

Influence of Breast Cancer and Metastases on Incidence of Diabetes

Tarah Ballinger (✉ tarahb@iu.edu)

Indiana University School of Medicine <https://orcid.org/0000-0002-6797-2758>

Ziyue Liu

Indiana University School of Medicine

Sarah A. El-Azab

Regenstrief Institute Inc

Andrea Broyles

Regenstrief Institute Inc

Theresa Guise

MD Anderson Endocrine Center: The University of Texas MD Anderson Cancer Center Endocrine Center

Erik A. Imel

Indiana University School of Medicine

Research Article

Keywords: breast cancer, bone metastases, diabetes, endocrine therapy, survivorship

Posted Date: February 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-191145/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

This is the preprint of the article published in final edited form as:

Ballinger, T., Liu, Z., El-Azab, S., Broyles, A., Guise, T., & Imel, E. (2021). Influence of Breast Cancer and Metastases on Incidence of Diabetes. <https://doi.org/10.21203/rs.3.rs-191145/v1>

Abstract

Purpose: Diabetes increases the risk of subsequent breast cancer. However, the inverse relationship of breast cancer to incident diabetes development is unclear. In preclinical models increased bone turnover due to bone metastases or endocrine therapies impacts insulin secretion. This analysis was conducted to estimate the incidence of diabetes after breast cancer and the influence of metastases and therapeutic agents.

Methods: This retrospective case-control study combined data from a large electronic health data exchange and the Indiana State Cancer Registry on breast cancer patients and controls between 2007 and 2017. Primary exposure was presence of breast cancer and bone or non-bone metastases. The primary outcome was frequency of incident diabetes detected by ICD codes, medication use, or laboratory results, compared between breast cancer cases and controls using conditional or ordinary logistic regressions.

Results: 36,083 cases and 36,083 matched controls were detected. Incident diabetes was higher in early stage breast cancer (OR 1.17, 95%CI 1.11-1.23, $p < 0.0001$) and metastatic breast cancer (OR 1.62, 95% CI 1.25-2.09, $p = 0.0002$), compared to controls. Bone metastases conferred higher odds of both pre-existing (OR 1.20, 95% CI 1.03-1.63, $p = 0.0272$) and incident diabetes (OR 1.64, 95% CI 1.19-2.25, $p = 0.0021$). Endocrine therapy was associated with reduced diabetes (OR 0.86, 95% CI 0.79-0.83, $p = 0.002$). Anti-resorptives reduced incident diabetes in those with bone metastases (OR 0.44, 95% CI 0.25-0.78, $p = 0.005$).

Conclusion: Breast cancer, especially with metastases, increases subsequent risk of diabetes. As patients with breast cancer live longer, identifying and managing diabetes may impact treatment delivery, cost, survival, and quality of life.

Intro

Breast cancer and its treatment have profound detrimental effects on bone resulting in significant morbidity, including fracture, frailty, and pain. In both the early stage and metastatic settings, the majority of breast cancer patients receive estrogen deprivation therapy, which significantly increases bone turnover[1, 2]. Furthermore, approximately 30% of patients develop incurable metastatic disease, the vast majority having bone metastases, furthering local bone destruction[3]. Whether through treatment- or tumor- induced bone destruction, resulting increases in bone turnover may have far-reaching systemic effects beyond just the skeletal system, including muscle weakness and alterations in glucose homeostasis.

In mouse models of breast cancer with bone metastases or estrogen deprivation, bone turnover contributes to muscle weakness. TGF β is released as a consequence of accelerated osteoclastic bone resorption and acts systemically to cause skeletal muscle weakness through NADPH oxidase 4 (Nox4) mediated oxidation of the calcium channel ryanodine receptor 1 (RyR1)[4, 5]. Similarly, recent preclinical

data has demonstrated that bone-derived TGF β also impacts the calcium release channel RyR2 in pancreatic β cells, impairing insulin secretion and glucose homeostasis[6-8]. While a high incidence of diabetes among women receiving anti-estrogen therapy has been reported[9], the mechanism remains unknown. Both bone loss and risk of diabetes are higher in patients taking aromatase inhibitors compared with tamoxifen. Thus, based on preclinical and clinical evidence, we hypothesized that breast cancer, associated metastases and medications influencing bone loss could result in hyperglycemia.

This hypothesized link between high bone turnover and glucose metabolism has potential significant clinical impact. Concurrent diagnoses of diabetes and breast cancer worsens both all-cause and breast cancer specific mortality[10-12]. Additionally, hyperglycemia further impairs bone quality[13], resulting in a detrimental feed-forward cycle. While there is an established link between diabetes and the subsequent development of breast cancer[14], the frequency with which patients with breast cancer develop new diabetes, and the influence of bone metastases and endocrine therapy on this relationship, is unknown.

