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BRIEF REPORT

Diabetes and differences in detection of incident invasive breast cancer

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Abstract

Many women diagnosed with breast cancer have chronic conditions such as diabetes that may impact other health behaviors. Our purpose was to determine if breast cancer screening and detection differs among women with and without diabetes. We conducted a cross-sectional analysis of a retrospective cohort of women aged 52–74 years diagnosed with incident stages I–III breast cancer enrolled in an integrated health plan between 1999 and 2014 with linkage to the Surveillance, Epidemiology and End Results registry ($n = 2040$). Screening data were taken from electronic health records. We used multivariable modified Poisson regression models with robust standard errors to estimate relative risks (RR) and 95% confidence intervals (CI) for outcomes of (i) receipt of screening in the 2 years prior to diagnosis; (ii) symptom-detected breast cancer; and (iii) diagnosis of locally advanced stage III breast cancer. Compared to women without diabetes, women with diabetes were similar with respect to receipt of screening mammography (78% and 77%), symptom-detected breast cancer (46% and 49%), and stage III diagnosis (7% and 7%). In multivariable models adjusting for age and year of diagnosis, race, BMI, Charlson comorbidity score and depression diagnosis no differences were observed in the outcomes by presence of diabetes. Further investigation is warranted to determine how diabetes acts as a mediating factor in adverse breast cancer outcomes.

Keywords Breast cancer · Diabetes · Cancer screening · Mammography

Introduction

Incidences of both breast cancer [1] and comorbid conditions such as diabetes [2] increase with age, leading to a growing population of women with competing needs for preventive services such as cancer screening and chronic condition care. It is estimated that more than half of older patients diagnosed with cancer will have one or more meaningful chronic conditions such as diabetes [3] that will impact their treatment and survival [4, 5].

The 2013 Institute of Medicine report, *Delivering High Quality Cancer Care* [6], calls for greater understanding of evidence-based cancer management in older adults with comorbid conditions. The relationship between diabetes and breast cancer is complex, with each affecting the other, and it remains unclear how and why comorbid diabetes results in less favorable outcomes in women with breast cancer. Reports from observational studies suggest that fewer women with diabetes receive screening mammography [7, 8] and this may be associated with the quality of diabetes care [9]. In the Women's Health Initiative clinical trials

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[10], while rates of mammography were similar in women with and without diabetes, both adherence to breast cancer screening guidelines and risk of invasive breast cancer differed by type of diabetes treatment, also indicating possible differences in breast cancer risk by diabetes severity or by specific diabetes medications hypothesized to influence breast cancer risk [11–13].

The purpose of this study was to determine if diabetes is associated with rates of breast cancer screening and whether type of cancer differed among women diagnosed with invasive breast cancer in a population-based cohort enrolled in a large integrated healthcare delivery system. We hypothesized that women with diabetes, having competing healthcare needs, had lower adherence to breast cancer screening guidelines, thereby leading to greater occurrence of symptom-detected breast cancer (rather than screen-detected) and diagnosis of later stage invasive cancers.

Methods

We utilized data from an existing cohort of women diagnosed with an incident, stage I or II breast cancer between 1990 and 2008 in the COmmonly Used Medications and Breast Cancer Outcomes (COMBO) study at Kaiser Permanente Washington (KPWA) [14–16]. We expanded the cohort through 2014 and added stage III breast cancer cases through all years. We included women who had no bilateral disease, had a definitive surgery for their incident breast cancer, and were enrolled at KPWA for at least 2 years prior to breast cancer diagnosis. Women were enrollees at KPWA, a non-profit integrated delivery system that provides comprehensive healthcare on a pre-paid basis to approximately 650,000 individuals throughout Washington State and parts of Idaho.

We conducted a cross-sectional analysis within this retrospective cohort of women ages 52–74 years at the time of their incident, invasive (stages I–III) breast cancer diagnosis between 1999 and 2014. We restricted to women ages 52–74 years since KPWA recommendations for breast cancer screening are every 2 years starting at age 50 in the general population and every year starting at age 40 among women at high risk [17]. There is no definitive recommendation for women aged 75 years and older. Data on screening were not available at KPWA prior to 1999 so the study was limited to 1999–2014 cases.

