Associations between Diabetes, Metformin, and Second Breast Cancer Among Women with Prior Ductal Carcinoma *In Situ*

Winnie Sze Ching Yeung

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2025

Committee:

Christopher Li

Anne McTiernan

Holly Harris

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Associations between Diabetes, Metformin, and Second Breast Cancer Among Women with Prior Ductal Carcinoma *In Situ*

Winnie Sze Ching Yeung

Chair of the Supervisory Committee:
Christopher Li
Department of Epidemiology

Background: Women with a history of ductal carcinoma in situ (DCIS) face a higher risk of second breast cancer, yet little is known regarding the association of type 2 diabetes and metformin use and risk of second breast cancer among women with a history of DCIS. **Methods**: We conducted a population-based nested case-control study within a cohort of women diagnosed with DCIS between 1995 and 2013, including 497 cases of second breast cancer and 965 matched controls. **Results**: Compared to those with no diabetes, we found that type 2 diabetes and diabetes duration were not significantly associated with second breast cancer risk. Compared with never users, recent metformin use was significantly associated with reduced risk (OR = 0.36; 95% CI: 0.14–0.95), particularly with ≥36 months of use (OR = 0.24; 95% CI: 0.07–0.86). **Conclusions**: These findings suggest that recent and long-term metformin use is associated with a reduced risk of second breast cancer among women with a history of DCIS. Further studies with larger diabetic populations and more complete medication histories should be conducted to confirm these findings and inform prevention strategies.

Introduction

As the most prevalent cancer among women, breast cancer accounted for 8.2 million 5-year prevalent cases globally in 2022, with 2.3 million new cases diagnosed in 2022 alone.[1] In the United States (US), approximately 30% of screen-detected breast cancers diagnosed are ductal carcinoma *in situ* (DCIS).[2] It has been shown that compared to women who have never had breast cancer before, a history of DCIS increases the risk of a second invasive breast cancer diagnosis by 340%.[3]

According to the Centers for Disease Control and Prevention (CDC), more than 38 million people in the United States were living with diabetes in 2021.[4] In adults, the disease affected men (15.4%) and women (14.1%) at similar rates, and the majority of cases (90–95%) were type 2 diabetes.[4,5]

Among women diagnosed with breast cancer, 16-20% have also been found to have type 2 diabetes.[6] Previous studies have identified type 2 diabetes as a risk factor for breast cancer and cancer-specific mortality. A meta-analysis published in 2012, found that women with type 2 diabetes had a 16% increased risk of breast cancer compared to women without diabetes when adjusted for BMI.[7] A 2013 systematic review and meta-analysis found that patients with breast cancer and concurrent diabetes had a 38% higher cancer-specific mortality risk.[8] While past studies have linked diabetes and breast cancer [9], there is limited knowledge on the association of diabetes and second breast cancer among women who have previously been diagnosed with DCIS.

A study published in 2021 found that the association between type 2 diabetes and breast cancer may be modified by metformin use.[10] Metformin is an oral type 2 diabetes treatment that

improves glycemic control without weight gain, counters insulin resistance, and has been associated with long term cardiovascular benefits.[11] As a first line biguanide medication, metformin is the most widely prescribed glucose-lowering medication.[12] In recent years, non-cancer drugs, including metformin, have been effectively repurposed as cancer treatments.[13] While early observational studies have found lower risks of breast cancer incidence among patients using metformin, conflicting results have been published regarding the role metformin treatment has on breast cancer risk.[14–16] To date, there has been no research examining the role metformin has on a second breast cancer diagnosis among women with a prior DCIS diagnosis and diabetes. In breast cancer patients without diabetes randomized to metformin versus placebo, the MA.32 trial found that metformin had no impact on invasive disease–free survival and was not significantly associated with the risk of second primary cancers.[17,18] The objective of this study was to examine the associations between diabetes, metformin use, and risk of second breast cancer among women with a prior DCIS diagnosis.

