danish National Registry of Patients; at diagnosis, by prescription | Danish Cancer Registry using ICD8 or ICD10 codes; all | Incident breast cancer cases; diagnosis of T2D |
| Morden, 2011 | USA | Retrospective cohort; all cancers | 2006 to 2008; mean (SD): 23.1 months (10.5 months) | 81,681 | Mean: 77.4 | Medicare Part D prescription database | ICD9 codes; all | Enrolled in the Part D prescription database, remained enrolled in the database for 4 months, ≥ 68 years old, at least 36 months of continuous fee-for-service |
| Chlebowski, 2012 | USA | Prospective cohort; breast cancer specific | 1993-2011; mean: 11.8 | 68,019 | Mean, SD: 64, 6.7 | Women's Health Initiative Clinical Trials database | SEER; invasive | Medical history or reporting use of GLM at any time. |
| Hsieh, 2012 | Taiwan | Retrospective cohort; all cancers | 2000 to 2008; NR | 10,189 | Mean, SD: 61.2, 14.0 | Taiwan's National Health Insurance database | ICD9 codes; all | Continuous drug coverage for at least one year, no prior diagnosis of cancer |
| Ruiter, 2012 | Netherlands | Retrospective cohort; all cancers | 1998 to 2008; NR | 85,259 | ≥18 | PHARMO Record Linkage System | ICD9 codes; all | All individuals with more than one prescription for GLM |
| Soffer, 2014 | USA | Retrospective cohort; breast and gynecological cancers | 1998 to 2004; median: 6.5 | 66,778 | ≥18 | Kaiser Permanete Southern California EMR | SEER; all | T2D diagnosis, users of GLM, no previous use of GLM |
| Tsilidis, 2014 | United Kingdom | Retrospective cohort; all cancers | 1987-2010; median: 5.1 | 95,820 | 35 to 90 | UK Clinical Practice Research Database | National Health Service Read Codes; post-menopausal | GLM prescription after 6 months of enrollment in database, no previous diagnosis of cancer |
| Chen, 2015 | Taiwan | Retrospective cohort; all cancers | 1998-2007; median: 2.5 | 7,325 | Median, IQR: 62.6, 20.4 | Longitudinal Health Insurance Dataset | ICD9 Codes; all | New onset T2D aged ≥ 30 years receiving a single hypoglycemic drug (monotherapy) for glycemic control without preexisting cancer at the index date |
| Kowall, 2015 | United Kingdom and Germany | Retrospective cohort; all cancers | 1995 to 2012; mean: 4.8 | 60,571 (UK);  19,692 (Germany) | 30 to 89 | Disease Analyzer database | ICD10 codes; all | T2D diagnosis, prescription of GLM, GLM were not prescribed prior to first diagnosis of T2D, no previous cancer diagnosis |
| Calip, 2016 | USA | Retrospective cohort; breast cancer specific | 1996-2011; median: 6.7 | 10,050 | Mean, SD: 61.6, 12.3 | Group Health Cooperative database | SEER; invasive | T2D diagnosis after index date, aged >40 years, enrolled in the database for at least 2 years |

Abbreviations: USA = United States of America; SD = standard deviation; NR = not reported; ICD = International Classification of Disease; SEER = Surveillance, Epidemiology, and End Results; T2D = type 2 diabetes; GLM = glucose lowering medication; IQR = interquartile range; EMR = electronic medical record