We conducted a retrospective matched cohort study to test the hypothesis that breast cancer, especially with extreme bone destruction of bone metastases, is associated with post-cancer development of diabetes when compared to matched controls without cancer in a large Indiana patient database. Additionally, we investigated the impact of endocrine therapies and skeletal protective therapies on this relationship.

Methods

Study design

This retrospective matched cohort study utilized data in the Indiana Network for Patient Care (INPC) database, a statewide clinical data exchange warehouse including over 100 healthcare entities including major hospitals, health networks, and insurance providers, encompassing data points from approximately two thirds of Indiana's population. Patients were not contacted for the study. The study was conducted in accordance with the Declaration of Helsinki; the protocol and waiver of consent was approved by the Indiana University Institutional Review Board. All patient data was de-identified for analysis.

Study population

Patients with and without breast cancer were extracted from the INPC, limited to women having available data from the years 2007 to 2017. Breast cancer patients were defined as women age 40 or older with a new diagnosis of breast cancer by ICD9 or ICD10 codes and no prior breast cancer codes in the two years before the index diagnosis date. Thus, the index date for breast cancer patients was the earliest occurrence of a diagnosis of breast cancer. To ensure accuracy of diagnosis, cancer diagnoses were confirmed in the Indiana State Department of Health Cancer Registry. Patients without breast cancer, i.e., controls, were randomly selected, birth year and race matched women age 40 or older having data in INPC during the same time period. Controls had no diagnosis of breast cancer ever. Breast cancer

patients and controls were excluded if they had a diagnosis of any other cancers, except non-melanoma skin cancer. The index date for controls was the earliest occurrence of clinical data in INPC in the calendar year meeting criteria to be a matched control. Data was extracted for each individual from 2 years before the index date through the end of available data in INPC for that individual during the years of the study.

Exposures and outcomes

The primary exposure is the presence or absence of breast cancer and of bone or non-bone breast cancer metastases. These were determined using a combination of ICD codes in the INPC and diagnoses and metastases data in the Indiana cancer registry. The primary outcome is the frequency of incident diabetes in the breast cancer patients compared to their matched controls. Secondary outcomes included frequency of diabetes development according to the following categories: breast cancer without metastases, breast cancer with bone metastases, and breast cancer with only non-bone metastases. Additional secondary outcomes included the influence of exposure to anti-estrogen therapies (aromatase inhibitors and/or selective estrogen receptor modulators [SERMs]), and exposure to skeletal protective anti-resorptive medications (bisphosphonates or denosumab). We investigated time to development of diabetes in the overall cohort and in the above subgroups, compared to controls.

Diabetes was defined using ICD9 or ICD10 codes, ordering or dispensing of diabetes medications, hemoglobin A1c \geq 6.5%, fasting glucose $>$ 140 mg/dl, or non-fasting glucose $>$ 200 mg/dL. A patient meeting one or more of these criteria was counted as having diabetes. Since the study relied on laboratory tests performed without access to associated text records, a fasting glucose $>$ 140 mg/dl was used instead of $>$ 126 mg/dl to decrease the chance of wrongly labeling a patient as having diabetes if the sample was not truly fasting. In order to avoid misclassifying patients with pre-existing diabetes as a new diagnosis simply because of new health care exposure after breast cancer diagnosis and new testing, diabetes was considered to be pre-existing if the above criteria occurred prior to the index date or $<$ 30 days after this index date. The incidence of new diabetes was defined as diabetes detected only beginning \geq 30 days after the index date. As an additional attempt to avoid misclassifying pre-existing diabetes as new, we also evaluated the occurrence of new diabetes beginning \geq 6 months after the index date.

When evaluating medication exposure, medication use in the two years preceding index date until the last available date was determined. Endocrine therapy use included aromatase inhibitors (letrozole, anastrozole, or exemestane), SERMs (tamoxifen or raloxifene), or GnRH agonists (leuprolide, goserelin). Endocrine therapy exposure was included if the patient was exposed for at least 1 year. Those patients who had exposure to an AI or SERM but for less than one year were excluded from the drug analysis. Anti-resorptives included the potent bisphosphonate zoledronic acid, as well as the RANK ligand inhibitor denosumab. Any exposure to these anti-resorptives was included as a positive exposure given their long-half life and potent efficacy.