Methods

Study Population

This study used a population-based nested case-control design within a cohort of 4,157 women identified in the In-Situ Survivors Involved in Gaining Health Answers Together (INSIGHT) study who were over 18 years old in Seattle-Puget Sound, Washington with a history of DCIS diagnosed between 1995 and 2013. Participants were identified through the Cancer Surveillance System, which is the Surveillance, Epidemiology and End Results (SEER) cancer registry that serves western Washington state.

Cases were identified as developing a second primary breast cancer at least 6 months after an initial DCIS diagnosis. Matched controls were identified through the registry as having no evidence of disease after the initial case of DCIS. Cases and controls were matched 1:2 on age (+/- 2 years), year of initial diagnosis of DCIS (+/- 2 years), county of residence at diagnosis, surgical treatment and radiation treatment (biopsy only, lumpectomy without radiation, lumpectomy with radiation, total mastectomy only), histology, grade of initial DCIS lesion, and disease-free survival time. Exclusion criteria included bilateral mastectomy for their initial DCIS, developed non-breast cancer, or less than 6 months of follow-up after primary DCIS diagnosis. Of the eligible 705 cases, who developed a secondary invasive or DCIS breast cancer between the year of their DCIS diagnosis and 2013, 497 women enrolled, and 965 controls were matched (women with DCIS who did not develop a second breast cancer between the year of their DCIS diagnosis and 2013) (Figure 1). The study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center (FHCRC).

At enrollment, medical record abstraction and phone interviews were conducted to collect information on demographic, epidemiologic, and clinical factors. If discrepancies arose between medical records and self-reported data, medical records were prioritized. Self-reported data was used if the participant refused medical record review. Epidemiologic risk factors, diabetes information, and medication use data were collected from date of first DCIS diagnosis to reference date. Reference dates were date of second breast cancer diagnosis for cases and controls were assigned a reference date based on their matched case. The primary outcome was a second breast cancer diagnosis; either invasive or in situ breast cancer at least 6 months after an initial DCIS diagnosis.

Participants were categorized as having a history of type 2 diabetes if a diagnosis of type 2 diabetes was indicated in their medical record or if participants self-reported that a physician or other health professional told them they had type 2 diabetes. Participants were classified as never having been diagnosed with diabetes if they self-reported that they had no history of any type of diabetes, including type 1, type 2, or gestational diabetes or if there was no indication that they had a history of any type of diabetes in their medical records. Participants with missing diabetes status, or diagnosed with an unknown type of diabetes, gestational diabetes, or type 1 diabetes but never type 2 diabetes were excluded from analysis (n=100 cases and n=286 controls). Diabetes duration was categorized as '<5 years' or '≥5 years' prior to second breast cancer diagnosis among patients with type 2 diabetes. Duration was calculated from date of type 2 diabetes diagnosis as indicated from medical records to reference date.

Recency of metformin use was categorized as 'recent', former', or 'never' as indicated in medical records or from self-reported medication use among participants with a history of diabetes. 'Recent' was defined as use of metformin within 6 months prior to their reference date. 'Former' was defined as last use of metformin ≥6 months prior to reference date. 'Never' was defined as never using metformin prior to reference date. Participants with missing metformin current use status were excluded from analysis (n=96 cases and n=282 controls). Missingness resulted either from incomplete medical records or from survey design, in which participants who did not report a history of diabetes were not subsequently asked about diabetes medication use. Among recent metformin users, duration was categorized as 6–35 months and ≥36 months to differentiate intermediate from long-term exposure while balancing distribution across groups; participants with <6 months of use were excluded from analysis as short-term exposure is unlikely to have biologically meaningful effects (n= 0).[19] Duration of use was defined by the

months of metformin use within 2 years before initial DCIS diagnosis until reference date. If medical records were not available, duration was calculated from self-report start and stop date of metformin use within 2 years before initial DCIS diagnosis until reference date.

