Diabetes, Abnormal Glucose, Dyslipidemia, Hypertension and Risk of Inflammatory and Other Breast Cancer

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Abstract

Background: Obesity has been associated with substantially higher risk of inflammatory breast cancer (IBC) than other breast cancer. Here, we assess whether comorbidities of obesity, namely diabetes, abnormal glucose, dyslipidemia, and hypertension, are differentially related to risk of inflammatory breast cancer and other breast cancers by tumor stage at diagnosis (localized/regional/distant/unstaged). Methods: We used linked SEER-Medicare data, with female breast cancer cases aged 66+ years identified by SEER registries (years 1992-2011). We divided first breast cancers into IBC (N=2306), locally advanced non-IBC (LABC) (N=10347), and other (N=197276). We selected female controls (N=200,000) from a stratified 5% random sample of Medicare recipients alive and breast cancer free. We assessed exposures until 12 months before diagnosis/selection using Medicare claims data. We estimated odds ratios (ORs) and 99.9% confidence intervals (CI) using unconditional logistic regression. Results: Diabetes was associated with increased risk of distant IBC (98.5% of IBC cases) (OR 1.44; 99.9% CI 1.21-1.71), distant (OR 1.24; 99.9% CI 1.09-1.40) and regional (OR 1.29 (99.9% CI 1.14-1.45) LABC, and distant (OR 1.23; 99.9% CI 1.10-1.39) and unstaged (OR 1.32; 99.9% CI 1.18-1.47) other breast cancers. Dyslipidemia was associated with reduced risk of IBC (OR 0.80; 95% CI 0.67-0.94) and other breast cancers except localized disease. Results were similar by tumor estrogen receptor status. Abnormal glucose levels and hypertension had little association with risk of any tumor type. Conclusion: Associations with diabetes and dyslipidemia were similar for distant stage IBC and other advanced tumors. Impact: If confirmed, such findings could suggest avenues for prevention.

Introduction

Inflammatory breast cancer (IBC) is a rare, poorly understood and particularly aggressive form of locally advanced breast cancer. It is characterized by diffuse erythema and edema and peau d'orange involving the majority of the breast, often with no underlying tumor mass (1-2). IBC constitutes approximately 2% of breast cancer cases in the United States, but accounts for 7% of breast cancer deaths (3). Other forms of locally advanced, non-IBC with direct invasion of the dermis or ulceration of the skin of the breast appear to be a distinct biologic entity from IBC with respect to clinical presentation, demographics, and tumor characteristics (4).

Few studies have examined whether the etiology of IBC differs from that of other types of breast cancer. In the largest epidemiologic study of IBC to date, obesity (a body mass index (BMI) ≥ 30 kg/m^2) *versus* normal BMI was associated with a three-fold or greater increase in risk of IBC in both pre- and post-menopausal women, significantly larger than the small increases in risk for other locally advanced breast cancer and other invasive postmenopausal breast cancer (5). These findings were consistent with a much smaller case-case study (6). First-degree family history of breast cancer and greater mammographic density were associated with increased IBC risk in a manner similar to non-inflammatory breast cancer (5). In contrast, associations with education level and age at first birth differed for IBC and other breast cancers of the same ER status (5).

In 2012, the U.S. National Cancer Institute introduced an initiative to determine how obesity, which has been linked to increase risk of breast cancer overall (7), promotes cancer development (8), with the hope that determining the molecular mechanisms could identify new ways to prevent and treat cancer. IBC and obesity have also been called "two of the most perplexing

problems in breast cancer." (9).

In previous studies of obesity and IBC, information on comorbidities of obesity, such as diabetes and the metabolic syndrome, were not available. Both of these conditions have themselves been linked to modest increases in breast cancer risk (10, 11). In this analysis using SEER-Medicare data, we assess the relationship between diabetes and some components of the metabolic syndrome, namely dyslipidemia, abnormal glucose (a diagnosis that excludes diabetes), and hypertension, on risk of IBC, other locally advanced breast cancer (LABC), and other invasive breast cancer without direct extension to the chest wall and/or skin of the breast (henceforth called other breast cancer), among women ages 66 years or older. We also accounted for stage at diagnosis of these tumor types. Elevated waist circumference, which is a component of the metabolic syndrome, and BMI are not routinely recorded in SEER-Medicare data, so we were unable to fully address risk associated with the metabolic syndrome itself and obesity, although we used the best available surrogate variables in supplemental analyses.

Materials and Methods

We developed a case-control study within the SEER-Medicare linked database (http://healthcaredelivery.cancer.gov/seermedicare/), with cases identified by SEER registries and information on medical exposures obtained from linked SEER-Medicare claims data (12). Medicare claims data included Part A coverage for hospital, skilled nursing facility, hospice and some home health care, as well as part B claims for physician and outpatient services (carried by about 96% of elderly part A beneficiaries). Almost 97% of persons age 65 and over in the United States are covered by Medicare.