A total of 2040 women were eligible for the cross-sectional study, with 1162 from the original COMBO study, and 878 newly identified for the expanded cohort (This study was approved by the institutional review board of the Kaiser Permanente Washington Health Research Institute.

Incident breast cancers and tumor characteristics were identified through linkage to the Cancer Surveillance System [18], a population-based cancer registry and member of the Surveillance, Epidemiology and End-Results (SEER) Program of the National Cancer Institute [19]. Patient and clinical characteristics were obtained through KPWA automated electronic health records and claims data [20], which included laboratory results, inpatient and outpatient diagnoses, procedures, health plan enrollment, pharmacy dispensings, and death (internal records, SEER, and Washington State death tapes) [21]. Additionally, data from KPWA included menopausal status [22] and linkage to the Breast Screening Recruitment and Reminder (BSRR) survey data, where approximately 98% of women aged ≥ 40 years completed a survey on factors associated with breast cancer at the time of each mammogram [23]. Data were captured from 2 years prior to breast cancer diagnosis through end of follow-up (earliest of death, disenrollment, or study end date).

The primary covariate of interest was presence of diabetes mellitus at breast cancer diagnosis. Diabetes was defined by having 1 + inpatient or 2 + outpatient International Classification of Diseases, 9th revision, Clinical Modification (ICD-9) diagnosis codes for diabetes (250.1, 250.2, 250.3, 250.8, 250.9, 250.0), any diabetes medication use (insulin and oral medications), and/or laboratory tests indicative of diabetes (HbA1c ≥ 7%, 1 fasting plasma glucose ≥ 200 mg/mL, or 2 fasting plasma glucose ≥ 126 mg/mL) in the 2 years prior to breast cancer diagnosis. Diabetes was further classified as uncontrolled during the 2 years prior by having HbA1c ≥ 8%, any fasting plasma glucose ≥ 200 mg/dL or any 2 fasting plasma glucose ≥ 126 mg/dL in 6 months. Diabetes was considered to be controlled if HbA1c and/or fasting plasma glucose were measured but did not meet any of the criteria for uncontrolled diabetes. Additional variables included age (52–59, 60–64, 65–69, 70–74 years), year of diagnosis (1999–2003, 2004–2008, 2009–2014), race (White, Black, Asian, other), body mass index (BMI) at diagnosis (< 25, 25–29, ≥ 30 kg/m^2), Charlson comorbidity score [24] at diagnosis (0, 1, ≥ 2), and depression during the 2 years prior to breast cancer diagnosis as indicated by ICD-9 diagnosis codes (yes/no).

Outcomes

Our primary outcomes of interest were: (i) adherence to breast cancer screening guidelines; (ii) occurrence of symptom-detected versus screen-detected breast cancer; and (iii) later-stage breast cancer at diagnosis. Adherence to breast cancer screening recommendations was defined as evidence of 1 + asymptomatic screening examination (mammography or breast magnetic resonance imaging [MRI]) in the 2-year period preceding breast cancer diagnosis per the recommendations provided within the integrated KPWA health system [17]. Symptom-detected breast cancer was defined as having no screening examinations in the 3 months prior

to breast cancer diagnosis. Otherwise, the breast cancer was screen detected. Later-stage breast cancer was defined as being diagnosed with American Joint Committee on Cancer (AJCC) [25] stage III versus stages I or II disease.

Statistical analyses

To evaluate the associations between diabetes and risks of each of the three outcomes, we estimated relative risks (RR) and 95% confidence intervals (CI) using a modified Poisson regression model with robust standard errors for a common binary outcome [26]. Two models were fit separately for each outcome. The first model included an adjustment for age at diagnosis only (categorical). The second model was a multivariable model including age and year of diagnosis, race, BMI at diagnosis, Charlson comorbidity score [24] at diagnosis, and depression at time of diagnosis.