Statistical Analyses

To examine the correlation between medical record and self-reported variables, Cohen's kappa coefficient was calculated. To examine the association between type 2 diabetes, metformin, and risk of second breast cancer among women with a history of DCIS, we conducted conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CI). Matched sets with missing data on modeled variables were excluded from analyses. All models were implicitly adjusted on matching factors for case/control matches (age, year of initial diagnosis, county of residence, surgical and radiation treatment, histology, grade of initial DCIS lesion, and disease-free survival time). Due to limited literature on risk factors for second breast cancer among patients previously diagnosed with DCIS potential confounders were evaluated using the change-in-estimate criterion for all models and retained in the final model if they altered the odds ratio by ≥10%, using only participants with complete data. When examining the association between type 2 diabetes and risk of second breast cancer, race, BMI at DCIS diagnosis, number of full-term pregnancies, menopausal status, and age at menarche were evaluated as potential confounders. The final model for diabetes status retained age at menarche as a confounder; the final diabetes duration model retained race and BMI as confounders. When examining the association between metformin use and risk of second breast cancer, adjuvant hormone therapy, aspirin use, statin use, race, BMI at DCIS diagnosis, number of full term pregnancies, menopausal status at DCIS diagnosis, and age of menarche were evaluated as potential confounders. Final models for recency and duration of metformin use retained all evaluated

variables as confounders. All analyses were conducted using RStudio (version 2021.09.0) with a two-sided p-value <0.05 considered as statistically significant.

Results

The 965 controls and 497 cases in this study had similar distributions of age, year of DCIS diagnosis, race and ethnicity, DCIS grade, and primary DCIS treatment (Table 1). Cases were somewhat less likely than controls to have used adjuvant hormonal therapy for DCIS, to have a lower BMI, and to have an earlier age at menarche. Among cases, the mean time from DCIS to second cancer diagnosis was 70.0 months.

In multivariable adjusted models, type 2 diabetes was not statistically significantly associated with risk of a second breast cancer diagnosis among women with a prior DCIS diagnosis (OR = 1.09, 95% CI: 0.63, 1.90) (Table 2). When evaluating duration of diabetes as of the reference date, neither a history of diabetes for <5 years (OR = 0.85; 95% CI: 0.41, 1.76) or ≥5 years (OR = 0.76; 95% CI: 0.42, 1.36) was associated with risk of a second breast cancer diagnosis compared to those without diabetes.

Recent metformin use was associated with a statistically significant lower risk of second breast cancer compared to never use (OR = 0.36; 95% CI: 0.14–0.95), while former use was not statistically significant (OR = 0.59; 95% CI: 0.18–2.0) (Table 3). Longer duration of recent metformin use (≥36 months) was associated with a statistically significant reduced risk (OR = 0.24; 95% CI: 0.07–0.86), but recent use for 6–35 months was not statistically significant (OR = 0.66; 95% CI: 0.15–2.93).

To assess potential confounding by indication, we conducted a sensitivity analysis restricted to only participants with a history of type 2 diabetes. Due to sample size limitations, these models were adjusted only for matching variables. Among women with both DCIS and diabetes, neither former or recent metformin use was associated with second breast cancer risk. There was a suggestion that recent metformin use for ≥36 months was associated with a reduced risk of a second breast cancer diagnosis but this risk estimate was within the limits of chance.

Data Validation

Cohen's kappa coefficients were calculated for variables with complete cases, where both interview and medical record data were used for analysis (diabetes status, recency of metformin use, and duration of metformin use). For diabetes status, the kappa coefficient was $\kappa = 0.795$ based on 895 complete participants. The kappa for metformin use was $\kappa = 0.722$, with 69 complete cases.