The study was limited to females, aged 66 years of age or older (to insure that subjects had sufficient time to accrue exposure information) with a minimum of 13 months of Medicare Part A and Part B preceding cancer diagnosis/selection. Months when subjects were enrolled in a health maintenance organization (HMO) were excluded because HMOs do not routinely submit individual claims. First breast cancers diagnosed between January 1, 1992 and December 31, 2011 were identified from 13 SEER registries and those diagnosed from January 1, 2000 to December 31, 2011 were identified from 18 SEER registries. Reasons for case exclusions are shown in Table 1. Cases were divided into IBC (N = 2306), LABC (N = 10347), and other breast cancers (N = 197276) (defined in Table 2). Estrogen receptor (ER) status and historic stage were available from the SEER registry data.

A total of 200,000 female controls were selected from the 5% random sample of Medicare recipients included in the SEER-Medicare database (12). Controls were frequency-matched to the calendar year of diagnosis and age distribution in 5-year categories of all breast cancer cases and were alive and breast cancer free as of July 1 of the calendar year of selection (12).

The following medical conditions were our exposures of interest: diabetes, abnormal glucose (excludes diabetes), dyslipidemia, and hypertension (Table 2). Because no specific ICD-9-CM code exists for elevated waist circumference and BMI is generally not recorded in Medicare claims, we were unable to fully assess risk associated with obesity and the metabolic syndrome. However, we used ICD-9-CM codes 278 (overweight, obesity, and other hyperalimentation), 783.1 (abnormal weight gain), and V77.8 (screening for obesity) to create a surrogate "obesity"

variable that we used for adjustment and in a definition of metabolic syndrome for supplemental analyses. We defined medical conditions as present if they met the claims definition at least 12 months prior to cancer diagnosis or selection. This 12-month window was chosen to minimize the potential effects of the symptoms or signs of breast cancer on the diagnosis of exposures, while still ensuring that all participants had at least one month out of the 13 months of Medicare coverage required for entrance into the study to assess exposure. ICD-9-CM diagnosis codes for both primary and secondary diagnoses were considered if there was at least one inpatient or two outpatient/physician claims with a minimum of 30 days between claims. We did supplemental analyses in which we excluded diagnoses made within a 24-month window before diagnosis/selection to further minimize any potential effect of incipient breast cancer on development or diagnosis of the medical conditions of interest.

We estimated odds ratios (OR) and confidence intervals(CIs) using unconditional logistic regression analyses. We present ORs with the following variables included in all models: age (continuous), year of diagnosis/selection in single years, race/ethnicity (white, black, mixed, Asian, Hispanic, North American Indian, other, unknown), grouped SEER region (western, northeastern, north-central, and southern), history of mammography (any mammography claim recorded from 12 months to a maximum of 48 months before case-control selection), number of physician visits between study entry and earliest of diagnosis/selection date (continuous). In addition, we included diabetes, abnormal glucose, dyslipidemia and hypertension individually and all together in the models. In supplemental analyses we added the surrogate "obesity" variable to the models. Our main analyses divided IBC, LABC, and other breast cancer cases by stage (local, regional, distant, unstaged) and additionally by the ER status of the tumors. We did

supplemental analyses of breast cancer overall compared to controls for comparison with other studies and analyses for each breast cancer subgroup (IBC, LABC, other breast cancers) without regard to stage. We also did sensitivity analyses excluding blacks, who have higher rates of IBC.

We accounted for multiple comparisons by using $\alpha=0.0009$ in calculating CIs. This α level was based on the Bonferroni correction ($\alpha=0.05/56$, with 56 the number of multivariate model comparisons for 7 case groups (by cancer type and stage) and 4 variables (diabetes, abnormal glucose, dyslipidemia, and hypertension) plus 14 case groups (by cancer type, stage, and ER-status) and 2 variables (diabetes and dyslipidemia). All CIs presented in the manuscript are 99.9% CIs. References in the text to statistical significance refer to these CIs excluding 1.00, unless otherwise noted. Statistical analyses were performed using SAS version 9.3 (SAS Institute).

Results

Approximately 67% of first breast cancer cases aged 66 and over, diagnosed between 1992 and 2011 were included in our analysis (Table 1). The major reasons for exclusion were not having a Medicare claim between their entry date and 1 year prior to breast cancer diagnosis (69% of exclusions) and not having 13 months of Medicare Part A, Part B, and no HMO between entry and diagnosis (24%) (Table 1). Those excluded for these reasons had a mean age of diagnosis of 74.4 years. The median duration of coverage among the 71,116 without a Medicare claim was approximately 29 months. Of cases excluded for these reasons, 1253 were IBC, 5,600 were LABC, and 88,887 were other breast cancers.

