Breast Cancer Research and Treatment (2019) 174:237–248
https://doi.org/10.1007/s10549-018-5059-5

EPIDEMIOLOGY

A nationwide study of breast cancer, depression, and multimorbidity among hospitalized women and men in the United States

Roger J. Zoorob[1] · Jason L. Salemi[1] · Maria C. Mejia de Grubb[1] · Sanjukta Modak[1] · Robert S. Levine[1]

Received: 7 November 2018 / Accepted: 16 November 2018 / Published online: 21 November 2018

Abstract

Purpose Breast cancer is the most common and second most deadly cancer for women in the US. Comorbidities like depression exacerbate the burden. This national study provides data on depression and comorbidity for both women and men with breast cancer.

Methods We conducted a serial cross-sectional analysis of the 2002–2014 National Inpatient Sample, the largest all-payer inpatient discharge database in the United States. We identified patients with primary site breast cancer, and captured information on their concomitant depression and other major chronic comorbidities. Logistic regression was used to generate adjusted odds ratios representing associations between patient and hospital characteristics and depression. Joinpoint regression was used to estimate temporal trends in depression rates.

Results Depression prevalence was higher for women than men, with little difference between cancer subtypes. Comorbidity burden was nearly twice as high for men. From 2002 to 2014, the average number of comorbidities doubled. Depression rates were highest for patients with four or more chronic comorbidities and those with unplanned hospitalizations. Significant yearly increases of 6–10% in depression were also observed.

Conclusions Breast cancer patient depression rates were higher than the general inpatient population with a strong gradient effect between increasing numbers of comorbidities and the odds of depression. Comorbidities, including mental health-related, negatively impact breast cancer prognosis, increasing cancer-specific mortality as well as mortality for other conditions. Unplanned hospitalization episodes in a patient with breast cancer can be noted as an opportunity for mental health screening and intervention.

Keywords Breast cancer · Depression · Comorbidity · HCUP · NIS

Background

In the United States (US), breast cancer is the most common cancer among women and has the second-highest mortality among all cancers [1]. In 2018, 266,120 new cases and 40,920 deaths related to breast cancer were estimated among women in the US [1]. Overall, incidence rates have remained stable in recent years, while mortality has improved due to screening and treatment efforts. Racial disparities persist, as African American women have similar incidence but higher mortality from breast cancer than other groups [1]. Risk factors like diet, exercise, obesity, tobacco, and alcohol are known contributors [2].

Less is known about how risk factors interact to influence health outcomes and healthcare utilization associated with breast cancer treatment. Concomitant depression appears to increase the cost of care and may have adverse effects on adherence to cancer treatment plans [3]. Although breast cancer is relatively rare in men (2550 new cases estimated in 2018) [1] and represents less than 1% of all breast cancer cases, diagnoses are often made at a more advanced stage since screening is not common. The paucity of data about male breast cancer impedes our ability to engage in primary and secondary prevention efforts.

Mood disturbances are common among patients with breast cancer, with about one-third of women undergoing treatment reporting some level of psychological distress that may persist long after treatment [4–7]. However, the

✉ Roger J. Zoorob
Roger.Zoorob@bcm.edu

[1] Department of Family and Community Medicine, Baylor College of Medicine, 3701 Kirby Dr., Suite 600, MS: BCM700, Houston, TX 77098, USA

overall prevalence of depressive disorders in patients with breast cancer remains unclear mainly due to variability in screening, criteria for defining depression, and the diversity of clinical risk factors [8, 9].

Previous studies have found that the number and severity of comorbidities at the time of cancer diagnosis has a significant impact on the probability of dying from non-cancer causes and also may influence cancer-specific survival [10]. High comorbidity burden has often been associated with less aggressive treatment and poor cancer outcomes even after treatment [10].

An examination of the triad of breast cancer, depression, and major comorbidities, and the differences between sexes, could fill a gap in knowledge informing improved quality of care and quality of life. While recent studies have investigated breast cancer and mental conditions using national inpatient databases [11], we are not aware of a previous study assessing temporal trends in the prevalence of depression in men and women with breast cancer, or investigating the impact of their overall chronic disease burden. We conducted a 13-year serial cross-sectional analysis of the associations between depression, major comorbidities, and other patient and hospital characteristics with male and female breast cancers. We also studied the temporal trends of comorbid depression between the years of 2002 and 2014.

Methods

Study design and data source

We conducted a retrospective cross-sectional analysis of inpatient hospitalizations in the US between January 1, 2002 and December 31, 2014, using data from the Healthcare Cost and Utilization Project's (HCUP's) National Inpatient Sample (NIS). The methodology used herein is modeled on previous works on comorbidity and disease outcomes by the study team [12]. The NIS collectively constitutes the largest all-payer publicly available inpatient database in the US. To create the sample annually, HCUP used a 2-stage cluster sampling design that first stratifies participating non-federal community hospitals by five characteristics: urban/rural location, number of beds, geographic region, type of ownership, and teaching status. Then, 20% of hospitals from each stratum are selected by using a systematic random sampling technique. In the second stage, all inpatient hospitalizations from hospitals selected during stage one are selected for inclusion in the NIS. Beginning in 2012, the NIS sampling strategy was changed to drawing a sample of hospitalizations from all hospitals. The NIS approximates a 20% systematic sample that is representative of the population of all inpatient hospitalizations on critical hospital and patient characteristics. To facilitate the use of the NIS to generate national frequency and prevalence estimates, HCUP calculates weights that account for the sampling design and then provides those weights with each annual database. In 2014, 45 states participated in the NIS—up from 35 states in 2002—and each year of the NIS contains approximately 7–8 million hospitalizations (representing over 35 million hospitalizations when weighted).