Discussion

To our knowledge, this is the first population-based study to examine the relationship between type 2 diabetes and risk of a second breast cancer among women with a prior DCIS diagnosis. Although no significant association was observed in our study, prior evidence from meta-analyses conducted in 2012 and 2023 have shown that type 2 diabetes is associated with a modest increase in risk of primary breast cancer (summary relative risks of 1.15 (95% CI: 1.09-1.21) and 1.16 (95% CI: 1.10-1.22).[7,20] Alternatively, a subsequent large population-based study found that while having type 2 diabetes did not increase risk, an increased duration of diabetes for 15 years or longer was associated with a reduced risk of breast cancer.[21] However, studies evaluating diabetes and subsequent cancer risk among breast cancer survivors have largely

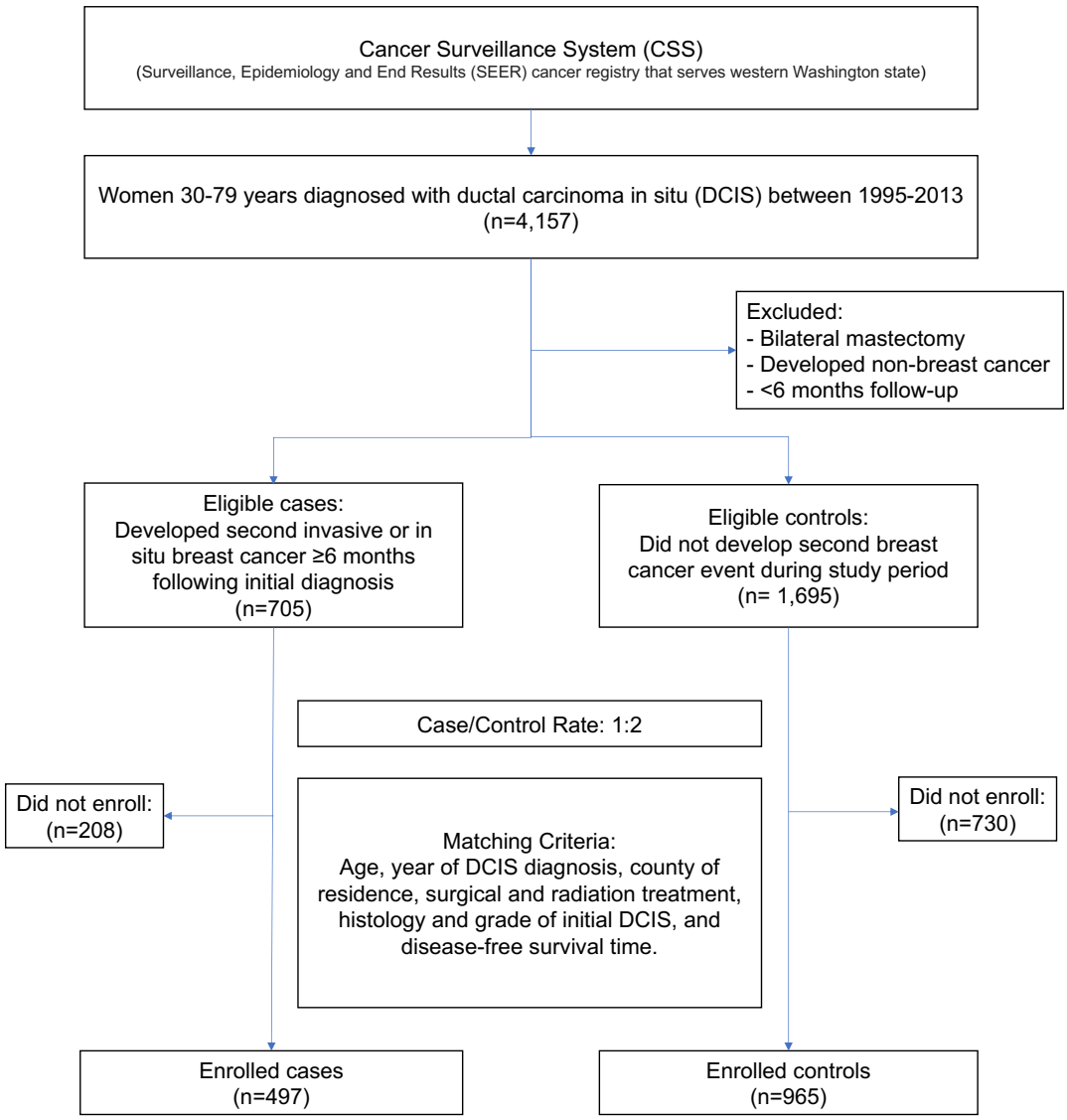
focused on women with primary invasive disease rather than non-invasive DCIS. [22,23] Differences in underlying study populations and cancer type (invasive vs. in situ) may contribute to variation in findings across studies