The stage and estrogen receptor status of included cases are shown in Table 3. Nearly all IBC cases were diagnosed at distant stage (98.5%), whereas LABC cases were diagnosed at both regional (46.5%) and distant (53.1%) stages and other breast cancer cases were diagnosed primarily at localized (71.4%) and regional (23.0%) stages. A higher percentage of IBC cases with known ER-status were ER-negative (ER-) (41.8%) than were other locally advanced (24.1%) cases or other breast cancer cases (15.2%). The stage distributions of the excluded cases were similar to those included, except that a somewhat higher percentage of excluded LABC cases were distant stage (59%). The ER status of the excluded cases was similar to those included (data not shown in Table).

Characteristics of controls and other characteristics of cases are shown in Table 4. Notably, the mean number of visits between eligibility and end-date was lower for IBC cases, LABC cases, and distant and unstaged other breast cancers than it was for controls and localized and regional other breast cancers. This variable and year of diagnosis/selection were negative confounding variables of some of the associations. A higher percentage of IBC, LABC, and distant and unstaged other breast cancer cases were black compared to localized breast cancer cases and controls. Among the controls, 22.4% had diabetes, 6.0% abnormal glucose, 50.9% dyslipidemia and 65.6% hypertension. Only 5.4% were classified as being “obese” using our surrogate variable (not shown in table). For all four variables, prevalence estimates were lower in earlier years than later years.

ORs (99.9% CIs) associated with diabetes, abnormal glucose, dyslipidemia, and hypertension, after mutual adjustment, for all breast cancers combined versus controls were 1.02 (99.9% CI 0.99-1.05), 1.02 (99.9% CI 0.98-1.07), 1.02 (99.9% CI 1.00-1.05), and 1.03 (99.9% CI 1.01-1.06), respectively.

ORs associated with diabetes, abnormal glucose, dyslipidemia, and hypertension both unadjusted and adjusted for each other by case group and stage *versus* controls are shown in Table 5. There were too few cases of IBC with stages other than distant to include in the table. Diabetes was associated with statistically significant increases in risk of distant IBC, regional and distant LABC, and distant and unstaged other breast cancer both with and without adjustment for the other medical conditions shown in the table. In contrast, diabetes was associated with a small but statistically significant decrease in risk of local stage breast cancers. Dyslipidemia was associated with statistically significant reductions in risk of all tumor types except for local other breast cancers, both before and after adjustment for other medical conditions, although the reduction in risk was minimal for regional other breast cancers. Abnormal glucose levels were not associated with risk of any tumor types, while hypertension was associated with slight reductions in risk of regional LABC and local breast cancer. Findings in Table 5 were either unchanged or very slightly attenuated towards the null after additional adjustment for the surrogate "obesity" variable, which itself was associated with ORs of 1.45 (99.9% CI 1.11-1.88) for distant IBC, 1.24 (99.9% CI 1.01-1.53) for regional LABC, 1.23 (99.9% CI for 0.97-1.53) for distant LABC, 1.02 (99.9% CI 0.97-1.07) for local other breast cancer,1.04 (99.9% CI 0.97-1.12) for regional other breast cancer, 1.16 (99.9% CI 0.97-1.38) for distant other breast cancer, and 1.13 (99.9% CI 0.93-1.37) for unstaged other breast cancer after adjustment for the variables

shown in the table. Results were similar when diagnoses within 24 months of cancer diagnosis/selection were excluded from the exposure variables (not shown).

Blacks compared to non-Hispanic whites were at increased risk of all tumor types except for localized and regional other breast cancers after adjustment for all medical conditions of interest. Results in Table 5 were very similar after blacks were eliminated from the analyses (not shown).

In Table 6 we show ORs associated with a cross classification of diabetes and dyslipidemia for all the case groups shown in Table 5. For distant IBC associations with diabetes were evident both in the absence and presence of dyslipidemia (OR = 1.30 and OR = 1.17/0.76 = 1.54, respectively). This was also true for unstaged other breast cancers. For other case groups, any association with diabetes was evident primarily in those with dyslipidemia (e.g. for regional LABC OR = 0.98/0.65 = 1.51). The inverse association with dyslipidemia was stronger in the absence of diabetes for all case groups except unstaged other disease.

After adjustment for diabetes, metabolic syndrome was not associated with risk of any breast cancer subtype.

ORs for ER+ and ER- IBC cases were similar as were those for ER+ and ER- LABC and other breast cancer cases by stage (Supplemental Table 1). Numbers of cases for these analyses are shown in Supplemental Table 2.

Discussion

Among Medicare participants aged 66 years of age and older, diabetes was associated with increased risk and dyslipidemia with decreased risk of IBC in women diagnosed with distant metastases, LABC diagnosed at a regional or distant stage, and other invasive breast cancers without direct extension to the chest wall and/or skin of the breast diagnosed at a distant stage or unstaged. Notably, diabetes and dyslipidemia were not associated with marked increases or decreases in risk of localized and regional other breast cancers. Abnormal glucose levels (the diagnosis of which captures less severe metabolic abnormalities than diabetes) and hypertension were not associated with marked increases or decreases in risk of any tumor type.