Results

In the cohort of 2040 women, 263 (13%) had diabetes at breast cancer diagnosis (Table 1). Characteristics defining diabetes in the cohort are presented in Supplemental Table 1, including the proportion of patients with any period of uncontrolled diabetes during the 2 years prior to breast cancer diagnosis (53%). Diabetes prevalence differed by race ($p < 0.01$), with lower prevalence among White women (205/1768, 12%) and higher among Black (16/69, 23%) and Asian (22/120, 18%) women. Women with diabetes were older (median age: 65 vs. 62 years, $p < 0.01$), had higher BMI (median: 33 vs. 28 kg/m^2, $p < 0.01$), greater comorbidity (Charlson score of ≥ 2: 15% vs. 4%, $p < 0.01$), higher prevalence of depression (23% vs. 17%, $p = 0.01$), and more primary care visits in the two years prior to breast cancer diagnosis (median: 8 vs. 5 visits, $p < 0.01$), but were similar with respect to 1st degree family history of breast cancer (27% vs. 27%, $p = 0.93$) and smoking status (current smoker: 7% vs. 5%, $p = 0.22$).

Compared with women without diabetes at breast cancer diagnosis, women with diabetes had similar rates of breast cancer screening in the 2 years prior to breast cancer diagnosis (78% vs. 77%), symptom-detected breast cancer (46% vs. 49%), and stage III breast cancer (7% vs. 7%) (Table 1). In multivariable analyses (Table 2), we found no significant differences in the relative risk of adherence to breast cancer screening among women with diabetes compared with women without diabetes (RR 1.05, 95% CI 0.98, 1.12; $p = 0.19$). Risks of symptom-detected (vs. screen-detected) breast cancer (RR 0.94, 95% CI 0.81–1.08; $p = 0.37$) or stage III (vs. stage I or II) breast cancer (RR 1.00, 95% CI 0.61–1.63; $p = 0.99$) also were similar between women with and without diabetes. Risk of these outcomes by controlled and uncontrolled diabetes was similar, though a modest association was suggested for a higher rate of screening in women with controlled diabetes (RR 1.08, 95% CI 0.99–1.18; $p = 0.07$) but not uncontrolled diabetes (RR 1.01, 95% CI 0.91–1.12; $p = 0.85$).

Discussion

In this large, population-based cohort of women enrolled in an integrated healthcare system in Washington State, we found similar rates of adherence to breast cancer screening, symptom-detected breast cancer, and risk of locally advanced (stage III) breast cancer among women with diabetes compared to women without diabetes. Women with controlled diabetes appeared to have slightly higher rates of screening, although confidence intervals included 1.0.

Diabetes is associated with increased cancer-specific and all-cause mortality [4, 5] in breast cancer patients. Observed associations between diabetes and adverse breast cancer outcomes are hypothesized to result from less aggressive breast cancer treatment or diabetes care, both of which could account for the increased mortality observed in women with diabetes and breast cancer. Another explanation is that diabetes care and management of other chronic comorbidities compete with other preventive care [27, 28] such as breast cancer screening; thus, less favorable outcomes may be owed to detection of symptomatic breast cancer at later stages. The opposite could also be true: patients with comorbidities make more primary care visits and have higher rates of interaction with the health system, thereby leading potentially to higher screening rates. One recent study from the Finnish Cancer Registry [29] indicated that despite similar rates of screening in women with and without diabetes, risks of locally advanced and metastatic breast cancer were greater in women with diabetes. Our overall findings indicate no significant association between diabetes and adherence to breast cancer screening or type of diagnosis; and women with breast cancer and diabetes in other KPWA studies had relatively well controlled disease (mean HbA1c, 7.0%) prior to and following cancer diagnosis [16]. However, our study indicated slightly higher rates of breast cancer screening among women with no periods of uncontrolled diabetes. Although not statistically significant, this raises questions regarding differences in screening by quality of diabetes care, which may be even more substantial in settings that are not integrated healthcare delivery systems.

There are limited data on the association between greater severity of diabetes and breast cancer screening and detection. Among women with diabetes in the Women's Health Initiative clinical trials [10], receipt of annual mammography was greater in metformin users, a first-line oral antidiabetic agent, compared with users of non-metformin oral

Table 1 Descriptive characteristics at breast cancer diagnosis by diabetes status