We also observed that both recent (within 6 months) and long-term (≥36 months) metformin use were associated with a reduced risk of second breast cancer among women with a prior history of DCIS. This is the first study to evaluate this relationship. Metformin's anti-cancer effects act through a number of pathways, including triggering AMP-inducible protein kinase pathways and indirect inhibition of the HER2 signaling cascade, a key driver of tumor growth in breast cancer cells.[24–26] Evidence regarding the relationship between metformin use and breast cancer risk is mixed. Our finding that long-term use of metformin reduces secondary breast cancer risk aligns with an observational study that found that women with type 2 diabetes who used metformin for more than 5 years had a decreased risk of breast cancer.[27] Alternatively, a recent meta-analysis found no significant reduction in breast cancer risk among metformin users, and lack of efficacy was observed in clinical trials that primarily evaluated metformin as an adjuvant or neoadjuvant treatment in breast cancer patients.[16,20,28] Likewise, the MA.32 randomized controlled trial reported no improvement in survival outcomes and no reduction in the risk of second primary cancers.[17,18] Nevertheless, combination therapies of metformin with other treatments, such as HER2-targeted drugs and chemotherapy, may still offer anti-cancer benefits.[13,26] Though our sensitivity analyses restricted to women with a history of type 2 diabetes were underpowered, they did suggest a protective effect among recent users for three years or longer mitigating concerns about potential confounding by indication. However, given that ours is the first study to report on the relationship between metformin use and risk of a second breast cancer among women with DCIS this finding should be interpreted cautiously, and further research is needed.

It is important to acknowledge the limitations of this study. This study was restricted to women in the Seattle-Puget Sound region and its predominantly non-Hispanic White population limiting its potential generalizability. However, it did utilize a population-based study design overcoming biases present from studies based on selected populations or single institutions. All observational studies are also vulnerable to various sources of bias and confounding. Recall bias was mitigated by our use of medical records as the primary source of exposure information. Key potential confounders were accounted for in the study's design as cases and controls were individually matched on a number of key variables. Additional variables were adjusted for in our statistical analyses. A further limitation is that missing information on metformin use was treated as missing rather than non-use; future analyses could evaluate the impact of categorizing missing data as never use.

While type 2 diabetes was not found to be associated with second breast cancer risk in women with prior DCIS in our study, recent and longer duration of metformin use was associated with reduced risk. These findings suggest further investigation into the potential role of metformin as an anti-cancer treatment in women with DCIS or other high-risk breast cancer populations is needed. Future studies with larger samples of patients with breast cancer and diabetes and more complete medication histories are warranted to clarify these associations and inform prevention strategies.

Figure 1. Study Design



Tables

Table 1. Demographic and clinical factors by case-control status, (N=1462)

	Control (N=965) n (%)	Case (N=497) n (%)
Age at DCIS diagnosis, years		
<50	317 (32.8)	170 (34.2)
50-59	326 (33.8)	166 (33.4)
60-69	217 (22.5)	107 (21.5)
70-79	105 (10.9)	54 (10.9)
Time from DCIS to 2nd cancer diagnosis, months		
Mean (SD)	68.8 (49.5)	70.0 (49.7)
Median [Min, Max]	57.0 [6.00, 213]	58.0 [6.00, 213]
Year of DCIS diagnosis		
1995-1997	255 (26.4)	115 (23.1)
1998-2000	208 (21.6)	129 (26.0)
2001-2004	266 (27.6)	127 (25.6)
2005-2013	236 (24.5)	126 (25.4)
Race/Ethnicity		
Hispanic White	15 (1.6)	12 (2.4)
Non-Hispanic White	871 (90.3)	435 (87.5)
Black	17 (1.8)	14 (2.8)
Asian/Pacific Islander	48 (5.0)	26 (5.2)
Native American	14 (1.5)	9 (1.8)
DCIS Grade		
Well differentiated	23 (2.4)	18 (3.6)
Moderately differentiated	242 (25.1)	104 (20.9)
Poorly differentiated	240 (24.9)	117 (23.5)
Undifferentiated	279 (28.9)	154 (31.0)
Primary DCIS treatment		
Biopsy only	12 (1.2)	13 (2.6)
Lumpectomy without radiation	250 (25.9)	125 (25.2)