Statistical analysis

Continuous variables were summarized by means with standard deviation (SD) and categorical variables were summarized as frequencies (percentages). Diabetes outcomes were compared between case and controls using odds ratios (95% confidence interval). Conditional logistic regressions were used when comparing breast cancer patients to their individually matched controls; ordinary logistic regressions were used when comparing among subgroups of breast cancer patients with regard to their metastasis conditions (any metastases, no metastases, bone metastases, non-bone metastases). The impact of medication exposure was also evaluated using multiple logistic regressions. In sensitivity analysis, time to diabetes was summarized by Kaplan- Meier curves and compared using Cox proportional hazard models with random effects for matching. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics

Between January 1, 2007 and December 31, 2017, a total of 36,083 new breast cancer patients and 36,083 matched controls were detected and their electronic medical record data were extracted from the INPC. Mean (SD) age was 62 (11.62) years and 83.8% of patients were White in both groups. In the total cohort including breast cancer patients and controls, Black patients had a higher proportion of diabetes compared to White patients (43.49% versus 26.84%, $p < 0.0001$) (see Table 1).

Diabetes diagnosis

Of the total number of patients with diabetes in both groups ($n = 20,409$), the majority (73.27%) met more than one criterion for diagnosis, the most common being diabetes diagnosis codes ($n = 15,596$), diabetes medications ($n = 14,567$), and elevated hemoglobin A1c ($n = 12,278$) (Table 2). The majority (66.4%) of diabetes was pre-existing before the index date ($n = 13,560$), including 17.24% ($n = 6,221$) of the breast cancer patients and 20.3% ($n = 7,339$) of the controls (OR 0.81, 95% CI 0.78 – 0.84, $p < 0.0001$). New diagnosis of diabetes ³ 30 days after index date occurred in 10.2% of breast cancer patients compared to 8.75% of controls (OR 1.18, 95% CI 1.13 – 1.25, $p < 0.0001$). When only including new onset diabetes ³ 6 months after breast cancer diagnosis, this relationship was unchanged (9.0% versus 7.8%, OR 1.17, 95% CI 1.10 – 1.24, $p < 0.0001$).

To determine whether differences in diabetes incidence were secondary to lack of laboratory evaluation, we investigated rates of glucose and hemoglobin A1c values one year before and one year after the index date between breast cancer patients and controls. In the year prior to index data, breast cancer patients were less likely to have laboratory measured glucose or hemoglobin A1c compared to controls (OR 0.87, 95% CI 0.81-0.93). In the 1 year after index date, breast cancer patients were now more likely to have these laboratory values measured (48.00% versus 40.51%. OR 1.42, 95% CI 1.38-1.47). This difference was primarily driven by non- fasting glucose measurements, which were likely drawn due to other purposes during the breast cancer treatment course. Hemoglobin A1c was significantly less likely to be

measured in breast cancer patients after diagnosis compared to controls (10.39% versus 14.67%, OR 0.66, 95% CI 0.63-0.69).

Post-index diabetes in breast cancer patients compared to controls

Figure 1 displays odds ratios (OR) and 95% CI for comparison of all breast cancer patients to the cohort of non-cancer controls. The OR for new diabetes ³ 30 days after breast cancer diagnosis or index date was higher in patients with early stage breast cancer compared to matched controls (OR 1.17, 95% CI 1.11-1.23, $p < 0.0001$), and significantly higher in those breast cancer with metastatic disease compared to matched controls (OR 1.62, 95% CI 1.25 – 2.09, $p = 0.0002$). The OR differed significantly between early stage versus metastatic patients ($p = 0.015$). When considering only those with new onset diabetes detected ³ 6 months after index date, these relationships were unchanged.

Given the hypothesis that increased bone turnover is associated with reduced insulin secretion and hyperglycemia, we also investigated the relationship between bone metastases and incident diabetes. As shown in Figure 1, both metastatic breast cancer cases with only non-bone metastases and those with bone metastases had significantly increased OR for new diagnosis of diabetes ≥ 30 days after index date (non-bone mets: OR 1.58, 95% CI 1.02-2.44, $p = 0.0393$; bone mets: OR 1.64, 95% CI 1.19 – 2.25, $p = 0.0021$). Notably, breast cancer cases with bone metastases were also more likely to have pre-existing diabetes (OR 1.30, 95% CI 1.03-1.63, $p = 0.0272$), a relationship that was not present in those without bone metastases.