	Diabetes ($n=263$)		No diabetes ($n=1777$)		p [a]
	n	%	*n*	%	
Characteristics at breast cancer diagnosis					
Diagnosis year					
1999–2003	72	(27.4)	531	(29.9)	0.38
2004–2008	74	(44.5)	535	(30.1)	
2009–2014	117	(44.5)	711	(40.0)	
Age, years					
Median	65		62		<0.01
52–54	17	(6.5)	229	(12.9)	<0.01
55–59	46	(17.5)	414	(23.3)	
60–64	55	(20.9)	442	(24.9)	
65–69	78	(29.7)	361	(20.3)	
70–74	67	(25.5)	331	(18.6)	
Menopausal status					
Pre-/peri-menopause	2	(0.8)	56	(3.3)	0.03
Post-menopause (or age ≥ 55 years)	251	(99.2)	1639	(96.7)	
Unknown and age < 55 years	10		82		
Race					
White	205	(78.5)	1563	(88.1)	<0.01
Black	16	(6.1)	53	(3.0)	
Asian	22	(8.4)	98	(5.5)	
Other	18	(6.9)	60	(3.4)	
Unknown	2		3		
Hispanic ethnicity					
No	239	(90.9)	1658	(93.4)	0.14
Yes	24	(9.1)	118	(6.6)	
Unknown			1		
Body mass index (kg/m^2)					
Median	33.3		27.6		<0.01
< 25.0	33	(12.7)	559	(31.6)	<0.01
25.0–29.9	53	(20.4)	587	(33.2)	
30.0–34.9	66	(25.4)	369	(20.9)	
35.0+	108	(41.5)	252	(14.3)	
Unknown	3		10		
Smoking status					
Current	17	(6.5)	96	(5.4)	0.22
Past	114	(43.3)	689	(38.8)	
Never/unknown	132	(50.2)	992	(55.8)	
Charlson comorbidity score					
0	175	(66.5)	1498	(84.3)	<0.01
1	49	(18.6)	215	(12.1)	
≥ 2	39	(14.8)	64	(3.6)	
1st degree family history of breast cancer					
No	174	(73.1)	1189	(73.4)	0.93
Yes	64	(26.9)	431	(26.6)	
Unknown	25		157		
Depression in 2 years prior					
No	202	(76.8)	1482	(83.4)	0.01
Yes	61	(23.2)	295	(16.6)	
Outcomes					

Table 1 (continued)

	Diabetes ($n=263$)		No diabetes ($n=1777$)		p [a]
	n	%	*n*	%	
Receipt of asymptomatic screening mammography or breast magnetic resonance imaging					
1 year prior to breast cancer diagnosis	177	(67.3)	1063	(59.8)	0.020
2 years prior to breast cancer diagnosis	206	(78.3)	1366	(76.9)	0.600
Detection of breast cancer					
Screened-detected	143	(54.4)	898	(50.5)	0.245
Symptom-detected	120	(45.6)	879	(49.5)	
Breast cancer stage					
I–II	245	(93.2)	1658	(93.3)	0.93
III	18	(6.8)	119	(6.7)	

[a]To test for differences of the characteristics between the two groups, we used χ^2 test for categorical variables and Wilcoxon rank-sum test for medians

Table 2 Results from multivariable modified Poisson regression models with robust standard errors comparing women with diabetes to women without diabetes for receiving asymptomatic breast screening, symptom-detected breast cancer and locally advanced stage III breast cancer

Outcomes	Age-adjusted model[a]			Multivariable-adjusted model[b]		
	RR	95% CI	*p*	RR	95% CI	*p*
Receipt of asymptomatic screening mammography or breast magnetic resonance imaging (yes versus no)						
No diabetes	1.00	Reference		1.00	Reference	
Diabetes	1.01	(0.94, 1.08)	0.82	1.05	(0.98, 1.12)	0.12
No diabetes	1.00	Reference		1.00	Reference	
Controlled diabetes	1.06	(0.98, 1.16)	0.16	1.08	(0.99, 1.18)	0.07
Any uncontrolled diabetes	0.97	(0.88, 1.07)	0.56	1.01	(0.91, 1.12)	0.85
Detection of breast cancer by symptoms (versus screening)						
No diabetes	1.00	Reference		1.00	Reference	
Diabetes	0.93	(0.81, 1.08)	0.35	0.94	(0.81, 1.08)	0.37
No diabetes	1.00	Reference		1.00	Reference	
Controlled diabetes	0.83	(0.66, 1.04)	0.11	0.88	(0.70, 1.11)	0.28
Any uncontrolled diabetes	0.99	(0.83, 1.18)	0.93	0.97	(0.81, 1.16)	0.74
Stage III (versus stages I or II)						
No diabetes	1.00	Reference		1.00	Reference	
Diabetes	1.07	(0.66, 1.72)	0.80	1.00	(0.61, 1.63)	0.99
No diabetes	1.00	Reference		1.00	Reference	
Controlled diabetes	1.22	(0.64, 2.35)	0.54	1.06	(0.55, 2.03)	0.86
Any uncontrolled diabetes	0.86	(0.64, 1.74)	0.68	0.97	(0.49, 1.94)	0.94