Previous meta-analyses have reported small associations between diabetes (10), prediabetes (13), and possibly elevated fasting glucose (14) and breast cancer risk. Our results for all breast cancers combined do not show these small increases in risk, but the increases in risk we found for later stage disease are consistent with other analyses by stage (15-17). Two meta-analyses reported little association between increasing levels of total cholesterol (18,19) and breast cancer risk, but reported an inverse association when preclinical bias was eliminated (18) or for HDL-C in postmenopausal women (19). Our results for dyslipidemia and regional and distant breast cancer, but not localized breast cancer, are consistent with these findings. To our knowledge, there are no analyses of these factors with relationship to risk of inflammatory or other locally advanced breast cancer, specifically.

In our analysis, the increased risk of IBC associated with diabetes was evident in those both with and without dyslipidemia, as was that for unstaged other breast cancers. For other case groups any increased risk associated with diabetes was evident only among those with dyslipidemia. Conversely, dyslipidemia in general was associated with greater reductions risk in the absence of diabetes. These differences could reflect chance findings or complex inter-relationships among metabolic disturbances and breast cancer. To our knowledge, similar findings have not been reported elsewhere.

Our results suggest that diabetes increases the aggressiveness of breast cancer. A number of biologic mechanisms have been hypothesized to link diabetes and cancer, namely effects of hyperglycemia, hyperinsulinemia, and inflammation (20). Chronic low-grade inflammation and activation of the immune system have also been hypothesized to link obesity, the metabolic syndrome and type 2 diabetes (21). The designation "inflammatory" breast cancer was derived from features of the disease such as erythema that are unique to this form of breast cancer. However, the relationship between inflammation and the development, proliferation, and progression of IBC is of great interest, but not well defined (22). Although obesity and diabetes are associated with increased plasma levels of inflammatory factors, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1β (19-20) that have been differentially overexpressed in IBC (22), we did not find major differences in the association of diabetes with IBC and other types of advanced breast cancer. We cannot rule out that medications used to treat diabetes may have influenced the results, but such medications, including insulin, metformin, specific sulfonylureas, thiazolidinediones, and DPP-4 inhibitors may possess anti-inflammatory properties (23, 24) and, consequently, would be expected to reduce risk.

Metformin has not been consistently linked to risk of breast cancer (25), nor have insulin and insulin analogs (26), although a modest increased risk of breast cancer with glargine *vs*. non-glargine treatment was reported.

The inverse association with dyslipidemia for more advanced breast cancers could reflect anti-oxidative and anti-inflammatory properties of HDL-C (19). Although statins, cholesterol lowering agents that have also demonstrated powerful anti-inflammatory effects (27), have not been associated with breast cancer risk in a meta-analysis (28), it is nevertheless possible that the reduction in risk of IBC and other breast cancers among those with dyslipidemia is related to the use of statins.

Major strengths of this analysis are the large number of IBC cases, the inclusion of other types of breast cancer according to stage at diagnosis, and the availability of information on exposures not assessed previously for IBC risk. Cases and controls are also population-based and, because of the widespread coverage by Medicare, representative of elderly adults living in the SEER areas.

Potential limitations of this analysis include the relatively limited window of exposure ascertainment, particularly in the youngest women and in the earliest years of diagnosis/selection. On average approximately 6 years of medical records were available. Thus, the SEER-Medicare data do not allow determination of original dates of diagnosis for the exposures of interest. Diabetes and dyslipidemia, for instance, could have been first diagnosed

many years before breast cancer diagnosis or more recently. Moreover, we excluded from the analysis many cases and non-cases with Medicare coverage but no claims filed or with insufficient duration of coverage. The cases excluded for these reasons tended to be several years younger on average than those included and to have shorter duration of Medicare coverage, but were not otherwise greatly different with regard to stage and estrogen receptor status. This limited ascertainment window and exclusions could lead to exposure misclassification. It is reassuring, however, that the prevalence estimates for three of the exposures considered in this analysis are relatively consistent with estimates from national surveys, albeit the time periods covered in our analysis and these surveys were not exactly the same. According to the National Health and Nutrition Examination Survey 1999-2004, the prevalence of dyslipidemia, diabetes, and hypertension in women 65 years of age and older were 58.7, 19.5, and 76.6 percent, respectively (29). These compare to prevalence estimates among the controls in our study of 50.9, 22.4, and 65.6 percent. National estimates for prevalence of abnormal glucose levels, such as impaired fasting glucose, vary widely depending on the definition used (30). Because the time period for exposure ascertainment in our study covered a major change in definition of impaired fasting glucose by the American Diabetes Association in 2003, we were unable to compare out estimates to national estimates.

Another potential limitation is the possibility that the medical conditions of interest could have been influenced by the cancer diagnoses themselves, particularly in patients with distant disease. We attempted to address this issue by excluding diagnoses of these conditions in the 12 months prior to cancer diagnosis and the equivalent time period for controls. We did further analyses excluding diagnoses of the conditions of interest in the 24 months prior to cancer

diagnosis/selection, with no change in the results. We also limited the analyses to first breast cancers as ascertained from the SEER data.