Table 1. Demographic and clinical factors by case-control status, (N=1462)

	Control (N=965) n (%)	Case (N=497) n (%)
Lumpectomy with radiation	491 (50.9)	253 (50.9)
Total mastectomy only	212 (22.0)	106 (21.3)
Adjuvant hormonal therapy for DCIS		
No	598 (62.0)	348 (70.0)
Yes	364 (37.7)	149 (30.0)
Adjuvant hormonal therapy for DCIS by type		
Tamoxifen only	259 (26.8)	109 (21.9)
Aromatase inhibitor only	20 (2.1)	9 (1.8)
Tamoxifen & aromatase only	22 (2.3)	5 (1.0)
BMI at DCIS diagnosis, kg/m^2		
<25	442 (45.8)	195 (39.2)
25-29	264 (27.4)	139 (28.0)
≥30	199 (20.6)	130 (26.2)
Age of Menarche, years		
<12	122 (12.6)	91 (18.3)
12-13	467 (48.4)	205 (41.2)
≥14	192 (19.9)	99 (19.9)
Menopausal status at DCIS diagnosis		
Pre-/perimenopausal	350 (36.3)	191 (38.4)
Postmenopausal	577 (59.8)	291 (58.6)
Number of full-term pregnancies		
0	193 (20.0)	106 (21.3)
1	135 (14.0)	79 (15.9)
2	324 (33.6)	150 (30.2)
≥3	271 (28.1)	144 (29.0)
Aspirin use		
No	662 (68.6)	329 (66.2)
Yes	107 (11.1)	61 (12.3)
Statin use		

Table 1. Demographic and clinical factors by case-control status, (N=1462)

	Control (N=965) n (%)	Case (N=497) n (%)
Never	386 (40.0)	228 (45.9)
≤6 months to reference date	59 (6.1)	28 (5.6)
>6 months to reference date	138 (14.3)	87 (17.5)

Table 2. Associations between diabetes and risk of second breast cancer diagnosis among women with a prior ductal carcinoma in situ (DCIS)

	Cases (n=469) n (%)	Controls(n=885) n (%)	OR (95% CI)
Diabetes status			
No diabetes	354 (89.2)	597 (87.9)	*Reference*
Type 2 diabetes	43 (10.8)	82 (12.1)	1.09 (0.63, 1.90)
Diabetes duration			
No diabetes	354 (89.4)	597 (88.0)	Reference
<5 years	18 (4.5)	27 (4.0)	0.85 (0.41, 1.76)
≥5 years	24 (6.1)	54 (8.0)	0.76 (0.42, 1.36)

* Implicitly adjusted for matching variables. Diabetes status model was additionally adjusted for age at menarche and diabetes duration model was additionally adjusted for race and BMI.

Table 3. Associations between metformin and risk of second breast cancer diagnosis among women with a prior ductal carcinoma in situ (DCIS)

	Cases (n=401) n (%)	Controls(n=683) n (%)	OR (95% CI)
Recency of metformin use			
Never	368 (91.8)	621 (90.9)	*Reference*
Former	11 (2.7)	24 (3.5)	0.59 (0.18, 2.0)
Recent	22 (5.5)	38 (5.6)	0.36 (0.14, 0.95)
6 - 35 months	8 (2.1)	11 (1.7)	0.66 (0.15, 2.93)
≥ 36 months	14 (3.6)	26 (4.0)	0.24 (0.07, 0.86)

*Implicitly adjusted for matching variables and additionally adjusted for adjuvant hormone therapy, aspirin use, statin use, race, BMI at DCIS diagnosis, number of full-term pregnancies, menopausal status at DCIS diagnosis, age at menarche.