[a]Model adjusted for age at diagnosis (categorical; 52–59, 60–64, 65–69, 70–74 years)

[b]Model adjusted for age at diagnosis (categorical; 52–59, 60–64, 65–69, 70–74 years), year of diagnosis (categorical; 1999–2003, 2004–2008, 2009–2014), race (white, non-white), body mass index at diagnosis (categorical; <25, 25–29, ≥ 30 kg/m^2), Charlson comorbidity score at diagnosis (categorical; 0, 1, ≥ 2), and depression at diagnosis (yes, no)

agents and women treated with insulin. In an analysis of the SEER-Medicare linked database [30], women ages 67 years and older with higher scores on the Diabetes Complications Severity Index (DCSI) [31] were more likely to be diagnosed at advanced stages compared with women with no diabetes-related complications. Receipt of annual or biennial mammography screening also differed by presence of diabetes complications. Those with DCSI scores of 3 and greater had lower adherence to mammography screening (47%) compared to those with a DCSI score of 0 (66%). When adjusting for differences in screening, no significant differences in risk of stage III/IV breast cancer were observed in

women with the highest DCSI scores compared to those with the lowest (OR 1.16, 95% CI 0.92, 1.46; $p=0.21$). Additional studies including younger women of breast cancer screening age not included in the SEER-Medicare database are warranted to confirm and fully characterize the association between glycemic control and breast cancer risk.

Strengths of our study include near complete longitudinal data on patient and disease characteristics and healthcare utilization. We were able to evaluate patient symptoms reported at the time of the screening exam as well as the indication designated by the radiologist to differentiate screening from diagnostic exams, characteristics that are unavailable in most research settings. In addition, while we lacked information on the duration of diabetes, we were able to classify women with diabetes using data on pharmacy dispensings, diagnostic codes, and laboratory values. This also made it possible to determine if women had a period of uncontrolled diabetes in the 2 years prior to diagnosis to characterize disease severity versus an index score (e.g., DCSI).

This study has its limitations, especially related to generalizability, screening misclassification, and provider screening recommendations. We evaluated a large population with health coverage and stable membership, minimal co-pays and co-insurance for preventive services such as mammography, and who received almost all of their care within an integrated healthcare delivery system. The majority of our population was White, yielding a limited proportion of women of racial/ethnic minority backgrounds. Our findings may not be generalizable to other settings or populations where disparities in screening mammography persist, including those without health coverage, living in medically underserved areas, or of low-income or racial/ethnic minorities [32]. Our study included only women diagnosed with invasive breast cancer and investigated possible mechanisms by which diabetes could be associated with poor breast cancer outcomes. Our results predominantly pertain to screening mammography and rates may be different for other modalities such as MRI, which made up only 1.7% of all asymptomatic screening exams in our cohort. While our methods and data were rigorous, misclassification of exposure and/or outcomes and residual confounding cannot be ruled out. It is possible, for example, that some mammograms were classified as diagnostic rather than screening, even if for screening. In addition, we assumed that women meeting the definition of having diabetes at any time during the two-year period had diabetes during the entire 2-year period. We, therefore, cannot assume temporality between the presence of diagnosed diabetes prior to the time of screening. We defined uncontrolled diabetes using laboratory data that indicated increased HbA1c and/or fasting plasma glucose at any time during the 2 years prior to breast cancer diagnosis. However, glycemic measures vary over time and diabetes control is also owed to other important factors such as diet and medication adherence, which are discussed elsewhere [16], and laboratory measures alone are not indicators of overall diabetes severity. This cross-sectional study was a combination of women with both incident and prevalent diabetes and thus differing durations of disease. We, therefore, cannot differentiate/distinguish any differing effects by time since diagnosis, which can be a loose proxy for disease severity. Finally, decisions about whether to seek preventive services such as mammography are complex. It was beyond the scope of this study to ascertain provider recommendations, patient beliefs, or patient attitudes regarding breast cancer screening, nor could we assess why women chose not to receive screening. Furthermore, we did not address who appropriately may not benefit from screening because of comorbidities and limited life expectancy.