Perhaps the major limitation of this analysis is the absence of information on BMI and consequently on overweight and obesity. Among studies included in the meta-analysis for diabetes (10), the hazard ratio for the study receiving nearly 70 percent of the weight was reduced from 1.29 to 1.12 when adjusted for BMI and other variables (31), suggesting that the estimates for diabetes and possibly other conditions included in our analysis, could be significantly attenuated after adjustment for BMI. Adjustment for our surrogate "obesity" variable based on ICD-9-CM codes 278, 783.1, and V77.8 resulted in only slight attenuation of the diabetes associations. This variable, however, seriously underestimated the prevalence of obesity in this population at only 5.4 percent. In 2007-2010 the prevalence of obesity (BMI >= 30) among women 65 years of age or older was 34.7 percent based on data from the National Health and Examination Survey (32). We must conclude that the sensitivity of the variable we have used as a surrogate for "obesity" is low and that there remains confounding of the diabetes-breast cancer association by obesity in our analysis. We note, however, that in spite of the limitations of our "obesity" surrogate variable, the risks of IBC and LABC associated with this variable remained elevated and statistically significant after adjustment for diabetes, and dyslipidemia. We were also unable to adjust for other factors that have been associated with both breast cancer risk and diabetes, namely physical activity and alcohol consumption (20).

Another limitation of the SEER-Medicare database is the availability of prescription data for only the years 2007-2011, so we did not include analyses of prescription data in our study. Finally, we were unable to examine these associations among pre-menopausal women or younger peri/postmenopausal women. However, in a previous case-control study, results for obesity and other risk factors for IBC did not vary according to menopausal status (5).

In conclusion, these data are the first report of associations between diabetes and dyslipidemia and risk of IBC and LABC. Results show increases in risk with diabetes and decreases in risk with dyslipidemia that are generally similar to those for similarly staged other breast cancers. Whether these associations are independent of obesity remains unclear. Our results suggest potentially important interactions between diabetes, dyslipidemia and breast cancer risk, which need further study. It is also unknown whether the medical conditions themselves or their treatments are associated with risk. Furthermore, associations need to be examined in younger women, particularly given that IBC is on average diagnosed at a younger age than other types of breast cancer (1) and associations with BMI and breast cancer in general are known to vary with menopausal status. Confirmation of these findings in other studies would lend further support to a possible different etiology of advanced stage breast cancers with regard to metabolic and inflammation related factors. Further understanding of these relationships could offer avenues for prevention.

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References

1. Anderson WF, Schairer C, Chen BE, Hance KW, Levine PH. Epidemiology of inflammatory breast cancer (IBC). Breast Dis. 2005, 2006;22:9–23.
2. Greene FL, Page DL, Fritz A, Balch CM, Haller DG, Morrow M. Breast. In: AJCC Cancer Staging Manual. 6th ed New York: Springer-Verlag; 2002. p. 225–6.
3. Hance KW, Anderson WF, Deveas SS, Young HA, Levine PH. Trends in inflammatory breast cancer incidence and survival: The Surveillance, Epidemiology, and End Results Program at the National Cancer Institute. J Natl Cancer Inst. 2005;97:966-74.
4. Anderson WF, Chu KC, Chang S. Inflammatory breast carcinoma and noninflammatory locally advanced breast carcinoma: distinct clinicopathologic entities? J Clin Oncol. 2003;21:2254–9.
5. Schairer C, Li Y, Frawley P, Graubard BI, Wellman RD, Buist DS, et al. Risk factors for inflammatory breast cancer and other invasive breast cancers. J Natl Cancer Inst. 2013;105:1373-84.
6. Chang S, Buzdar AU, Hursting, SD. Inflammatory breast cancer and body mass index. J Clin Oncol. 1998;16:3731–5.
7. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status – A meta-analysis. Int J Cancer 2009;124:698-712.
8. Varmus H, Harlow E. Provocative questions in cancer research. Nature 2012;481:436–7.
9. Amiri-Kordestani L, Kamangar F, Zujewski JA. Inflammatory breast cancer: yet another risk of the obesity epidemic? J Natl Cancer Inst. 2013;105:1340-2.
10. De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg. 2013;100:1421-9.
11. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, et al. Metabolic syndrome and postmenopausal breast cancer: systemic review and meta-analysis. Menopause 2013;20:1301-9.
12. Engels EA, Pfeiffer RM, Ricker W, Wheeler W, Parsons R, Warren JL. Use of surveillance, epidemiology, and end results-medicare data to conduct case-control studies of cancer among the US elderly. Am J Epidemiol. 2011;174:860–70.
13. Huang Y, Cai X, Qiu M, Chen P, Tang H, Hu Y, et al. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia 2014;57:2261-9.
14. Boyle P, Koechlin A, Pizot C, Boniol M, Robertson C, Mullie P, et al. Blood glucose concentrations and breast cancer risk in women without diabetes: a meta-analysis. Eur J Nutr. 2013;52:1533-40.
15. Lipscombe LL, Fischer HD, Austin PC, Fu L, Jaakkimainen RL, Ginsburg O, et al. The association between diabetes and breast cancer stage at diagnosis: a population-based study. Breast Cancer Res Treat. 2015;150:613-20.