Population

Our target population consisted of patients aged 18 years or older with a diagnosis of breast cancer admitted to hospitals in the United States between January 1, 2002 and December 31, 2014. We used the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes for each patient's principal diagnosis and up to 14 secondary diagnoses (up to 24 beginning in 2009, and up to 30 beginning in 2014 due to data availability). We selected hospitalizations with breast cancer in women using any principal diagnosis or secondary diagnosis in the 174.0-174.9 ICD-9-CM code range, and breast cancer in men as having any principal diagnosis or secondary diagnosis of 175.0 or 175.9. Only malignant neoplasms were considered; a diagnosis of carcinoma in-situ alone did not meet our case definition. We then used the presence of additional diagnosis codes for secondary malignant neoplasms (196.0–198.9) to differentiate between non-metastatic and metastatic cancer in which the breast was the primary site.

The primary outcome was a concomitant diagnosis (principal or secondary) of depression among patients with breast cancer. This was defined by the presence of one or more of the following ICD-9-CM codes: 296.20–26 (major depressive disorder, single episode); 296.30–36 (major depressive disorder, recurrent episode); 300.4 (dysthymic disorder); 301.12 (chronic depressive personality disorder); 309.0 (adjustment disorder with depressed mood); 309.1 (prolonged depressive reaction); and 311 (depressive disorder, not elsewhere classified).

For each inpatient hospitalization, the NIS database captures various sociodemographic, clinical, and hospital characteristics. Patient age in years was categorized as 18–29; 30–39; 40–49; 50–59; 60–69; 70–79; and ≥ 80. Self-reported race/ethnicity, which is reported differently across states, was standardized by first grouping this as Hispanic or non-Hispanic, and then further classifying the non-Hispanics by race (non-Hispanic white, black, or other). Insurance status was based on the primary payer for the hospitalization, and was classified into government, private, and other. Socioeconomic status was estimated from the median household income in the patient's zip code of residence, and estimated values were classified into quartiles.

Clinical characteristics included the presence and number of chronic comorbidities based on a previously established

list of 20 chronic conditions that were identified and recommended by the US Department of Health and Human Services (HHS) to promote consistency and comparability in assessing the occurrence of chronic conditions in the US [12, 13]. The conditions include hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, arthritis, asthma, autism spectrum disorder, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, dementia (including Alzheimer's and other senile dementias), hepatitis, HIV, osteoporosis, schizophrenia, substance use disorders, depression, and cancer. Since the study population was defined by breast cancer status, and depression is the primary study outcome, these two conditions were excluded from comorbidity counts in our analyses; however, where data are presented to compare comorbidities among female and male breast cancer patients, we excluded cancer but not depression.

We also considered several characteristics of the treating hospital that are captured within the NIS databases, including US census region (Northeast, Midwest, South, and West), hospital size based on the number of short-term acute beds in a hospital (small, medium, large), and location/teaching status (urban-teaching, urban-non-teaching, and rural).

Statistical analysis

Descriptive statistics were used to outline the distribution of sociodemographic, clinical, and hospital characteristics in breast cancer patients by cancer subtype (non-metastatic versus metastatic), and compared the prevalence of depression in each study subgroup. We used NIS-provided sampling weights to calculate national estimates of the frequency and prevalence of depression among hospitalized patients with breast cancer for men and women separately. Unconditional logistic regression was used to generate adjusted odds ratios (OR) and 95% confidence intervals (CI) representing the association between depression and each characteristic.

Joinpoint regression was used to estimate and describe temporal trends in the occurrence of depression among hospitalized patients with breast cancer for men and women separately. Joinpoint regression is particularly useful for identifying changes in the frequency of events over time [14]. First, joinpoint regression assumes that a single trend best describes outcome rates over time; therefore, it fits the data to a straight line (one with no joinpoints). A joinpoint is then added to the model, and a Monte Carlo permutation test is used to determine whether it offers a statistically significant improvement to the model. The process of adding joinpoints continues iteratively until an optimal number of joinpoints are identified. Each joinpoint reflects a statistically significant change in the temporal trend, and the model estimates the annual percent change (APC) to describe how the rate of depression changes within each distinct time interval [15]. HCUP-provided trend files were used to account for a changing NIS sampling design during the study period and to ensure consistency of sampling weights and study variables over time [16]. Statistical analysis was performed with SAS, version 9.4 (SAS Institute, Cary, NC, USA), and trend analyses used the Joinpoint Regression Program, version 4.5.0.1. A 5% type I error rate was assumed for all hypothesis tests (two-sided). Since NIS data are de-identified and publicly available, this study was classified as exempt by the Baylor College of Medicine Institutional Review Board.

Results

Between 2002 and 2014, there were more than 2.3 million women and approximately 21,000 men who had inpatient hospitalizations involving breast cancer in the US. Among women, 41% had metastatic disease, compared to 46% among men. The distribution of key sociodemographic, clinical, and hospital characteristics among the study population, stratified by sex and cancer subtype, is shown in Table 1. The prevalence of depression for these patients was higher for women (10.5%) than men (7.5%), with little difference between metastatic and non-metastatic disease. The diagnosis assigned to more than 70% of patients with depression was the non-specific 311 ICD-9-CM code representing "depressive disorder, not elsewhere specified," whereas the most common specific diagnoses included major depressive disorder or dysthymic disorder. While nearly two in three women with breast cancer had one or more chronic comorbidities, four in five men did (Fig. 1). For non-metastatic breast cancer, 64% of men had 2 or more comorbidities, compared to 47% of women. Moreover, men had nearly twice the rate of high multimorbidity (≥ 4 comorbidities) than women. In both men and women, hypertension was the most prevalent of all chronic conditions considered (44% for female breast cancer, 53.6% for male breast cancer), and in both sexes, the comorbidity burden has increased substantially over time. In 2002, women with breast cancer had on average 1.1 chronic comorbidities. This increased steadily to 2.0 by 2014 (Fig. 2a). Among men, the average number of chronic comorbidities doubled from 1.4 in 2002 to 2.8 in 2014 (Fig. 2b).