Impact of endocrine therapy and skeletal protective drugs on incident diabetes

In order to determine how medications that increase or decrease bone turnover impact these associations, we investigated use of endocrine therapy and antiresorptive agents. In patients with at least one year of exposure to endocrine therapy for non-metastatic breast cancer ($n = 12,262$), the OR for new onset DM was decreased (OR 0.86, 95% CI 0.79-0.93, $p = 0.002$). This was similar for those ever receiving an aromatase inhibitor ($n = 9,017$; OR 0.89, 95% CI 0.82-0.98, $p = 0.0018$) or a SERM ($n = 4,831$; OR 0.86, 95% 0.76-0.98, $p = 0.023$). We did not include metastatic breast cancer patients in this analysis due to variable and inconsistent clinical use of these medications in that setting, often for shorter durations of time.

In the cohort of patients with bone metastases, 197 (33%) received a potent antiresorptive agent. In this group, exposure to zoledronic acid or denosumab was associated with a significantly reduced odds of incident diabetes (OR 0.44, 95% CI 0.25-0.78, $p = 0.005$). Results were similar for subjects exposed to both potent antiresorptives and endocrine therapy (OR 0.51, 95% CI 0.28-0.94, $p = 0.029$).

Conclusions

In this large population of breast cancer patients from a state cancer registry, we demonstrate an increased odds for incident diabetes after breast cancer, and in particular metastatic breast cancer,

compared to matched control women without breast cancer. While a relationship between pre-existing diabetes and increased risk of breast cancer has been established, this is the first study to our knowledge to explore the reverse relationship between pre-existing early stage versus metastatic breast cancer and subsequent diabetes incidence.

Including metastatic patients in this investigation is of particular importance. Breast cancer is an increasing survivable disease; prognosis for those with incurable metastatic disease is now measured in years and 30% of patients with bone-only disease are still living more than 10 years later[15]. The long-term sequelae of breast cancer and its treatment have been under-appreciated, particularly for those with metastatic disease. In early stage breast cancer, diabetes is associated with increased health care costs, treatment related side effects, worse quality of life, and inferior survival outcomes[16, 17]. While there is a notable lack of investigation of the impact of diabetes in the presence of metastatic breast cancer, similar impact likely exists. A small retrospective study indicated worse survival in patients with metastatic breast cancer who had poor glycemic control, compared to those who were normoglycemic[18].

There are complex biologic mechanisms linking insulin resistance to tumorigenesis[19]; however, it is likely that worse survival in patients with co-existing diabetes and breast cancer goes beyond biology and is further negatively impacted by less intensive diabetic monitoring and more diabetic complications. Prior work has found that patients undergoing cancer treatment perform less diabetes self-management behaviors, including exercise, diet control, blood glucose monitoring, and adherence with oral antidiabetic medications[20, 21]. Major barriers to the management of diabetes in the presence of cancer include lack of prioritization of diabetes by both patients and providers, and a lack of assigned responsibility for diabetes management[22]. This is consistent with our finding of significantly fewer hemoglobin A1C measurements after breast cancer diagnosis compared to the controls without cancer, even among those diagnosed with diabetes.

Contrary to our hypothesis, the rate of incident diabetes was lower among those receiving endocrine therapy for early stage breast cancer. In a case-control analysis by Hamood et al. of Israeli early stage breast cancer patients, endocrine therapy was associated with an increased risk of subsequent diabetes (HR 2.4, 95% CI 1.26- 4.55, $p = 0.008$)[9]. This was most significant for aromatase inhibitors, which more strongly increase bone turnover, compared with tamoxifen. This finding supports preclinical data linking bone turnover to impaired insulin secretion and insulin resistance²⁸ through TGF- β mediated oxidation of RyR2 in pancreatic beta cells and alterations of osteocalcin, respectively. While the population used in our study is larger and represents a community based, diverse sample, important covariates are missing that were included in the Hamood analysis. Information such as body composition or rates of physical activity were not available for our analysis; these variables are important as obesity, adiposity, and chronic inflammation may worsen during endocrine therapy and impact both risk of diabetes and bone turnover.

Conversely, another case-control study[23] in early stage breast cancer patients over age 65 found tamoxifen to be associated with increased risk of diabetes (OR 1.24, 95% CI 1.08-1.42, $p = 0.002$), while

no association was found for aromatase inhibitors. The authors theorized that tamoxifen may increase incidence of diabetes by influencing insulin resistance, while the lack of association with aromatase inhibitors was attributed to a small sample size. In both of these case-control analyses, cases and controls had breast cancer, thus no conclusions could be made about the influence of a cancer diagnosis on diabetes incidence.