**Table 2. Summary of Main Outcomes for Breast Cancer Incidence**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study (Author, Year)** | **Users of metformin (n)** | **Comparator; number of users (n)** | **Breast cancer events (metformin; comparator(s))** | **Treatment duration** | **Adjusted variables** | **OR/HR, 95% CI** | **Newcastle-Ottawa Scale Score** |
| Currie, 2009\* | NR | Sulfonylureas; NR  Insulin; NR | 305;  305; 305 | NR | Age, sex, smoking status, diagnosis of prior cancer, HbA1c, diabetes duration | 1.02 (0.71-1.45);  0.93 (0.69-1.27) | 6 |
| Libby, 2009\* | 4085 | Non-metformin; 4085 | 24;  41 | NR | Age, sex, smoking, deprivation, BMI, HbA1c, insulin use, and sulphonylurea use | 0.60 (0.32-1.10) | 7 |
| Bosco, 2011 | 1250 | Other GLM; 2197 | ≥ 1 year: 96; 1154  > 5 years: 35; 418 | ≥ 1 year  > 5 years | Complications due to diabetes, clinical obesity, age at index date, post-menopausal hormone use, multiple imputations to impute missing parity | ≥ 1 year:  0.81 (0.63-0.96)  >5 years:  0.83 (0.56-1.22) | 8 |
| Morden, 2011\* | 15,286 | Insulin; NR | NR | NR | Age category, race/ethnicity, diabetes complications, obesity diagnosis, oral estrogen use, Part D low-income subsidy (a poverty indicator), CCI and tobacco exposure diagnosis | 1.28 (1.05-1.57) | 6 |
| Chlebowski, 2012 | 556 | Other GLM; 2177 | 104;  129 | NR | Age at menopause, parity, age at first birth, breastfeeding, smoking, alcohol, BMI, physical activity, use of estrogen + progesterone, mammogram, bilateral oophorectomy, mammogram, and race/ethnicity | 0.75 (0.57-0.99) | 9 |
| Hsieh, 2012\* | 2048; | Sulfonylureas; 2804  Insulin;  338 | 19;  48; 5 | ≥ 1 year | Age | 0.57 (0.33-0.97)  0.61 (0.22-1.67) | 6 |
| Ruiter, 2012\* | 52,698 | Sulfonylurea; 32,591 | 207;  217 | Cumulative exposure | Age at first GLM prescription, sex, year in which the first GLM prescription was dispensed, number of unique drugs used in the year, and number of hospitalizations in the year before the start of the GLM | 0.95 (0.91-0.98) | 6 |
| Soffer, 2014\* | 4887 | Non-metformin;  14,865 | NR | ≥1 year | Age, race/ethnicity, estrogen receptor therapy status, statin use, CCI, and outpatient utilization. | 0.89 (0.74-1.09) | 8 |
| Tsilidis, 2014\* | 51,484 | Sulfonylureas; 18,264 | 307;  153 | ≥1 year | Smoking status, BMI, alcohol consumption status, use of aspirin or NSAIDs, use of statins, use of exogenous hormones in women, diabetes duration (in days), and year of the first GLM prescription | 1.03 (0.82-1.31) | 8 |
| Chen, 2015\* | 2223 | Sulfonylureas; 3965 | 6;  14 | NR | Age, sex, CCI, smoking-related diagnosis, alcohol use, morbidity, obesity, pancreatitis, hypertension, hyperlipidemia, monthly household income, and urbanization level | 0.80 (0.30-2.12) | 7 |
| Kowall, 2015\* | NR | Sulfonylureas; NR  Insulin; NR | 96;  24; 23; 14 | ≥ 1 year  ≥ 5 years  ≥ 1 year | Age at first diabetes medication, sex, country, time between diagnosis of T2D and prescription of drug, obesity, hypertension, hyperlipidemia, prevalence of microcomplications (retinopathy, neuropathy, or nephropathy), CCI, use of anti-hypertensives, use of antithrombotic agents, use of aspirin, use of statins, use of nonsteroidal anti-inflammatory drugs, and use of contraceptives | ≥ 1 year (sulfonylurea): 1.06 (0.65-1.72);  ≥ 5 years (sulfonylurea):  0.50 (0.19-1.29);  ≥ 1 year (insulin): 0.94 (0.51-1.72) | 6 |
| Calip, 2016 | 5700 | Non-metformin (never use); 4350 | 135; NR | 1-2.9 years,  ≥ 3 years | Use of other GLM, age study entry year, smoking status, menopausal status, CCI, statin use, menopausal hormone therapy | 1-2.9 years:  0.39 (0.19-0.80)  ≥ 3 years:  1.14 (0.68-1.91) | 8 |