The patient and hospital-level characteristics associated with depression were generally similar for both men and women, and were highest in patients with four or more chronic comorbidities, those with an unplanned hospitalization, and those in the Midwestern US (Table 2). Among women hospitalized with breast cancer, higher rates of depression were observed in non-Hispanic white patients, and in those between 40 and 69 years of age. In contrast, for men hospitalized with a breast cancer diagnosis, depression was more common for Native American

Table 1 Distribution of selected patient sociodemographic, clinical, and hospital characteristics among inpatient discharges to men and women aged 18 years or older with a diagnosis of breast cancer, National Inpatient Sample, United States, 2002–2014

	Female breast cancer type				Male breast cancer type			
	Malignant non-metastatic		Metastatic		Malignant non-metastatic		Metastatic	
	n^a	%[a]	n^a	%[a]	n^a	%[a]	n^a	%[a]
All discharges	1,370,303	100.0	973,158	100.0	11,343	100.0	9654	100.0
Age group (years)								
18–29	8022	0.6	6461	0.7	63	0.6	55	0.6
40–49	208,449	15.2	161,775	16.6	669	5.9	905	9.4
50–59	290,311	21.2	239,192	24.6	1557	13.7	1807	18.7
60–69	308,586	22.5	230,459	23.7	3113	27.4	2723	28.2
70–79	270,690	19.8	170,915	17.6	3264	28.8	2466	25.5
≥ 80	220,811	16.1	110,009	11.3	2539	22.4	1510	15.6
Race/ethnicity								
Non-Hispanic white	828,974	60.5	565,253	58.1	7436	65.6	5930	61.4
Non-Hispanic black	154,920	11.3	133,727	13.7	1521	13.4	1411	14.6
Hispanic	87,475	6.4	67,541	6.9	492	4.3	470	4.9
Asian/Pacific Islander	30,084	2.2	21,823	2.2	114	1.0	106	1.1
Native American	4686	0.3	2924	0.3	30	0.3	14	0.1
Other	28,785	2.1	20,802	2.1	309	2.7	186	1.9
Unknown/unreported	235,379	17.2	161,089	16.6	1441	12.7	1,537	15.9
Household income								
Lowest quartile	337,036	24.6	243,799	25.1	2746	24.2	2620	27.1
2nd quartile	330,900	24.1	235,730	24.2	2736	24.1	2245	23.3
3rd quartile	330,456	24.1	234,269	24.1	2765	24.4	2209	22.9
Highest quartile	343,766	25.1	238,100	24.5	2834	25.0	2432	25.2
Primary payer								
Government (medicare/medicaid)	649,248	47.4	419,393	43.1	7187	63.4	5435	56.3
Private	128,632	9.4	124,621	12.8	668	5.9	897	9.3
Other (self-pay, charity)	533,626	38.9	379,926	39.0	2976	26.2	2,675	27.7
Discharge status								
Died	23,383	1.7	66,856	6.9	234	2.1	681	7.1
Routine	975,199	71.2	550,248	56.5	7166	63.2	5,215	54.0
Short-term hospital	15,001	1.1	14,838	1.5	178	1.6	134	1.4
Another type of facility	132,491	9.7	134,402	13.8	1452	12.8	1528	15.8
Home health care	219,158	16.0	201,837	20.7	2205	19.4	1998	20.7
Against medical advice	3621	0.3	2665	0.3	84	0.7	80	0.8
Discharged alive, unknown destination	585	0.0	1494	0.2	10	0.1	10	0.1
Timing of discharge								
Weekday	1,209,902	88.3	831,488	85.4	9900	87.3	8284	85.8
Weekend	160,396	11.7	141,670	14.6	1443	12.7	1369	14.2
Number of chronic conditions[c]								
None	418,704	30.6	352,569	36.2	1856	16.4	2215	22.9
1 comorbidity	309,564	22.6	248,942	25.6	2249	19.8	2215	22.9
2 comorbidities	257,232	18.8	175,139	18.0	2232	19.7	2022	20.9
3 comorbidities	181,912	13.3	105,180	10.8	1933	17.0	1475	15.3
≥ 4 comorbidities	202,891	14.8	91,329	9.4	3074	27.1	1727	17.9
Severity of illness subclass[b]								
Minor loss of function	572,828	41.8	201,607	20.7	3883	34.2	1778	18.4
Moderate loss of function	544,878	39.8	351,827	36.2	4204	37.1	3418	35.4

Table 1 (continued)

	Female breast cancer type				Male breast cancer type			
	Malignant non-metastatic		Metastatic		Malignant non-metastatic		Metastatic	
	n^a	$\%^a$	n^a	$\%^a$	n^a	$\%^a$	n^a	$\%^a$
Major loss of function	200,864	14.7	345,475	35.5	2592	22.9	3508	36.3
Extreme loss of function	41,040	3.0	66,489	6.8	571	5.0	855	8.9
Hospital census region								
Northeast	284,260	20.7	205,102	21.1	3040	26.8	2372	24.6
Midwest	321,425	23.5	222,044	22.8	2456	21.7	2328	24.1
South	506,453	37.0	361,315	37.1	3725	32.8	3257	33.7
West	258,165	18.8	184,698	19.0	2123	18.7	1696	17.6
Hospital type								
Rural	162,879	11.9	101,626	10.4	1207	10.6	1084	11.2
Urban, non-teaching	529,088	38.6	373,834	38.4	4515	39.8	3651	37.8
Urban, teaching	672,735	49.1	494,429	50.8	5589	49.3	4881	50.6
Hospital size								
Small	181,065	13.2	120,262	12.4	1525	13.4	1304	13.5
Medium	339,408	24.8	232,476	23.9	2918	25.7	2286	23.7
Large	844,229	61.6	617,150	63.4	6868	60.5	6027	62.4
Depression diagnosis								
No	1,224,768	89.4	872,095	89.6	10,589	93.4	8829	91.5
Yes	145,535	10.6	101,063	10.4	754	6.6	825	8.5
Planned hospitalization								
No	675,540	49.3	621,482	63.9	6002	52.9	6382	66.1
Yes	694,764	50.7	351,676	36.1	5341	47.1	3271	33.9

[a]Weighted to estimate national frequency and proportion of hospitalizations in each population subgroup; the sum of all groups may not add up to total because of missing data

[b]The severity of illness subclass is estimated with use of a propriety algorithm developed by 3M™ Health Information Systems and is based on each patient's age, sex, comorbidities, and diagnoses and procedures received during their stay