Table 4. Associations between metformin and risk of second breast cancer diagnosis among women with a prior ductal carcinoma in situ (DCIS) and diabetes

	Cases (n=39) n (%)	Controls(n=81) n (%)	OR (95% CI)
Recency of metformin use			
Never	14 (35.9)	25 (30.9)	*Reference*
Former	9 (23.1)	21(25.9)	0.85 (0.27 – 2.43)
Recent	16 (41.0)	35 (43.2)	0.96 (0.38 – 2.42)
6 - 35 months	7 (23.3)	11 (18.3)	1.4 (0.42, 4.89)
≥ 36 months	9 (30.0)	24 (40.0)	0.78 (0.27, 2.20)

* Adjusted for matching variables.

References

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F. Global Cancer Observatory: Cancer Today. Published online 2024. https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf

2. Lehman CD, Arao RF, Sprague BL, et al. National Performance benchmarks for modern screening digital mammography: update from the Breast Cancer Surveillance Consortium. *Radiology*. 2017;283(1):49-58. doi:10.1148/radiol.2016161174

3. Soerjomataram I, Louwman WJ, van der Sangen MJC, Roumen RMH, Coebergh JWW. Increased risk of second malignancies after in situ breast carcinoma in a population-based registry. *Br J Cancer*. 2006;95(3):393-397. doi:10.1038/sj.bjc.6603231

4. Centers for Disease Control and Prevention. National Diabetes Statistics Report. Centers for Disease Control and Prevention. May 15, 2024. Accessed August 20, 2025. https://www.cdc.gov/diabetes/php/data-research/?CDC_AAref_Val=https://www.cdc.gov/diabetes/data/statistics-report/index.html

5. Centers for Disease Control and Prevention. Type 2 Diabetes. Centers for Disease Control and Prevention. May 15, 2024. Accessed August 20, 2025. https://www.cdc.gov/diabetes/about/about-type-2-diabetes.html

6. Jarvandi S, Pérez M, Schootman M, Jeffe DB. Pre-existing diabetes in early-stage breast cancer patients is associated with lack of improvement in quality of life 2 years after diagnosis. *Int J Behav Med*. 2016;23(6):722-729. doi:10.1007/s12529-016-9577-4

7. Boyle P, Boniol M, Koechlin A, et al. Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer*. 2012;107(9):1608-1617. doi:10.1038/bjc.2012.414

8. De Bruijn KMJ, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CHJ. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *Br J Surg*. 2013;100(11):1421-1429. doi:10.1002/bjs.9229

9. Eketunde AO. Diabetes as a Risk Factor for Breast Cancer. *Cureus*. 2020;12(5):e8010. doi:10.7759/cureus.8010

10. Park YM, Bookwalter DB, O'Brien KM, Jackson CL, Weinberg CR, Sandler DP. A Prospective Study of Type 2 diabetes, metformin use, and risk of breast cancer. *Ann Oncol Off J Eur Soc Med Oncol*. 2021;32(3):351-359. doi:10.1016/j.annonc.2020.12.008

11. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet*. 1998;352(9131):854-865. doi:10.1016/S0140-6736(98)07037-8

12. Bailey CJ. Metformin: historical overview. *Diabetologia*. 2017;60(9):1566-1576. doi:10.1007/s00125-017-4318-z

13. Kirtonia A, Gala K, Fernandes SG, et al. Repurposing of drugs: An attractive pharmacological strategy for cancer therapeutics. *Semin Cancer Biol*. 2021;68:258-278. doi:10.1016/j.semcancer.2020.04.006