\* = studies that also included other cancers; Abbreviations: NR = not reported; OR = odds ratio; HR = hazard ratio; 95% CI = 95% confidence interval; CCI = Charleston Comorbidity Index; BMI = body mass index; T2D = type 2 diabetes; HbA1c = hemoglobin A1c; GLM = glucose lowering medication; NSAID = nonsteroidal anti-inflammatory drug;

**Table 3. Study Characteristics of the included studies for metformin and all-cause mortality for breast cancer patients**

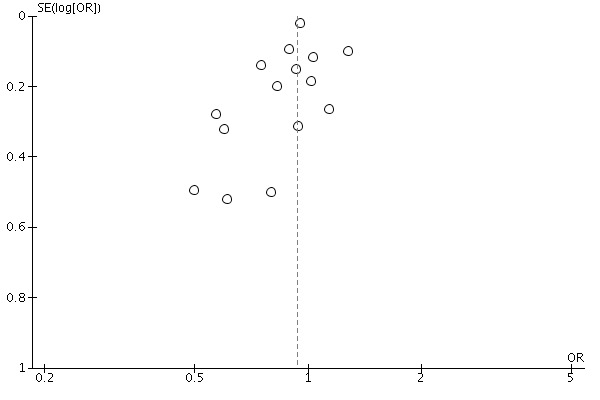
|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study (Author, Year)** | **Location of Study** | **Study Design** | **Study duration; Follow up period (years)** | **Total Sample Size** | **Age (years)** | **Exposure ascertainment** | **Outcome Ascertainment; type of breast cancer** | **Inclusion Criteria** |
| He, 2011 | USA | Retrospective; breast cancer specific | 1998 to 2010;  median 47.6 months (range 0.3 to 152.2 months) | 1988 | NR | MD Anderson Breast Cancer Management System Database | Tumor registry or through mailed questionnaires or Social Security Death Index; HER2+ breast cancer | Consecutive patients with stage ≥ 2 HER2+ breast cancer |
| Bayraktar, 2012 | USA | Retrospective; breast cancer specific | 1997 to 2007; median: 62 months (1 to 176 months) | 1448 | NR | MD Anderson Breast Cancer Management System Database | NR; triple negative breast cancer | Triple negative breast cancer patients who were receiving adjuvant chemotherapy, |
| Lega, 2013 | Canada | Retrospective; breast cancer specific | 1997 to 2008;  mean (SD): 4.5 (3.0) | 2361 | Mean, SD: 77.4, 6.3 | Ontario Diabetes Database | Ontario Cancer Registry or Registered Persons Database; all | Women with incident diabetes, aged 66 years or older |
| Peeters, 2013 | Denmark | Retrospective; breast cancer specific | 1996 to 2008;  Metformin: median (IQR): 1.8 (0.8-3.8)  Non-metformin: median (IQR): 2.6 (0.9-4.4) | 1058 | 60 to 82 | Denmark National Hospital Discharge Register and National Pharmacological Database | Death certificate register; all | Females (aged 18+) receiving treatment for diabetes who had a diagnostic code for breast cancer between 1997 and 2007 |
| El-Benhaway, 2014 | Egypt | Retrospective; breast cancer specific | Jan 2008 to Dec 2008;  median 46 months (22-60) | 439 | NR | University of Alexandria records | University of Alexandria records; stage I to III breast cancer | Pathologically proved stage I to III breast cancer |
| Oppong, 2014 | USA | Retrospective; breast cancer specific | 2000 to 2005;  median 87 months (range: 6.9 to 140.4) | 141 | 38 to 80 years | EMR: Memorial Sloan Keating Cancer Centre | EMR; all | Patients who reported a diagnosis of T2D and received systematic chemotherapy for stages I to III breast cancer |
| Xiao, 2014 | China | Retrospective; breast cancer specific | 2002 to 2006; median 70 months (10– 120 months) | 5785 | NR | Tianjin Medical Database | EMR; luminal breast cancer | Luminal type breast cancer between 2002 to 2006 |
| Calip, 2015 | USA | Retrospective; breast cancer specific | 1990-2008; median: 6.5 | 4216 | Mean, SD: 6.8, 3.8 | Group Health Database | SEER database; stage I and II | ≥ 18 years, residing in Washington State, incident, histologically confirmed stage I and II breast cancer (non-bilateral) between 1990 and 2008 |
| Kim, 2015 | South Korea | Retrospective; breast cancer specific | 1997 to 2007;  median 100.3 months | 6967 | NR | Asan Medical Centre Breast Cancer Database | EMR; all | Patients who were diagnosed with breast cancer and underwent surgery. |
| Xu, 2015 | USA | Retrospective; all cancers | 1995 to 2010; NR | Vanderbilt: 5796  Mayo: 8939 | NR | EMR from Mayo Clinic and Vanderbilt | EMR from Vanderbilt University Medical Center and Mayo Clinic; all | ≥18 years, incident cancer diagnosis excluding non-melanoma skin cancers between 1995 and 2010 |
| Vissers, 2015 | United Kingdom | Retrospective; breast cancer specific | 1998 to 2009; mean 4.4 years | 1057 | Mean, SD: 70.6, 11.3 | Clinical Practice Research Datalink | National Cancer Data Repository and the Office of National Statistics; all | Cohort of female breast cancer patients, diagnosed between 1998 and 2009, type 2 diabetes was identified |