In a study of Taiwanese survivors of early stage breast cancer matched to controls without cancer[24], breast cancer patients had a higher risk of developing diabetes than non-cancer controls (HR 1.14, 95% CI = 1.08 – 1.20), as seen in our study; however, this observation was only present in tamoxifen users. Consistent with our findings, aromatase inhibitor treatment was associated with a reduced risk of diabetes (HR 0.59, 95% CI 0.43- 0.80). Future work in prospective studies is needed to validate these findings, and to evaluate the influence of body composition and lifestyle habits on the development of comorbid conditions in women receiving endocrine therapy for early stage breast cancer.

Notably, we found an over 50% reduction in the incidence of diabetes in patients with bone metastases who received potent medication to inhibit bone turnover using zoledronic acid or denosumab. Preclinical work demonstrates that mice with increased bone resorption have impaired insulin secretion through effects of systemic bone-derived TGF- β mediated oxidation of RyR2 in pancreatic beta cells. Furthermore, insulin is a target gene of TGF- β ; amplified TGF- β signaling to the effector protein Smad3 in these cells represses insulin transcription and reduces insulin secretion[25, 26]. Bisphosphonates block osteoclastic bone resorption and the release of TGF- β into the systemic circulation⁴. Thus, drugs that block bone resorption have the potential to block suppression of insulin release and will be the subject of future prospective studies. Risk of diabetes is important in this population with bone metastases, as hyperglycemia contributes to poor bone quality and increased fracture risk[13]. Further increases in bone turnover from diabetes may create a feed forward cycle resulting in progressively worsening bone frailty and metabolic impairments. Additionally, patients in this analysis with bone metastases had a higher rate of pre-existing diabetes. This supports data indicating that increases in bone turnover may start long before a clinical diagnosis of bone metastases and the subsequent complications. For example, the randomized AZURE trial of adjuvant zoledronic acid for early stage breast cancer found a clear association between elevated baseline bone turnover markers and later development of in-bone recurrences, but not of metastases outside of bone[27].

Strengths of this study include the mechanistically-based hypothesis that is supported by preclinical models. Additionally, the study included very large sample size, validation of cancer cases within the state cancer registry, and exclusion of patients from both groups having other cancers. Range of age, race, and health care systems make these results generalizable across many populations and variables.

This study has several limitations. The INP includes only medical information that is supplied to the information exchange, thus is subject to selection bias of patient use and physicians' testing and management choices. Additionally, there is potential detection bias as the codes in the EMR do not guarantee a condition is present or absent; the EMR only includes codes for what is interpreted and

recorded by a provider. However, we did confirm cancer diagnoses in the state cancer registry. In addition, few patients (<4%) had their diabetes detected based on laboratory values alone without other corroborating evidence of codes and medications; additionally, the majority (73%) were detected by multiple criteria, assuring that the diagnosis of diabetes in these patients was more certain. Additionally, bone turnover markers and bone density results were not available for this analysis, preventing analysis of potential bone changes. Finally, patients may also refuse to start certain medications, or to stop them early due to side effects. Since our analysis focused on structured, coded data, we were not able to assess reasons for or against use of various medications in individual patients. This was not a randomized controlled trial of the effects of various medications. It is possible that patients receiving certain medications were otherwise less at risk for development of diabetes due to unknown confounders. For example, there may be covariates such as body composition, diet, and physical activity that were not possible to collect in this analysis but may influence outcomes.

As more patients are cured of breast cancer and those with metastatic breast cancer continue to live longer, identification and management of diabetes will be imperative given its impact on treatment delivery, quality of life, health care costs, and survival. While the mechanism linking breast cancer to diabetes is unknown, this analysis and that from other studies support preclinical data connecting increased bone turnover to impaired glucose hemostasis. This relationship warrants prospective clinical evaluation and investigation of the impact of skeletal protective therapy on systemic effects of bone destruction.

Declarations

Funding source: This study was funded by the grants P30AR072581 from NIAMS at the NIH and an IU Multiple Center Collaboration Pilot grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of interest: The authors declare no relevant conflicts of interest.

Availability of data: Data is available upon reasonable request to the corresponding author.