[c]Includes 20 chronic conditions selected by the Office of the Assistant Secretary for Health, US Department of Health and Human Services for investigating multiple chronic conditions in the US population. Conditions include hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, diabetes, arthritis, asthma, autism spectrum disorder, chronic kidney disease, chronic obstructive pulmonary disease, dementia (including Alzheimer's and other senile dementias), hepatitis, HIV, osteoporosis, schizophrenia, substance abuse disorders (drug and alcohol), depression, and cancer. Since the study population was defined by breast cancer status, cancer was excluded from the comorbidity count

and Hispanic patients, and those 18–49 years of age. Multivariable modeling adjusting for confounders revealed that increasing numbers of comorbidities was associated with increasing odds of depression. Compared to patients with no comorbidity, those with severe multimorbidity (≥ 4 conditions) experienced a near threefold increased odds of depression among women with breast cancer (OR 2.80, 95% CI 2.69, 2.91) and almost 3.5 times increase for men (OR 3.47, 95% CI 2.25, 5.35). For both men and women with breast cancer, depression was approximately 40% more likely to be diagnosed during an unplanned, compared to a planned, hospitalization (women OR 1.37, 95% CI 1.33, 1.40; men OR 1.43, 95% CI 1.08, 1.90). For women, increasing age was associated with decreased odds of depression, Non-Hispanic whites had the highest odds of a diagnosis of depression, and publicly insured patients had higher odds of depression compared to those who were privately insured or uninsured. For men, higher odds of depression were observed in metastatic cancer as compared to non-metastatic cancer, and non-Hispanic blacks were half as likely to receive a depression diagnosis than non-Hispanic whites (Table 2).

From 2002 to 2014, we observed a significant increase in the prevalence of depression among all groups. For women with non-metastatic disease, depression rates increased from 6.5 to 15.7%; and for metastatic, 5.9–14.8%. For men, rates

of depression were 4.6–13.8% for metastatic, and 4.7–9.8% for non-metastatic (Fig. 3). For both men and women, this translated into between a 6% and 10% increase in the rates of diagnosed depression *each year*.

Conclusions

The purpose of this study was to assess the prevalence, temporal trends, and associated clinical correlates in patients with breast cancer. To our knowledge, this is the first study to investigate this triad in both men and women with breast cancer using over a decade of data from the largest national all-payer, inpatient discharge database. Our results suggest that the prevalence of depression among patients hospitalized with breast cancer was higher compared to the general inpatient population among women (10.5% vs. 8.5%) and men (7.5% vs. 4.8%); however, the sex disparity for depression was higher in the general population than in our sample of patients with breast cancer [17]. Previous studies have reported prevalence estimates ranging from 10 to 25% for depression among female patients with breast cancer [3, 17]. In a small study of men with breast cancer in the United Kingdom ($n = 160$), depressive symptoms were reported by only 1% of the participants [18]. Yet, we did not find any previous reports of depression among men with breast cancer in the US. Nevertheless, the lower prevalence of breast cancer in men might explain the paucity of literature and the lack of data regarding mental health among this patient population. This study not only estimates the inpatient prevalence of depression among men with breast cancer, but also emphasizes the need for increased awareness and information about mood disturbances in men with breast cancer and sex-specific information needs considering that depression prevalence among men with other cancers can be much higher (e.g., ranges 7–18% in prostate cancer [3, 19]).

Overall, depression rates increased between 6 and 10% each year between 2002 and 2014 among both women and men with breast cancer. A recent study in the Military Health System also found that between 2007 and 2014, mood and adjustment disorders increased by 7% (from 21

Fig. 2 Temporal trends in the mean number of chronic comorbidities among hospitalizations of patients aged 18 years or older with a diagnosis of breast cancer in both men and women, National Inpatient Sample, United States, 2002–2014. **a** Female breast cancer, **b** Male breast cancer. The x-axis represents the year of hospitalization and the y-axis represents the number of chronic comorbidities. Circles represent the mean. Includes 20 chronic conditions selected by the Office of the Assistant Secretary for Health, US Department of Health and Human Services for investigating multiple chronic conditions in the US population. Conditions include hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, diabetes, arthritis, asthma, autism spectrum disorder, chronic kidney disease, chronic obstructive pulmonary disease, dementia (including Alzheimer's and other senile dementias), hepatitis, HIV, osteoporosis, schizophrenia, substance abuse disorders (drug and alcohol), depression, and cancer. Since the study population was defined by breast cancer status, cancer was excluded from the comorbidity count