Abbreviations: USA=United States of America; NR=not reported; HER2=human epidermal growth factor receptor 2; IQR=interquartile range; SEER=Surveillance, Epidemiology, and End Results; EMR = electronic medical record; T2D=type 2 diabetes; SD=standard deviation

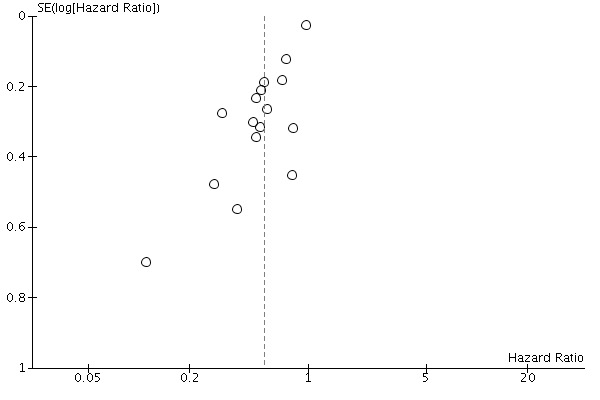
**Table 4. Summary of Main Outcomes for all-cause Mortality**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study (Author, Year)** | **Users of metformin (n)** | **Comparator; number of users (n)** | **Deaths (metformin; comparator(s))** | **Treatment Duration** | **Adjusting variables** | **HR, 95% CI** | **Newcastle Ottawa Scale Score** |
| He, 2011 | 88 | Non-user of metformin; 66 | NR; NR | At diagnosis and during follow-up | Age, BMI, ER/PR status, insulin therapy and insulin secretagogue therapy | 0.52 (0.28-0.97) | 8 |
| Bayraktar, 2012 | 63 | Non-metformin; 67 | 20;23 | During adjuvant chemotherapy | Age, body weight, tumor size, nodal status, nuclear grade, lymphovascular invasion, type of adjuvant chemotherapy | 0.82 (0.44-1.52) | 8 |
| Lega, 2013 | 1094 | Non-metformin; 1267 | 175; 835 | Cumulative metformin exposure | Sulfonylurea, insulin, TZD use, age at breast cancer diagnosis, duration of diabetes, before breast cancer, comorbidity score based on adjusted clinical group score at time of cohort entry, breast cancer treatments received within 1 year of diagnosis (surgery, radiotherapy, chemotherapy, aromatase inhibitor, tamoxifen), and exposure to glucose-lowering drugs before breast cancer diagnosis | 0.97 (0.92-1.02) | 8 |
| Peeters, 2013 | 508 | Non-metformin; 550 | 112; 176 | Prescription of metformin in the past 3 months after cancer diagnosis | Age, CCI, number of years between January 1, 1997 and the date of breast cancer diagnosis, and use of concomitant medication during follow-up: metformin, sulfonylureas, thiazolidinediones, other antidiabetic drugs, hormone replacement therapy, and statins in the past 6 months | 0.74 (0.58-0.96) | 7 |
| El-Benhaway, 2014 | 25 | Non-metformin; 14 | NR | During adjuvant chemotherapy | Age at presentation, ER and PR, lymph node status, tumor grade, clinical stage | 0.11 (0.03-0.44); | 5 |
| Oppong, 2014 | 76 | Non-metformin; 65 | 10; 12 | Metformin use at baseline (at time of breast cancer diagnosis) or at the time of diabetes diagnosis if that occurred within 6 months | Age, hormone receptor status, and stage | 0.80 (0.33-1.96) | 7 |