Authors contributions:

Conceptualization: Tarah Ballinger, Theresa Guise, Erik Imel

Methodology: Tarah Ballinger, Ziyue Liu, Andrea Broyles, Theresa Guise, Erik Imel

Formal analysis: Ziyue Liu, Sarah El-Azab, Andrea Broyles

Data interpretation: Tarah Ballinger, Ziyue Liu, Theresa Guise, Erik Imel

Writing – original draft: Tarah Ballinger

Writing – review and editing: Tarah Ballinger, Ziyue Liu, Theresa Guise, Erik Imel

Funding acquisition: Tarah Ballinger, Theresa Guise, Erik Imel

Ethics approval: The study was conducted in accordance with the Declaration of Helsinki; the study protocol and waiver of patient consent was approved by the Indiana University Institutional Review Board

References

1. Eastell R, Adams JE, Coleman RE, Howell A, Hannon RA, Cuzick J, Mackey JR, Beckmann MW, Clack G (2008) Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 26(7):1051–1057
2. Coleman RE, Banks LM, Girgis SI, Kilburn LS, Vrdoljak E, Fox J, Cawthorn SJ, Patel A, Snowdon CF, Hall E et al (2007) Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. *Lancet Oncol* 8(2):119–127
3. Coleman RE (2001) Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 27(3):165–176
4. Waning DL, Mohammad KS, Reiken S, Xie W, Andersson DC, John S, Chiechi A, Wright LE, Umanskaya A, Niewolna M et al (2015) Excess TGF-beta mediates muscle weakness associated with bone metastases in mice. *Nat Med* 21(11):1262–1271
5. Wright LE, Harhash AA, Kozlow WM, Waning DL, Regan JN, She Y, John SK, Murthy S, Niewolna M, Marks AR et al (2017) Aromatase inhibitor-induced bone loss increases the progression of estrogen receptor-negative breast cancer in bone and exacerbates muscle weakness in vivo. *Oncotarget* 8(5):8406–8419
6. Santulli G, Pagano G, Sardu C, Xie W, Reiken S, D'Ascia SL, Cannone M, Marziliano N, Trimarco B, Guise TA et al (2015) Calcium release channel RyR2 regulates insulin release and glucose homeostasis. *J Clin Invest* 125(11):4316
7. Yamamoto WR, Bone RN, Sohn P, Syed F, Reissaus CA, Mosley AL, Wijeratne AB, True JD, Tong X, Kono T et al (2019) Endoplasmic reticulum stress alters ryanodine receptor function in the murine pancreatic beta cell. *J Biol Chem* 294(1):168–181
8. Sjöholm A, Hellerstrom C (1991) TGF-beta stimulates insulin secretion and blocks mitogenic response of pancreatic beta-cells to glucose. *Am J Physiol* 260(5 Pt 1):C1046–C1051
9. Hamood R, Hamood H, Merhasin I, Keinan-Boker L (2018) Diabetes After Hormone Therapy in Breast Cancer Survivors: A Case-Cohort Study. *J Clin Oncol* 36(20):2061–2069
10. Lega IC, Austin PC, Fischer HD, Fung K, Krzyzanowska MK, Amir E, Lipscombe LL (2018) The Impact of Diabetes on Breast Cancer Treatments and Outcomes: A Population-Based Study. *Diabetes Care* 41(4):755–761
11. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, Brancati FL, Wolff AC (2011) Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol* 29(1):40–46

12. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH (2009) Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. *J Clin Oncol* 27(13):2170–2176
13. Moayeri A, Mohamadpour M, Mousavi SF, Shirzadpour E, Mohamadpour S, Amraei M (2017) Fracture risk in patients with type 2 diabetes mellitus and possible risk factors: a systematic review and meta-analysis. *Ther Clin Risk Manag* 13:455–468
14. Maskarinec G, Jacobs S, Park SY, Haiman CA, Setiawan VW, Wilkens LR, Le Marchand L (2017) Type II Diabetes, Obesity, and Breast Cancer Risk: The Multiethnic Cohort. *Cancer Epidemiol Biomarkers Prev* 26(6):854–861
15. Parkes A, Clifton K, Al-Awadhi A, Oke O, Warneke CL, Litton JK, Hortobagyi GN (2018) Characterization of bone only metastasis patients with respect to tumor subtypes. *NPJ Breast Cancer* 4:2
16. Hershey DS, Given B, Given C, Von Eye A, You M (2012) Diabetes and cancer: impact on health-related quality of life. *Oncol Nurs Forum* 39(5):449–457
17. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE (2008) The impact of diabetes on survival following breast cancer. *Breast Cancer Res Treat* 109(2):389–395
18. Villarreal-Garza C, Shaw-Dulin R, Lara-Medina F, Bacon L, Rivera D, Urzua L, Aguila C, Ramirez-Morales R, Santamaria J, Bargallo E et al (2012) Impact of diabetes and hyperglycemia on survival in advanced breast cancer patients. *Exp Diabetes Res* 2012:732027
19. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL et al (2009) Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 101(1):48–60
20. Hershey DS, Tipton J, Given B, Davis E (2012) Perceived impact of cancer treatment on diabetes self-management. *Diabetes Educ* 38(6):779–790
21. Tan X, Feng X, Chang J, Higa G, Wang L, Leslie D (2016) Oral antidiabetic drug use and associated health outcomes in cancer patients. *J Clin Pharm Ther* 41(5):524–531
22. Goebel J, Valinski S, Hershey DS (2016) Improving Coordination of Care Among Healthcare Professionals and Patients With Diabetes and Cancer. *Clin J Oncol Nurs* 20(6):645–651
23. Lipscombe LL, Fischer HD, Yun L, Gruneir A, Austin P, Paszat L, Anderson GM, Rochon PA (2012) Association between tamoxifen treatment and diabetes: a population-based study. *Cancer* 118(10):2615–2622
24. Sun LM, Chen HJ, Liang JA, Li TC, Kao CH (2014) Association of tamoxifen use and increased diabetes among Asian women diagnosed with breast cancer. *Br J Cancer* 111(9):1836–1842
25. Lin HM, Lee JH, Yadav H, Kamaraju AK, Liu E, Zhigang D, Vieira A, Kim SJ, Collins H, Matschinsky F et al (2009) Transforming growth factor-beta/Smad3 signaling regulates insulin gene transcription and pancreatic islet beta-cell function. *J Biol Chem* 284(18):12246–12257
26. Yadav H, Quijano C, Kamaraju AK, Gavrilova O, Malek R, Chen W, Zervas P, Zhigang D, Wright EC, Stuelten C et al (2011) Protection from obesity and diabetes by blockade of TGF-beta/Smad3

signaling. Cell Metab 14(1):67–79

27. Brown J, Rathbone E, Hinsley S, Gregory W, Gossiel F, Marshall H, Burkinshaw R, Shulver H, Thandar H, Bertelli G et al (2018) Associations Between Serum Bone Biomarkers in Early Breast Cancer and Development of Bone Metastasis: Results From the AZURE (BIG01/04) Trial. J Natl Cancer Inst 110(8):871–879

Tables

Table 1. Demographic characteristics of breast cancer patients and matched controls

	Controls	Breast Cancer (All)	Breast Cancer (No Metastases)	Breast Cancer (Any Metastases)	Breast Cancer (Non-Bone Metastases)	Breast Cancer (Bone Metastases)
Total N	36,083	36,083	34,475	1,608	591	1,017
Age (mean ± SD)	62.02 ±11.62	62.22 ±11.62	62.27 ±11.62	61.00 ±11.50	61.63 ±11.80	60.63 ±1.31
Race						
White n (%)	30,226 (83.77%)	30,226 (83.77%)	28,953 (83.98%)	1,273 (79.17%)	471 (79.70%)	802 (78.86%)
Black n (%)	2,795 (7.75%)	2,795 (7.75%)	2,622 (7.61%)	173 (10.76%)	73 (12.35%)	100 (9.83%)
Other n (%)	3,062 (8.49%)	3,062 (8.49%)	2,900 (8.41%)	162 (10.07%)	47 (7.95%)	115 (11.31%)

Table 2: Diabetes detection in the electronic health record

Diabetes criteria	Overall (N=20,409)	Controls (N=10,509)	Breast Cancer (N=9,900)
Number detected by criteria:			
Diagnosis Codes	15,596 (76.42)	8,155 (77.60)	7,441 (75.16)
Medications	14,567 (71.38)	7,431 (70.71)	7,136 (72.08)
Hgb A1C \geq6.5%	12,278 (60.16)	6,396 (60.86)	5,882 (59.41)
Fasting glucose >140 mg/dl	772 (3.78)	422 (4.02)	350 (3.54)
Nonfasting glucose >200 mg/dl	9,751 (47.78)	4,880 (46.44)	4,871 (49.20)
Number detected by single criterion:			
Diagnosis code alone	2,748 (13.46)	1,498 (14.25)	1,250 (12.63)
Medications alone	1,994 (9.77)	935 (8.90)	1,059 (10.70)
Hgb A1C \geq6.5% alone	686 (3.36)	365 (3.47)	321 (3.24)
Fasting glucose >140 mg/dl alone	26 (0.13)	17 (0.16)	9 (0.09)
Nonfasting glucose >200 mg/dl alone	0 (0)	0 (0)	0 (0)
Total diagnosed by single criterion	5,454 (26.72)	2,815 (26.79)	2,639 (26.66)
Number detected by multiple criteria:			
2 criteria	4,269 (20.92)	2,174 (20.69)	2,095 (21.16)
3 criteria	4,319 (21.16)	2,256 (21.47)	2,063 (20.84)
4 criteria	5,820 (28.52)	2,967 (28.23)	2,853 (28.82)
5 criteria	547 (2.68)	297 (2.83)	250 (2.53)
Total diagnosed by 2 or more criteria	14,955 (73.28)	7,694 (73.21)	7,261 (73.34)