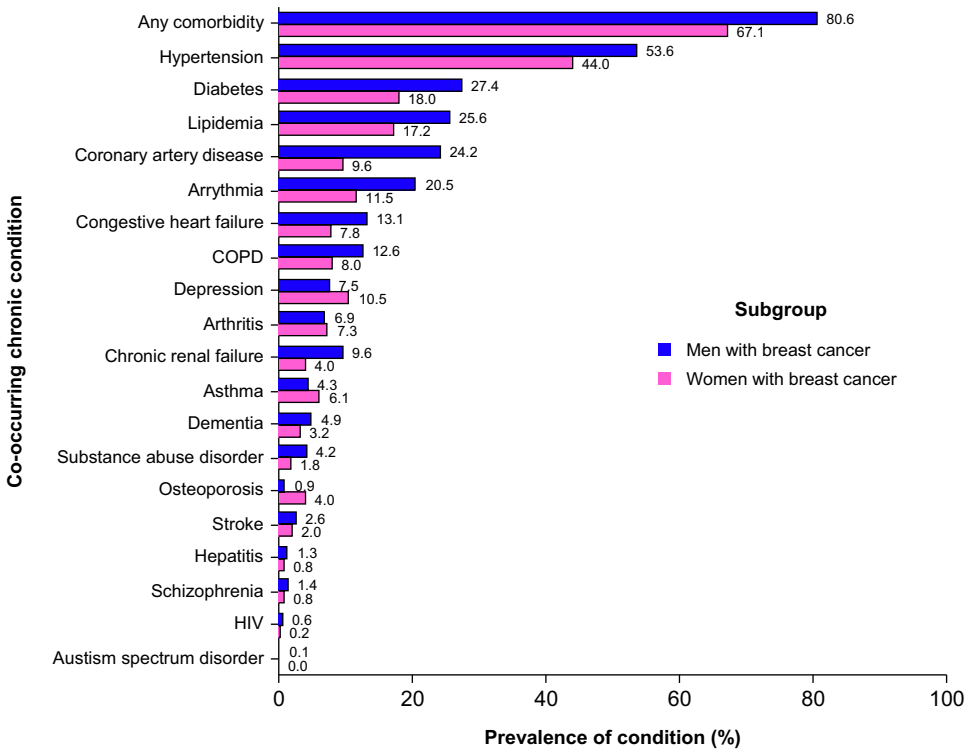
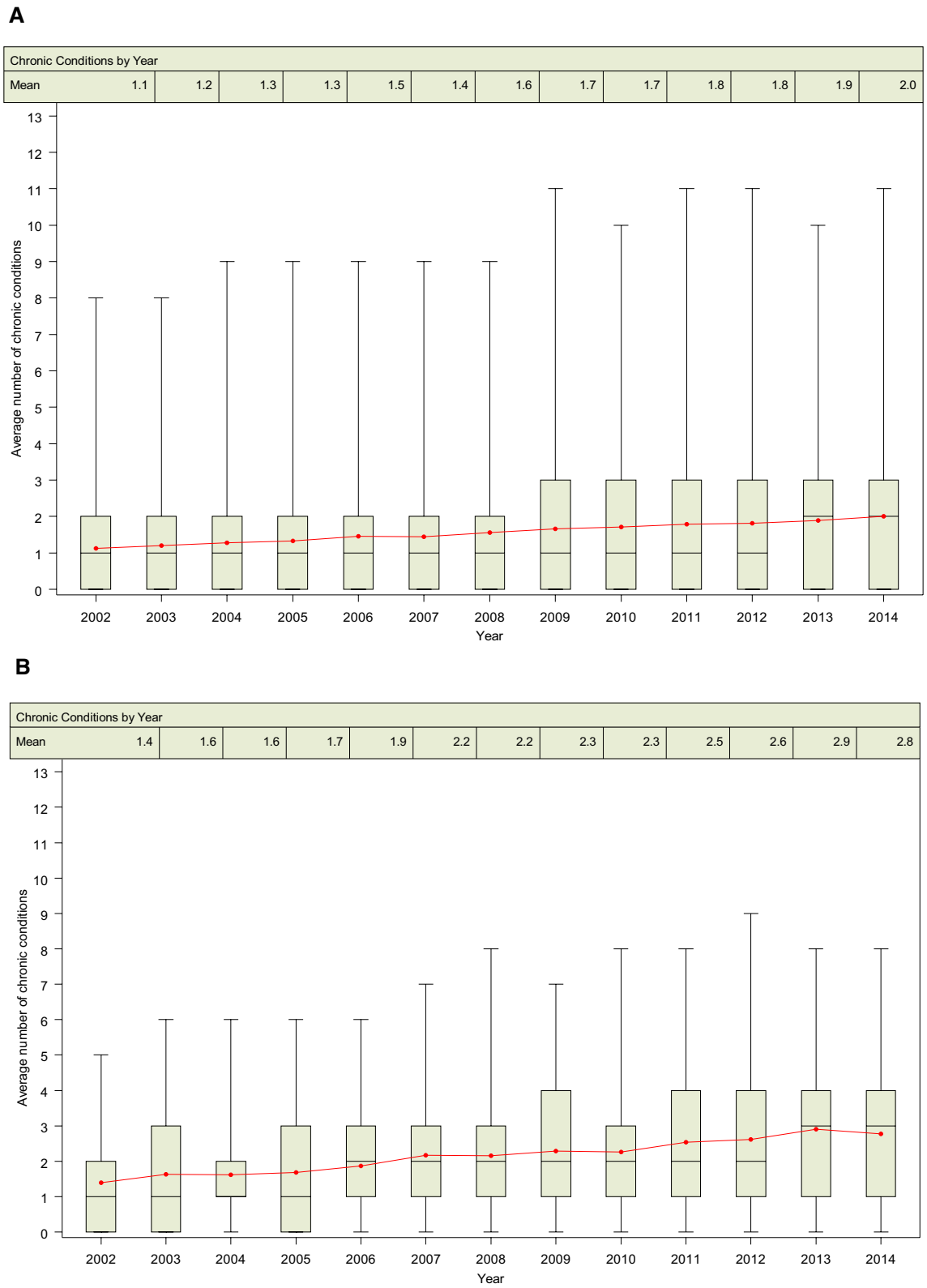


Fig. 1 Rates of depression and other chronic conditions among hospitalizations of patients aged 18 years or older with a diagnosis of breast cancer in both men and women, National Inpatient Sample, United States, 2002–2014. The x-axis represents the percentage of inpatient hospitalizations with each condition. Patients with multiple chronic conditions were counted separately for each condition. Includes 20 chronic conditions selected by the Office of the Secretary for Health, US Department of Health and Human Services for investigating multiple chronic conditions in the US population. Conditions include those listed in the figure and cancer; however, since the study population was defined by breast cancer status, cancer was excluded from the figure



to 28%) among patients with breast cancer [3]. Depression diagnosis time trends may indicate more recognition, better diagnosis or seeking care, or documentation and coding practices. Previous studies have reported that cancer stage is a key predictor of psychological distress particularly at the time of diagnosis. The complexities of the treatment

Table 2 Crude rates of depression and adjusted odds ratios assessing predictors of an inpatient diagnosis of depression among hospitalizations of patients aged 18 years or older with a diagnosis of breast cancer in men and women, National Inpatient Sample, United States, 2002–2014