Conclusions

We found no significant association between diabetes and breast cancer screening and detection, although our findings are suggestive of possible differences with controlled diabetes. Further research is needed to characterize how diabetes severity and duration of disease impacts breast cancer quality of care, and how this may lead to adverse outcomes.

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Compliance with ethical standards

Conflict of interest Author O.Y. has received funding for research unrelated to the contributions as co-author of this work. This funder had no role in the design, interpretation or conclusions of this study. The other authors declare that they have no conflict of interest.

Ethical approval This study was approved by the institutional review board of the Kaiser Permanente Washington Health Research Institute.

References

1. American Cancer Society (2015) Breast Cancer Facts & Figures 2015-2016. American Cancer Society, Atlanta
2. Menke A, Casagrande S, Geiss L, Cowie CC (2015) Prevalence of and trends in diabetes among adults in the United States, 1988-2012. JAMA 314(10):1021–1029. https://doi.org/10.1001/jama.2015.10029
3. Ritchie CS, Kvale E, Fisch MJ (2011) Multimorbidity: an issue of growing importance for oncologists. J Oncol Pract 7(6):371–374. https://doi.org/10.1200/JOP.2011.000460

4. 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. https://doi.org/10.1200/JCO.2009.27.3011
5. Gold HT, Makarem N, Nicholson JM, Parekh N (2014) Treatment and outcomes in diabetic breast cancer patients. Breast Cancer Res Treat 143(3):551–570. https://doi.org/10.1007/s10549-014-2833-x
6. Institute of Medicine (U.S.), Committee on Quality of Health Care in America (2013) In: Levit L, Balogh E, Nass S, Ganz PA (eds) Delivering high-quality cancer care: charting a new course for a system in crisis. Institute of Medicine, Washington (DC)
7. Beckman TJ, Cuddihy RM, Scheitel SM, Naessens JM, Killian JM, Pankratz VS (2001) Screening mammogram utilization in women with diabetes. Diabetes Care 24(12):2049–2053
8. Lipscombe LL, Hux JE, Booth GL (2005) Reduced screening mammography among women with diabetes. Arch Intern Med 165(18):2090–2095. https://doi.org/10.1001/archinte.165.18.2090
9. Tabaei BP, Herman WH, Jabarin AF, Kim C (2005) Does diabetes care compete with the provision of women's preventive care services? Diabetes Care 28(11):2644–2649
10. Chlebowski RT, McTiernan A, Wactawski-Wende J, Manson JE, Aragaki AK, Rohan T, Ipp E, Kaklamani VG, Vitolins M, Wallace R, Gunter M, Phillips LS, Strickler H, Margolis K, Euhus DM (2012) Diabetes, metformin, and breast cancer in postmenopausal women. J Clin Oncol 30(23):2844–2852. https://doi.org/10.1200/JCO.2011.39.7505
11. Alimova IN, Liu B, Fan Z, Edgerton SM, Dillon T, Lind SE, Thor AD (2009) Metformin inhibits breast cancer cell growth, colony formation and induces cell cycle arrest in vitro. Cell Cycle 8(6):909–915
12. Col NF, Ochs L, Springmann V, Aragaki AK, Chlebowski RT (2012) Metformin and breast cancer risk: a meta-analysis and critical literature review. Breast Cancer Res Treat 135(3):639–646. https://doi.org/10.1007/s10549-012-2170-x
13. Bronsveld HK, ter Braak B, Karlstad O, Vestergaard P, Starup-Linde J, Bazelier MT, De Bruin ML, de Boer A, Siezen CL, van de Water B, Siezen CL, van de Laan JW, Schmidt MK (2015) Treatment with insulin (analogues) and breast cancer risk in diabetics; a systematic review and meta-analysis of in vitro, animal and human evidence. Breast Cancer Res 17:100. https://doi.org/10.1186/s13058-015-0611-2
14. Wirtz HS, Buist DS, Gralow JR, Barlow WE, Gray S, Chubak J, Yu O, Bowles EJ, Fujii M, Boudreau DM (2013) Frequent antibiotic use and second breast cancer events. Cancer Epidemiol Biomark Prev 22(9):1588–1599. https://doi.org/10.1158/1055-9965.EPI-13-0454