| Xiao, 2014 | Luminal A: 84;  Luminal B (high ki67): 140;  Luminal B (HER2+): 51 | Non-metformin;  117;  201;  87; | NR | NR | Age, BMI, amenorrhea, the presence of cardiovascular and cerebrovascular disease, pathological stage, pathological type, lymph node involvement, vessel carcinoma embolus, and the chemotherapy and endocrine regimen | Luminal A  0.28 (0.11-0.66)  Luminal B (high ki67)  0.31 (0.18-0.54)  Luminal B (HER2+)  0.49 (0.25-0.98) | 9 |
| Calip 2015 | 381 | Non-metformin; NR | NR | ≥ 1 dispensing of medication during follow-up | Other medication classes of interest; age at diagnosis; diagnosis year; stage; hormone receptor; primary treatment for initial BC; endocrine therapy for the incident BC; BMI, smoking status, menopausal status, CCI; statin use; prescription non- steroidal anti-inflammatory medication use, Cox-2 inhibitors, aspirin; receipt of screening mammogram in the 12 months prior to events | 0.55 (0.38-0.79) | 8 |
| Kim, 2015 | 202 | Non-metformin; 184 | NR | NR | Age, BMI, tumor size, lymph node metastasis, ER, PR, and HER2-neu status, and systemic treatment | 0.53 (0.35-0.80) | 7 |
| Vissers, 2015 | Prevalent diabetes: 688 | Prevalent diabetes:  Never use; 369 | Prevalent  174; 174 | <2 years use  ≥ 2 years use | Age at BC diagnosis, diabetes duration before BC, year of BC diagnosis, BC treatment (surgery, radiotherapy, chemotherapy and hormone therapy within 6 months after BC diagnosis), hormone replacement therapy prior to BC 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 BC diagnosis | Prevalent:  <2 years  0.9 (0.70-1.16)  ≥ 2 years:  0.7 (0.49-0.99) | 7 |
| Xu, 2015\* | Vanderbilt:  9% of 2218  Mayo Clinic: 12% of 3029 | Vanderbilt:  Non-metformin: 4% of 903  Insulin: 3% of 377  Mayo Clinic:  Non-metformin: 7% of 1629  Insulin: 7% of 1426 | NR | After cancer diagnosis | Age at cancer diagnosis, sex, race, BMI, insulin use, tobacco use, tumor type, and tumor stage | Vanderbilt:  Non-metformin:  0.47 (0.26-0.86)  Insulin:  0.38 (0.13-1.05)  Mayo Clinic:  Non-metformin:  0.49 (0.31-0.77)  Insulin:  0.57 (0.34-0.95) | 7 |

\* = studies that also included other cancers; Abbreviations: CCI = Charleston Comorbidity Index; BMI=body mass index; NR=not reported; ER= estrogen receptors; PR=progesterone receptors; HER2=human epidermal growth factor receptor; BC=breast cancer; COX2=cyclooxygenase-2; TZD=thiazolidinediones;



**Figure 1. Egger’s Funnel plot for metformin and incidence of breast cancer**



**Figure 2. Egger’s Funnel plot for metformin and all-cause mortality**