16. Hou G, Zhang S, Zhang X, Wang P, Hao X, Zhang J. Clinical pathological characteristics and prognostic analysis of 1,013 breast cancer patients with diabetes. Breast Cancer Res Treat. 2013;137:807-16.
17. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. Med Care 2005;43:132-40.
18. Touvier M, Fassier P, His M, Norat T, Chan DSM, Blacher J, et al. Cholesterol and breast cancer risk: a systematic review and meta-analysis of prospective studies. British J Nutrition 2015;114:347-57.
19. Ni H, Liu H, Gao R. Serum lipids and breast cancer risk: a meta-analysis of prospective cohort studies. PLoS ONE [serial on the internet]. 2015 Nov [cited 2016 Nov 16];10(11):[15 p.]. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0142669
20. Giovannucci E, Harlah DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674-85.
21. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105:141-50.
22. Fouad TM, Kogawa T, Reuben JM, Ueno NT. The role of inflammation in inflammatory breast cancer. In:Aggarwal BB et al. eds. Inflammation and Cancer, Advances in Experimental Medicine and Biology. Basel:Springer; 2014. p. 53-73.
23. Knudsen SH, Pedersen BK. Targeting inflammation through a physical active lifestyle and pharmaceuticals for the treatment of type 2 diabetes. Curr Diab Rep. 2015;15:82-91.
24. Salazar JJ, Ennis WJ, Koh TJ. Diabetes medications: impact on inflammation and wound healing. Journal of Diabetes and Its Complications 2015;30:746-52.
25. Soranna D, Scotti L, Zambon A, Bosetti C, Grassi G, Catapano A, et al. Cancer risk associated with metformin and sulfonylurea in type 2 diabetes: a meta-analysis. The Oncologist 2012:17:813-22.
26. Karlstad Ø, Starup-Linde J, Vestergaard P, Hjellvik V, Bazelier MT, Schmidt MK, et al. Use of insulin and insulin analogs and risk of cancer-systematic review and meta-analysis of observational studies. Current Drug Safety 2013;8:333-48.
27. Jain MK, Ridker PM. Anti-inflammatory effects of statins:clinical evidence and basic mechanisms. Nature Reviews|Drug Discovery 2005;4:977-87.
28. Undela K, Srikanth V, Bansal D. Statin use and risk of breast cancer: a meta-analysis of observational studies. Breast Cancer Res Treat. 2012;135:261-9.
29. McDonald M, Hertz RP, Unger AN, Lustik MB. Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among United States Adults Aged 65 and older. J Gerontol A Biol Sci Med Sci. 2009;64A:256-63.
30. Prevalence of diabetes and impaired fasting glucose in adults – United States, 1999-2000. MMWR 2003;52:833-7.
31. Redaniel MT, Jeffreys M, May MT, Ben-Shlomo Y, Martin RM. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. Cancer Causes Control 2012;23:1785-95.

32. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010;303:235-41.

Table 1. Reasons for breast cancer exclusion

First breast cancer cases aged 66 and over, diagnosed between 1992 and 2011	N = 313159
Reason for Exclusion	**# Excluded**
Cases diagnosed only at autopsy or death	3431
Cases without a known month of cancer diagnosis	1636
Not living in the included SEER registries at the time of diagnosis	2408
Did not have a Medicare claim between their entry date and 1 year prior to the breast cancer diagnosis	71166
Did not have 13 months of Medicare Part A, Part B, and no HMO between entry and diagnosis	24574
Death date was prior to cancer date	15
Number of breast cancers included in the analysis	N = 209929