Patient of hospital characteristic	Female breast cancer		Male breast cancer	
	Depression rate % (95 CI)	Adjusted OR Est (95% CI)	Depression rate % (95 CI)	Adjusted OR Est (95% CI)
All hospitalizations	10.5 (10.3, 10.7)	N/A[a]	7.5 (6.7, 8.4)	N/A[a]
Age group (years)				
18–29	6.8 (5.7, 7.9)	1.00 (reference)	12.1 (− 1.4, 25.6)	1.00 (reference)
30–39	9.2 (8.8, 9.7)	**1.33 (1.11, 1.60)***	10.9 (1.5, 20.4)	0.66 (0.13, 3.36)
40–49	10.8 (10.5, 11.2)	**1.40 (1.17, 1.67)***	11.6 (8.2, 15.0)	0.62 (0.16, 2.39)
50–59	12.1 (11.7, 12.4)	**1.27 (1.06, 1.51)***	7.8 (5.7, 9.8)	0.36 (0.09, 1.38)
60–69	11.3 (11.0, 11.6)	0.88 (0.73, 1.05)	8.6 (6.9, 10.2)	0.31 (0.08, 1.19)
70–79	9.4 (9.1, 9.6)	**0.59 (0.49, 0.70)***	6.2 (4.7, 7.6)	**0.19 (0.05, 0.73)***
≥80	8.6 (8.3, 8.9)	**0.45 (0.38, 0.54)***	5.8 (4.1, 7.5)	**0.15 (0.04, 0.57)***
Race/ethnicity				
Non-Hispanic white	11.9 (11.6, 12.1)	1.00 (reference)	8.0 (6.9, 9.1)	1.00 (reference)
Non-Hispanic black	7.5 (7.2, 7.8)	**0.46 (0.44, 0.48)***	5.8 (4.0, 7.6)	**0.54 (0.37, 0.80)***
Hispanic	8.8 (8.3, 9.2)	**0.64 (0.60, 0.68)***	10.1 (5.8, 14.5)	1.14 (0.68, 1.93)
Asian/Pacific Islander	4.4 (4.0, 4.9)	**0.31 (0.28, 0.35)***	1.4 (-1.3, 4.1)	0.16 (0.02, 1.26)
Native American	10.1 (8.5, 11.8)	**0.70 (0.59, 0.84)***	11.4 (-9.9, 32.7)	2.07 (0.23, 18.42)
Unknown/unreported	8.7 (8.1, 9.4)	**0.66 (0.60, 0.71)***	8.8 (1.7, 15.8)	0.93 (0.42, 2.08)
Cancer type				
Malignant non-metastatic	10.6 (10.4, 10.8)	1.00 (reference)	6.6 (5.6, 7.7)	1.00 (reference)
Metastatic	10.4 (10.1, 10.6)	**0.94 (0.92, 0.97)***	8.5 (7.3, 9.8)	**1.31 (1.03, 1.68)***
Household income				
Lowest quartile	10.1 (9.8, 10.4)	1.00 (reference)	7.4 (5.8, 9.0)	1.00 (reference)
2nd quartile	10.8 (10.6, 11.1)	**1.06 (1.02, 1.09)***	8.0 (6.2, 9.8)	1.17 (0.82, 1.67)
3rd quartile	11.0 (10.7, 11.3)	**1.09 (1.05, 1.13)***	7.4 (5.8, 9.0)	1.04 (0.72, 1.50)
Highest quartile	10.3 (10.0, 10.6)	**1.06 (1.02, 1.10)***	7.5 (5.8, 9.2)	1.21 (0.83, 1.76)
Primary payer				
Government (medicare/medicaid)	11.0 (10.8, 11.2)	1.00 (reference)	7.9 (6.9, 9.0)	1.00 (reference)
Private	10.0 (9.7, 10.2)	**0.83 (0.80, 0.85)***	6.6 (5.2, 8.1)	**0.68 (0.50, 0.93)***
Other (self-pay, charity)	9.2 (8.6, 9.9)	**0.82 (0.77, 0.87)***	7.2 (3.7, 10.7)	0.80 (0.45, 1.43)
Discharge status				
Routine	9.7 (9.5, 10.0)	1.00 (reference)	6.7 (5.7, 7.8)	1.00 (reference)
Died	7.2 (6.8, 7.6)	**0.70 (0.66, 0.74)***	6.8 (3.3, 10.4)	0.82 (0.45, 1.51)
Against medical advice	12.5 (10.6, 14.3)	1.03 (0.87, 1.22)	8.9 (-0.8, 18.6)	1.05 (0.31, 3.51)
Discharged alive	12.6 (12.3, 12.9)	**1.29 (1.26, 1.32)***	8.9 (7.5, 10.4)	1.20 (0.92, 1.56)
Timing of discharge				
Weekday	10.2 (10.0, 10.4)	1.00 (reference)	7.2 (6.3, 8.0)	1.00 (reference)
Weekend	12.5 (12.2, 12.9)	**1.05 (1.03, 1.08)***	9.8 (7.3, 12.2)	1.18 (0.87, 1.62)
Number of chronic conditions[b]				
None	7.0 (6.8, 7.3)	1.00 (reference)	4.0 (2.7, 5.3)	1.00 (reference)
1 Comorbidity	11.1 (10.8, 11.3)	**1.80 (1.74, 1.85)***	6.4 (4.7, 8.0)	**1.73 (1.11, 2.70)***
2 Comorbidities	12.2 (11.9, 12.5)	**2.17 (2.10, 2.24)***	7.3 (5.5, 9.1)	**2.18 (1.39, 3.41)***
3 Comorbidities	13.1 (12.7, 13.4)	**2.41 (2.31, 2.50)***	8.9 (6.8, 11.0)	**2.69 (1.69, 4.29)***
≥4 Comorbidities	15.0 (14.7, 15.4)	**2.80 (2.69, 2.91)***	11.2 (9.1, 13.2)	**3.47 (2.25, 5.35)***
Hospital census region				
Northeast	9.8 (9.4, 10.3)	1.00 (reference)	7.5 (5.9, 9.1)	1.00 (reference)
Midwest	12.1 (11.6, 12.6)	**1.25 (1.18, 1.33)***	8.7 (6.8, 10.6)	1.00 (0.69, 1.45)
South	10.0 (9.7, 10.4)	**1.08 (1.02, 1.14)***	7.1 (5.6, 8.5)	0.86 (0.62, 1.20)