Figures

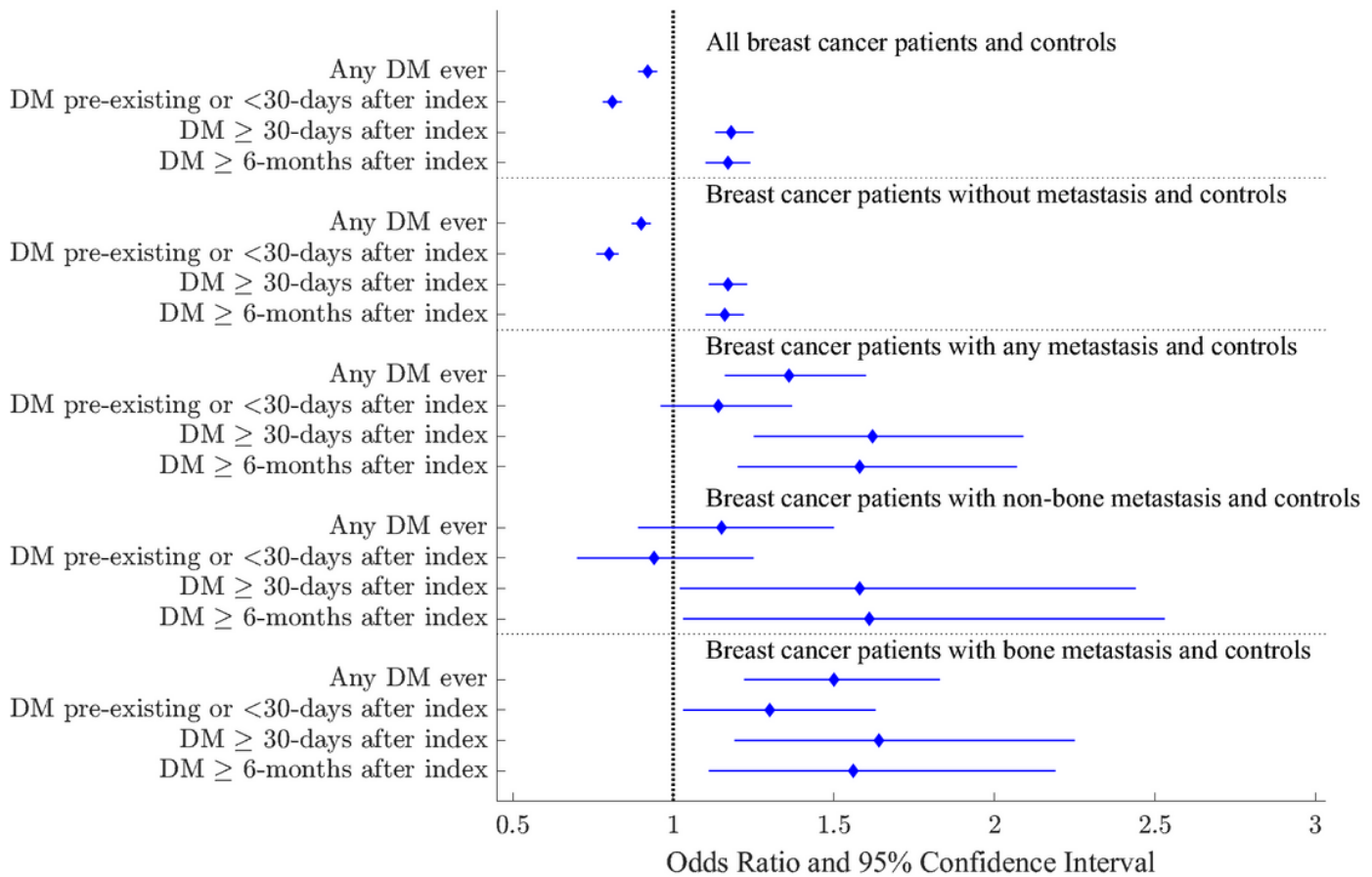


Figure 1

Odds ratio for diabetes mellitus (DM) between breast cancer patients without and with metastases, compared to age and race matched controls.