Table 2 Codes used to define breast cancer groups and medical conditions

Outcomes	**Codes**
Inflammatory breast cancer (IBC)	ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant) and Site and Morphology Histologic Type ICD-0-3 = 8530 or Extent of Disease - Historic EOD 10 – extent (1998-2003) = 70 or Extent of Disease – CS.CS extension (2004+) = 71,73, 600, 710, 715, 720, 725, 730, 750, 780 or AJCC TNM = T4d
Locally Advanced Non-Inflammatory Breast Cancer (LABC)	ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant) and Site and Morphology Histologic Type ICD-0-3 ^= 8530 and (Extent of Disease - Historic EOD 10 – extent (1998-2003) = 40, 50, 60 or Extent of Disease – CS.CS extension (2004+) = 400, 410, 510, 512, 514, 516, 518-520, 575, 580, 585, 605, 610, 612-613, 615, 620, 680 or Stage – AJCC.Derived AJCC Stage Group, 7th ed (2010+) = IVA, IVA1, IVA2, IVB, IVC or Stage – AJCC.AJCC stage 3rd edition (1988-2003) = 40, 41, 42
Other invasive breast cancers	ICD-O-3 site codes C50.0-C50.9 where behavior = 3 (malignant) and not included in IBC and LABC groups
Exposures	
Diabetes	ICD-9-CM diagnosis codes 250; 357.2x for polyneuropathy in diabetes; 362.0x for diabetic retinopathy; 366.41 for diabetic cataract; 249.xx for secondary diabetes.
Abnormal glucose	ICD-9 = 790.2x (abnormal glucose) or 790.6 (other abnormal blood chemistry)
Dyslipidemia	ICD-9 = 272
Hypertension	ICD-9 = 401-404 or 405 (secondary hypertension)
Variable created for supplemental analyses	
Surrogate for “obesity”	ICD-9 278, 783.1, V77.8
Metabolic Syndrome	ICD-9-CM diagnosis code 277.7 or presence of at least three of the following conditions: elevated waist circumference/central obesity (we use obesity (ICD-O 278, 783.1, V77.8) as a surrogate for elevated waist circumference); dyslipidemia (ICD-9 = 272), hypertension (ICD-9 = 401-404 or 405 (secondary hypertension)), and impaired fasting glucose (790.2x or 790.6).

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Table 3. Tumor characteristics of inflammatory breast cancer (IBC), locally advanced non-inflammatory breast cancer (LABC), and other invasive breast cancer cases

Characteristic	IBC N = 2306	LABC N = 10347	Other invasive breast cancer N=197276
	N (%)[a]		
Stage			
Localized	3 (0.1)	0	140803 (71.4)
Regional	22 (1.0)	4806 (46.5)	45402 (23.0)
Distant	2271 (98.5)	5490 (53.1)	4758 (2.4)
Unstaged	10 (0.4)	51 (0.5)	6313 (3.2)
ER Status			
Positive	1071 (57.6)[b]	5758 (75.5)[b]	142477 (84.6)[b]
Negative	778 (41.8)[b]	1838 (24.1)[b]	25524 (15.2)[b]
Borderline	11 (0.6)[b]	33 (0.4)[b]	420 (0.3)[b]
Unknown	446 (19.3)[c]	2718 (26.3)[c]	28855 (14.6)[c]

[a] Percentages don't add to 100 because of rounding.
[b] Percentage of those with known ER status.
[c] Percentage of all breast cancers of that type.

Table 4. Characteristics of controls and inflammatory breast cancer (IBC), locally advanced non-inflammatory breast cancer (LABC), and other invasive breast cancer cases by stage.

	Controls	IBC	LABC		Other Breast Cancer			
	N = 200,000	Distant N = 2271	Regional N = 4806 # (%)	Distant N = 5490 # (%)	Local N = 140803 # (%)	Regional N = 45402 # (%)	Distant N = 4758 # (%)	Unstaged N = 6313 # (%)
Mean age (years)	76.8	77.4	80.4	77.7	76.4	76.2	78.0	81.8
Mean year of diagnosis/selection	2003	2003	2003	2001	2003	2003	2007	2003
Median (minimum, maximum) months between eligibility and diagnosis/selection	70.0 (13.0, 138.1)	72.0 (13.0, 143.1)	75.0 (13.0, 143.1)	66.0 (13.0, 143.1)	72.0 (13.0, 143.1)	70.0 (13.0, 143.1)	77.0 (13.0, 143.1)	71.0 (13.0, 143.1)
Mean number of visits between eligibility and end date	109.5	99.9	95.9	79.7	123.8	122.9	89.8	97.3
Black N (%)	16065 (8.0)	262 (11.5)	557 (11.6)	603 (11.0)	9199 (6.5)	3984 (8.8)	567 (11.9)	633 (10.0)
Diabetes N (%)	44755 (22.4)	619 (27.3)	1203 (25.0)	1073 (19.5)	29863 (21.2)	10732 (23.6)	1439 (30.2)	1544 (24.5)
Abnormal glucose N (%)	12080 (6.0)	123 (5.4)	273 (5.7)	173 (3.2)	8653 (6.2)	2728 (6.0)	399 (8.4)	394 (6.2)
Dyslipidemia N (%)	101828 (50.9)	1014 (44.7%)	1939 (40.4)	1622 (29.5)	74765 (53.1)	22869 (50.4)	2831 (59.5)	2489 (39.4)
Hypertension N (%)	131147 (65.6)	1445 (63.6)	3092 (64.3)	3042 (55.4)	92355 (65.9)	29928 (65.9)	3473 (73.0)	4179 (66.2)

Table 5. Odds ratios (ORs) (99.9% confidence intervals (CI)) for inflammatory breast cancer (IBC), locally advanced non-inflammatory breast cancer (LABC), and other invasive breast cancer cases by stage for studied medical conditions