Table 2 (continued)

Patient of hospital characteristic	Female breast cancer		Male breast cancer	
	Depression rate % (95 CI)	Adjusted OR Est (95% CI)	Depression rate % (95 CI)	Adjusted OR Est (95% CI)
West	10.3 (9.9, 10.7)	**1.16 (1.09, 1.23)***	6.9 (4.9, 8.8)	0.86 (0.58, 1.27)
Hospital size				
Small	10.9 (10.4, 11.4)	1.00 (reference)	7.6 (5.3, 9.9)	1.00 (reference)
Medium	10.6 (10.2, 11.0)	0.98 (0.93, 1.04)	7.9 (6.1, 9.6)	1.06 (0.71, 1.58)
Large	10.4 (10.1, 10.7)	0.98 (0.93, 1.03)	7.4 (6.3, 8.4)	0.97 (0.67, 1.40)
Hospital type				
Rural	10.5 (10.1, 10.9)	1.00 (reference)	7.8 (5.5, 10.1)	1.00 (reference)
Urban, non-teaching	10.1 (9.9, 10.4)	0.98 (0.93, 1.03)	7.5 (6.0, 8.9)	0.93 (0.62, 1.39)
Urban, teaching	10.8 (10.5, 11.1)	1.04 (0.99, 1.10)	7.5 (6.3, 8.7)	0.83 (0.56, 1.22)
Planned hospitalization				
Planned	8.4 (8.2, 8.6)	1.00 (reference)	5.3 (4.3, 6.4)	1.00 (reference)
Unplanned	12.2 (12.0, 12.5)	**1.37 (1.33, 1.40)***	9.1 (7.9, 10.3)	**1.43 (1.08, 1.90)***
Year/era of hospitalization				
2002–2005	7.0 (6.7, 7.2)	1.00 (reference)	4.9 (3.5, 6.3)	1.00 (reference)
2006–2008	9.6 (9.2, 9.9)	**1.31 (1.25, 1.36)***	6.3 (4.5, 8.0)	1.16 (0.76, 1.76)
2009–2011	12.0 (11.6, 12.4)	**1.61 (1.53, 1.68)***	7.8 (6.1, 9.6)	1.39 (0.93, 2.07)
2012–2014	14.4 (14.2, 14.7)	**1.91 (1.83, 1.99)***	10.8 (8.9, 12.7)	**1.82 (1.26, 2.63)***

Bolded and starred values represent adjusted odds ratios that are statistically significant

OR odds ratios, *CI* confidence interval

[a]The 'All Hospitalizations' row is intended to provide overall proportion of hospitalizations with a diagnosis of depression. No multivariable modeling applies to this row

[b]Includes 20 chronic conditions selected by the Office of the Assistant Secretary for Health, US Department of Health and Human Services, for investigating multiple chronic conditions in the US population. Conditions include hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, diabetes, arthritis, asthma, autism spectrum disorder, chronic kidney disease, chronic obstructive pulmonary disease, dementia (including Alzheimer's and other senile dementias), hepatitis, HIV, osteoporosis, schizophrenia, substance abuse disorders (drug and alcohol), depression, and cancer. Since the study population was defined by breast cancer status, cancer was excluded from the comorbidity count

including side effects of radiotherapy and hormone therapy, such as nausea, weight gain, pain, and fatigue, may also cause mood disturbances, and breast surgery may generate concerns about body image [4, 20–22]. Insomnia, which is strongly linked with depression [23, 24], is another common problem for patients with breast cancer. On the other hand, the psychological effects of treatment factors on men with breast cancer remain unknown.

We observed a strong gradient effect between increasing numbers of comorbidities and the odds of depression in patients with breast cancer. In our study, comparing the absence of major comorbidities other than cancer, severe multimorbidity (≥4 conditions) was associated with about threefold increased odds of depression for both men and women. The risk of depression increasing with higher comorbidity burden is consistent with the literature spanning a variety of primary health conditions [12, 25].

In addition, men with breast cancer had almost double the rate of severe multimorbidity compared to women. In our data, 74% of men with breast cancer were 60 years and older, compared to 55% of the women. Comorbidity generally increases with increasing age, and it may be the cause behind age-related differences in cancer diagnosis, treatment, and outcome. One significant finding of the study is that most of the chronic comorbidities identified among patients with breast cancer were diseases such as hypertension, diabetes mellitus, hyperlipidemia, CAD, CHF, and COPD; all of which are strongly associated with lifestyle behaviors. The high prevalence of physical inactivity in the breast cancer population (40%) confirms the lack of exercise and increasing body weight noted in previous studies [26, 27]. Patients with cancer who are sedentary have shown worse depressive symptoms [27].

Moreover, comorbidities, including mental health-related, negatively impact overall breast cancer prognosis, increasing both breast cancer-specific mortality as well as mortality rates for other conditions. We also found that depression was approximately 40% more likely to be diagnosed during an unplanned, compared to a planned, hospitalization in both women and men. Unplanned hospitalizations are unexpected admissions for management of a severe disease