15. Boudreau DM, Yu O, Chubak J, Wirtz HS, Bowles EJ, Fujii M, Buist DS (2014) Comparative safety of cardiovascular medication use and breast cancer outcomes among women with early stage breast cancer. Breast Cancer Res Treat 144(2):405–416. https://doi.org/10.1007/s10549-014-2870-5
16. Calip GS, Hubbard RA, Stergachis A, Malone KE, Gralow JR, Boudreau DM (2015) Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment. Pharmacoepidemiol Drug Saf 24(1):75–85. https://doi.org/10.1002/pds.3660
17. Kaiser Permanente Washington Breast Cancer Screening. https://wa.kaiserpermanente.org/healthAndWellness?item=%2Fcommon%2FhealthAndWellness%2Ftests%2Fscreenings%2Fmammogram.html Accessed 4 Mar 2019
18. Cancer Surveillance System (contract No. N01-CN-67009) Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, Bethesda MD http://www.fhcrc.org/en/labs/phs/projects/cancer-surveillance-system.html
19. Surveillance Epidemiology and End Results (SEER) Program Overview of the SEER Program http://seer.cancer.gov/about/overview.html
20. Saunders KW, Davis RL, Stergachis A (2005) Group health cooperative. In: Strom BL (ed) Pharmacoepidemiology, 4th edn. Wiley, Hoboken, pp 223–239
21. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, Allen LA, Nekhlyudov L, Goddard KA, Davis RL, Habel LA, Yood MU, McCarty C, Magid DJ, Wagner EH, Pharmacovigilance Study T (2012) Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 104(17):1293–1305
22. Phipps AI, Ichikawa L, Bowles EJ, Carney PA, Kerlikowske K, Miglioretti DL, Buist DS (2010) Defining menopausal status in epidemiologic studies: a comparison of multiple approaches and their effects on breast cancer rates. Maturitas 67(1):60–66. https://doi.org/10.1016/j.maturitas.2010.04.015
23. Kaiser Permanente Washington Breast Cancer Surveillance Registry. https://www.kpwashingtonresearch.org/our-research/research-areas/cancer/breast-cancer-surveillance/. Accessed 4 Mar 2019
24. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45(6):613–619
25. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, Borgen PI, Clark GM, Edge SB, Hayes DF, Hughes LL, Hutter RV, Morrow M, Page DL, Recht A, Theriault RL, Thor A, Weaver DL, Wieand HS, Greene FL (2003) Staging system for breast cancer: revisions for the 6th edition of the AJCC cancer staging manual. Surg Clin North Am 83(4):803–819
26. Zou G (2004) A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 159(7):702–706
27. Jensen LF, Pedersen AF, Andersen B, Vestergaard M, Vedsted P (2015) Non-participation in breast cancer screening for women with chronic diseases and multimorbidity: a population-based cohort study. BMC Cancer 15:798. https://doi.org/10.1186/s12885-015-1829-1
28. Diaz A, Kang J, Moore SP, Baade P, Langbecker D, Condon JR, Valery PC (2017) Association between comorbidity and participation in breast and cervical cancer screening: a systematic review and meta-analysis. Cancer Epidemiol 47:7–19. https://doi.org/10.1016/j.canep.2016.12.010
29. Murto MO, Artama M, Pukkala E, Visvanathan K, Murtola TJ (2018) Breast cancer extent and survival among diabetic women in a Finnish nationwide cohort study. Int J Cancer 142(11):2227–2233. https://doi.org/10.1002/ijc.31250
30. Alenzi EO, Madhavan SS, Tan X (2018) Association of the severity of diabetes-related complications with stage of breast cancer at diagnosis among elderly women with pre-existing diabetes. Breast Cancer Res Treat 167(1):183–193. https://doi.org/10.1007/s10549-017-4477-0
31. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB (2012) Validating the adapted Diabetes Complications Severity Index in claims data. Am J Manag Care 18(11):721–726
32. Yasmeen S, Xing G, Morris C, Chlebowski RT, Romano PS (2011) Comorbidities and mammography use interact to explain racial/ethnic disparities in breast cancer stage at diagnosis. Cancer 117(14):3252–3261. https://doi.org/10.1002/cncr.25857