14. Chlebowski RT, McTiernan A, Wactawski-Wende J, et al. Diabetes, metformin, and breast cancer in postmenopausal women. *J Clin Oncol Off J Am Soc Clin Oncol*. 2012;30(23):2844-2852. doi:10.1200/JCO.2011.39.7505

15. Yang T, Yang Y, Liu S. Association between Metformin Therapy and Breast Cancer Incidence and Mortality: Evidence from a Meta-Analysis. *J Breast Cancer*. 2015;18(3):264-270. doi:10.4048/jbc.2015.18.3.264

16. Corleto KA, Strandmo JL, Giles ED. Metformin and Breast Cancer: Current Findings and Future Perspectives from Preclinical and Clinical Studies. *Pharmaceuticals*. 2024;17(3):396. doi:10.3390/ph17030396

17. Goodwin PJ, Chen BE, Gelmon KA, et al. Effect of Metformin vs Placebo on Invasive Disease–Free Survival in Patients With Breast Cancer: The MA.32 Randomized Clinical Trial. *JAMA*. 2022;327(20):1963-1973. doi:10.1001/jama.2022.6147

18. Goodwin PJ, Chen BE, Gelmon KA, et al. Effect of Metformin Versus Placebo on New Primary Cancers in Canadian Cancer Trials Group MA.32: A Secondary Analysis of a Phase III Randomized Double-Blind Trial in Early Breast Cancer. *J Clin Oncol*. 2023;41(35):5356-5362. doi:10.1200/JCO.23.00296

19. Pottegård A, Friis S, Stürmer T, Hallas J, Bahmanyar S. Considerations for pharmacoepidemiological studies of drug-cancer associations. *Basic Clin Pharmacol Toxicol*. 2018;122(5):451-459. doi:10.1111/bcpt.12946

20. Lu Y, Hajjar A, Cryns VL, et al. Breast cancer risk for women with diabetes and the impact of metformin: A meta-analysis. *Cancer Med*. 2023;12(10):11703-11718. doi:10.1002/cam4.5545

21. Xiong F, Wang J, Nierenberg JL, et al. Diabetes mellitus and risk of breast cancer: a large-scale, prospective, population-based study. *Br J Cancer*. 2023;129(4):648-655. doi:10.1038/s41416-023-02345-4

22. Hardell KNL, Schonfeld SJ, Ramin C, Vo JB, Morton LM. Association between diabetes and subsequent malignancy risk among older breast cancer survivors. *JNCI Cancer Spectr*. 2024;8(3):pkae036. doi:10.1093/jncics/pkae036

23. Li CI, Daling JR, Tang MTC, Malone KE. Relationship between Diabetes and Risk of Second Primary Contralateral Breast Cancer. *Breast Cancer Res Treat*. 2011;125(2):545-551. doi:10.1007/s10549-010-1035-4

24. Han G, Gong H, Wang Y, Guo S, Liu K. AMPK/mTOR-mediated inhibition of survivin partly contributes to metformin-induced apoptosis in human gastric cancer cell. *Cancer Biol Ther*. 2015;16(1):77-87. doi:10.4161/15384047.2014.987021

25. Wheaton WW, Weinberg SE, Hamanaka RB, et al. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. *eLife*. 2014;3:e02242. doi:10.7554/eLife.02242

26. Bashraheel SS, Kheraldine H, Khalaf S, Moustafa AEA. Metformin and HER2-positive breast cancer: Mechanisms and therapeutic implications. *Biomed Pharmacother*. 2023;162:114676. doi:10.1016/j.biopha.2023.114676

27. Bodmer M, Meier C, Krähenbühl S, Jick SS, Meier CR. Long-Term Metformin Use Is Associated With Decreased Risk of Breast Cancer. *Diabetes Care*. 2010;33(6):1304-1308. doi:10.2337/dc09-1791

28. Cejuela M, Martin-Castillo B, Menendez JA, Pernas S. Metformin and Breast Cancer: Where Are We Now? *Int J Mol Sci*. 2022;23(5):2705. doi:10.3390/ijms23052705