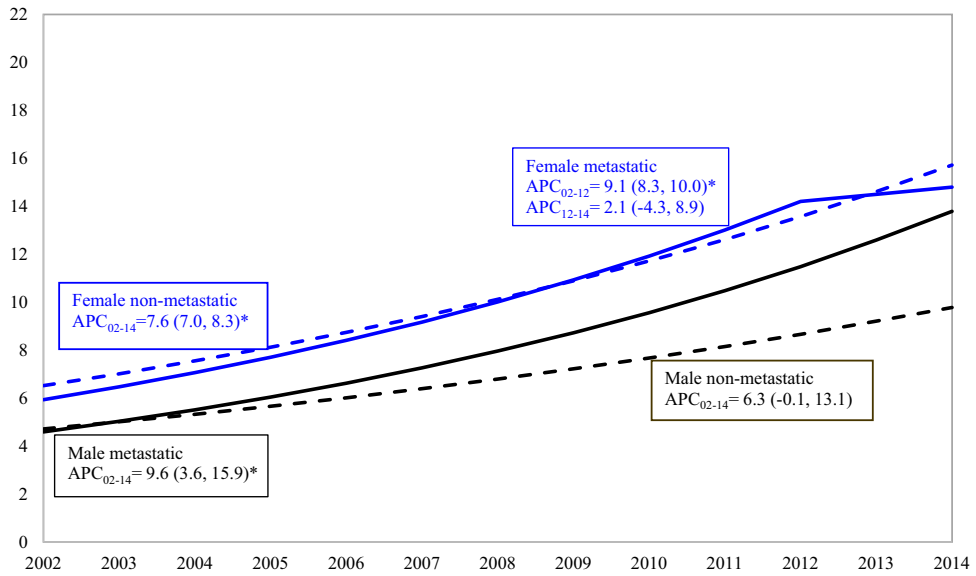


Fig. 3 Overall trends in depression among hospitalizations of patients aged 18 years or older with a diagnosis of breast cancer in men and women, National Inpatient Sample, United States, 2002–2014. The *x*-axis represents the year of hospitalization and the *y*-axis represents the percentage of inpatient hospitalizations with a diagnosis of depression. Lines represent the temporal trend estimated by joinpoint regression. Annual percent change (APC) is expressed as a point estimate, with the 95% confidence limits in parentheses. Includes 20 chronic conditions selected by the Office of the Assistant Secretary for Health, US Department of Health and Human Services for investigating multiple chronic conditions in the US population. Conditions include hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmias, hyperlipidemia, stroke, diabetes, arthritis, asthma, autism spectrum disorder, chronic kidney disease, chronic obstructive pulmonary disease, dementia (including Alzheimer's and other senile dementias), hepatitis, HIV, osteoporosis, schizophrenia, substance abuse disorders (drug and alcohol), depression, and cancer. Since the study population was defined by breast cancer status, and depression in the primary study outcome, these conditions were excluded from the comorbidity count

or treatment-related event that cannot be controlled in the outpatient setting [28]. As discussed above, the strong gradient effect between comorbid conditions and depression could also be a strong predictor of unplanned hospitalizations. Therefore, an unplanned hospitalization episode in a patient with breast cancer can be noted as a potential identifiable event for mental health screening and intervention point for improving quality of life among this population.

Standard routine screening and treatment for mood disorders should be part of quality cancer care. Early and frequent mental health assessments are essential not only to improving quality of life, but also to avoiding unnecessary hospital admissions that could reduce system-wide costs. Psychological/behavioral interventions are helpful for addressing comorbid depression and breast cancer, especially cognitive behavioral therapy [21–24, 29, 30]. Complementary and integrative therapies are widely used and some are known to be beneficial, spurring further investigation [31].

Strengths and limitations

Our findings should be considered in light of several key limitations. First, the HCUP data lack information on disease stage, which precludes the analysis of any advanced-disease association with hospital admissions as well as increased risk of depression. In addition, each year's patient population had individuals at all stages of cancer, from newly diagnosed to late-stage, and in all phases of the cancer continuum. The serial cross-sectional samples provided in the NIS, in an effort to maintain confidentiality, do not include personal identifiers that permit linkage of hospitalizations for the same person over time. In this study, we cannot distinguish whether two hospitalizations for breast cancer are hospitalizations for two different individuals or two hospitalizations for the same person. Due to the high likelihood of counting the same patients multiple times during the course of their cancer treatment (if they have a breast cancer-related diagnosis code during each hospitalization), our prevalence data and assessment of longitudinal trends should be interpreted with caution. Third, our diagnosis of breast cancer and of all chronic comorbidities rely solely on ICD-9-CM codes documented during the hospital stay, which are subject to human error. Diagnoses are not necessarily indicative of histopathologically confirmed cases, and for depression, diagnoses may be based on a variety of criteria made by healthcare providers with different specialty areas. However, the HCUP databases permit investigation of extremely large samples of hospitalized patients from all payers, and that are representative of all hospitalized patients in the US. This

study explores a variety of key sociodemographic, clinical, and hospital-level characteristics within an estimated population of 2.3 million women and 21,000 men with breast cancer across nearly all 50 states, an investigation which would not be possible by reviewing medical records, given the current fragmentation of clinical data.

Author contributions RZ was the primary contributing author and participated in writing all sections of the manuscript and conceptualization of the study. JS led the study design and served as database manager and lead statistician, as well as participating in drafting the methods and results sections. SM assisted in statistical analysis, writing the methods and results sections, and preparing figures and tables. MDG participated in writing the manuscript, reviewing literature, organizing references and introduction and conclusion sections. RL was instrumental in the conceptualization of the study design and served as editor and methodology evaluator. All authors contributed significantly to the study design, writing, analysis, and read and approved the final manuscript.

Data availability National Inpatient Sample (NIS) data are available from the Healthcare Cost and Utilization Project (https://www.hcup-us.ahrq.gov/tech_assist/centdist.jsp). Data are available to all researchers following a standard application process and signing of a data-use agreement. The authors confirm that they had no special access to the data used in this study (2002–2014 data from the Healthcare Cost and Utilization Project's National Inpatient Sample [NIS]). The authors paid a fee to access the NIS data used in this study, with a fee schedule in accordance with the HCUP Central Distributor, the entity that accepts, processes, and fulfills applications for the purchase of HCUP databases, and manages data use agreements (DUAs) for all data users (https://www.distributor.hcup-us.ahrq.gov/). Future researchers interested in purchasing and using HCUP databases will be required to complete the Web-based HCUP Data Use Agreement (DUA) Training (https://www.hcup-us.ahrq.gov/tech_assist/dua.jsp). Further instructions for submitting an application for purchasing HCUP Databases can be found at https://www.distributor.hcup-us.ahrq.gov/.

Compliance with ethical standards

Competing interests The authors of this work certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval NIS data are de-identified and publicly available. The Baylor College of Medicine Institutional Review Board classified this study as exempt.

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