	IBC	LABC		Other Breast Cancer			
	Distant N = 2271	Regional N = 4806	Distant N = 5490	Local N = 140803	Regional N = 45402	Distant N = 4758	Unstaged N = 6313
	OR (99.9% CI)[b]	OR (99.9% CI)[b]	OR (99.9% CI)[b]	OR (99.9% CI)[b]	OR (99.9% CI)[b]	OR (99.9% CI)[b]	OR (99.9% CI)[b]
Diabetes							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes[a]	1.34 (1.13-1.58)	1.17 (1.04-1.32)	1.17 (1.03-1.31)	0.92 (0.89-0.95)	1.03 (0.98-1.07)	1.16 (1.03-1.29)	1.25 (1.13-1.39)
Yes[b]	1.44 (1.21-1.71)	1.29 (1.14-1.45)	1.24 (1.09-1.40)	0.92 (0.89-0.95)	1.04 (0.99-1.09)	1.23 (1.10-1.39)	1.32 (1.18-1.47)
Abnormal glucose							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes[a]	0.89 (0.65-1.22)	0.89 (0.71-1.10)	0.82 (0.63-1.07)	0.98 (0.93-1.03)	0.95 (0.88-1.03)	0.86 (0.72-1.03)	1.07 (0.89-1.28)
Yes[b]	0.87 (0.63-1.19)	0.89 (0.72-1.11)	0.83 (0.64-1.08)	0.99 (0.95-1.04)	0.95 (0.88-1.03)	0.86 (0.71-1.03)	1.05 (0.88-1.26)
Dyslipidemia							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes[a]	0.83 (0.70-0.97)	0.72 (0.64-0.81)	0.73 (0.66-0.82)	1.02 (1.00-1.05)	0.95 (0.91-0.98)	0.81 (0.73-0.90)	0.78 (0.70-0.86)
Yes[b]	0.80 (0.67-0.94)	0.72 (0.64-0.81)	0.70 (0.63-0.79)	1.05 (1.02-1.08)	0.94 (0.90-0.98)	0.79 (0.71-0.89)	0.75 (0.68-0.83)
Hypertension							
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes[a]	0.93 (0.79-1.09)	0.85 (0.76-0.95)	1.00 (0.91-1.11)	0.96 (0.94-0.99)	1.00 (0.96-1.04)	0.92 (0.81-1.03)	0.95 (0.86-1.05)
Yes[b]	0.93 (0.78-1.10)	0.89 (0.79-1.00)	1.05 (0.95-1.17)	0.97 (0.94-0.99)	1.01 (0.97-1.05)	0.95 (0.84-1.09)	0.97 (0.88-1.08)

[a] Variables included in the model: age, race/ethnicity, region, year of selection/diagnosis, number of visits between eligibility and end date, mammogram.

[b] Variables included in the model: age, race/ethnicity, region, year of selection/diagnosis, number of visits between eligibility and end date, mammogram, all medical conditions in the table.

[c] Confidence intervals assuming $\alpha = .0009$ ($\alpha = 0.05/56$ multivariate model comparisons in tables 5 and Supplemental Table 1)

Table 6. ORs (99.9% confidence intervals (CIs)) associated with the cross-classification of diabetes and dyslipidemia for IBC, LABC, and other breast cancers by stage.

	IBC	LABC		Other Breast Cancer			
	Distant N = 2271	Regional N = 4806	Distant N = 5490	Local N = 140803	Regional N = 45402	Distant N = 4758	Unstaged N = 6313
	OR[a] (99.9% CI)	OR[a] (99.9% CI)	OR[a] (99.9% CI)	OR[a] (99.9% CI)	OR[a] (99.9% CI)	OR[a] (99.9% CI)	OR[a] (99.9% CI)
Neither diabetes nor dyslipidemia	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Dyslipidemia but no diabetes	0.76 (0.63-0.92)	0.65 (0.57-0.75)	0.66 (0.58-0.75)	1.04 (1.01-1.07)	0.93 (0.89-0.98)	0.77 (0.67-0.87)	0.74 (0.66-0.83
Diabetes but no dyslipidemia	1.30 (0.99-1.71)	1.05 (0.87-1.27)	1.09 (0.91-1.29)	0.89 (0.85-0.94)	1.01 (0.94-1.09)	1.09 (0.87-1.37)	1.28 (1.10-1.50)
Both diabetes and dyslipidemia	1.17 (0.93-1.46)	0.98 (0.83-1.14)	0.94 (0.79-1.11)	0.97 (0.93-1.00)	0.98 (0.93-1.04)	0.98 (0.84-1.15)	0.99 (0.86-1.15)
p-value[b] for interaction between diabetes and dyslipidemia	0.11	<0.0001	0.0002	0.04	0.17	0.04	0.47

[a]Other variables included in the model: age, race/ethnicity, region, year of selection/diagnosis, number of visits between eligibility and end date, mammogram, abnormal glucose, and hypertension.

[b]p-value is for diabetes*dyslipidemia in a model that includes the following variables: age, race/ethnicity, region, year of selection/diagnosis, number of visits between eligibility and end date, mammogram, abnormal glucose, hypertension, diabetes, dyslipidemia, and diabetes*dyslipidemia.

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