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An observational study of the prevalence and incidence of comorbid conditions in older women with breast cancer

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Background: Longitudinal analyses of comorbid conditions in women with breast cancer are few.
Methods: Using Surveillance, Epidemiology, and End Results–Medicare data, we included 51 950 women aged ≥66 years with *in situ* and stage I to IV breast cancer diagnosed in 1998–2002. We identified the prevalence and incidence of 34 comorbid conditions in these women, as well as in a matched cohort without cancer whose rates were standardized to the age and race/ethnicity distribution of the cancer patients. We also estimated rates of office encounters and diagnostic or testing procedures during the 12 months before diagnosis.
Results: The prevalence of most conditions at diagnosis was comparable among breast cancer and noncancer patients. New conditions after diagnosis were more common in breast cancer patients, and the incidence rates increased with higher stage at diagnosis. Before diagnosis, women presenting with stage IV disease had 41% [95% confidence interval (CI) 38% to 43%] fewer physician encounters and 34% (95% CI 24% to 31%) fewer unique diagnostic tests than women diagnosed with carcinoma *in situ*.
Conclusions: Many comorbid conditions are identified as a consequence of the breast cancer diagnosis. There appears to be an important contribution from a lack of interaction with the health care system before diagnosis.

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introduction

Breast cancer is a common disease in women, and its incidence increases with age [1, 2]. Understanding the interplay between breast cancer and comorbid conditions is important because comorbidities influence decisions about the appropriate course of treatment and are independent risk factors for survival [3–5]. In addition, comorbidities may limit patients' eligibility for clinical trials, and consequently, the generalizability of study results to the overall population [6]. For these reasons, comorbidity burden is a key component of the diagnosis and treatment process as well as postcancer care.

If higher stage at diagnosis were related to greater comorbidity burden, as might be hypothesized, it would suggest that comorbidity considerations become more complicated for women with more advanced-stage breast cancer. Although there is no direct evidence of a significant reservoir of undiagnosed comorbid conditions that increases with stage, there are studies showing that more screening procedures and more ambulatory care visits are each associated with earlier stage at diagnosis [7, 8]. Based on this, it would be reasonable to surmise that those patients who do not seek care for signs and symptoms of cancer, or who delay screening, may ignore other health issues as well [9]. Such undiagnosed conditions would be expected to be picked up in the extensive testing and related evaluations conducted after cancer diagnosis. In the clinical trial setting, any conditions not identified at diagnosis could complicate the analysis and interpretation of the trial data. However, despite its relevance to patient care, the incidence of new comorbid conditions after cancer diagnosis has not, to our knowledge, been compared across stages, or to a control population of individuals without cancer.

Therefore, the purpose of this study was threefold: to quantify the comorbidity burden at the time of diagnosis by comparing the prevalence of a variety of conditions in women with and without breast cancer; to estimate the previously undetected comorbidity burden elicited after cancer diagnosis by estimating incidence rates for a variety of conditions in these women; and to explore whether the identification of comorbid conditions in breast cancer patients is related to the degree of precancer interaction with the health system in these women.

methods

data source

This study used the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, which links SEER cancer registry data with Medicare data. Medicare-eligible persons are primarily individuals aged ≥65 in the United States, although other younger populations are included based on disability or specific medical conditions [10–12]. Our dataset also included a separately created 5% random sample of noncancer patients from the Medicare program in the same catchment areas as those used in the SEER program for use as a reference (i.e. control) population.

study population and observation period

Patients were diagnosed with *in situ* and stage I to IV breast cancer between 1 January 1998 and 31 December 2002 and had Medicare claims available from 1997 through 2005. Women with previous primary cancer diagnoses in the SEER registry were excluded as were women who died in the month of diagnosis. Follow-up was based on data for covered health care services, including hospital, physician, and outpatient claims. Cancer and noncancer subjects were at least 66 years old to allow at least 12 months of Medicare claims data for identifying prevalent conditions before diagnosis. All patients were required to have both Part A and B Medicare coverage (i.e. fee-for-service) during the observation period, and all patients in managed care plans were excluded because detailed medical claims are not available for these individuals. Follow-up ended at the earliest of the following events: end of the observation period, end of Part A and B coverage, or death.

An identically sized cohort of women without cancer (i.e. noncancer patients) was created by matching on both time of diagnosis and geographic area to the cohort of women with cancer (other variables were controlled using stratification and adjustment as discussed below). For time matching, the SEER month and year of cancer diagnosis for each cancer patient were used to identify potential noncancer matches who had appropriate Medicare coverage on the same date. The first day of this month was assigned as the diagnosis index date for both the breast cancer patient and her randomly selected noncancer control. For geographic area matching, the county of residence was used first and the state of residence was used if no county match was available. Subjects in the noncancer cohort were known to be cancer-free through 2002.

patient characteristics

For women with breast cancer, the SEER data were the source for identifying the date of cancer diagnosis, cancer site, and tumor characteristics. Stage at breast cancer diagnosis was based on the SEER–Modified American Joint Committee on Cancer (AJCC) stage variable [13]. Hormone receptor status included estrogen receptor (ER) and progesterone receptor status (PR). For all patients, age was given in years at the diagnosis index date. Race/ethnicity was based on the following categories: white, black, Hispanic, or other (predominately American Indian, Native Alaskan, Pacific Islander, and Asian).

The algorithm from the National Cancer Institute (NCI) for constructing a comorbidity index was also used for all patients to estimate a modified Charlson Comorbidity Index incorporating the adaptations suggested by Deyo and Romano (excluding cancer as a condition) [14–16]. Scores were categorized into 0, 1, and ≥2.

definitions of comorbid conditions

Medicare claims data were used for identifying prevalent and incident conditions of interest throughout the observation period. Supplemental Appendix Table S1 (available at *Annals of Oncology* online) provides the International Classification of Diseases, ninth edition (ICD-9) codes used to identify the 34 conditions in both breast cancer and noncancer women [17]. These conditions were chosen to represent common comorbid conditions in older adults, as well as common consequences of chemotherapy (referred to as 'adverse events'). Diagnoses recorded on claims for inpatient stays were counted at the time of their first occurrence. Diagnoses in outpatient facility and physician claims were assessed similarly to the NCI comorbidity algorithm, which requires two diagnoses at least 30 days apart to identify a comorbidity (taking the

Table 1. Demographic characteristics of the breast cancer and noncancer patient cohorts

Characteristic		Breast cancer patients *N* (%)	Noncancer patients *N* (%)
Age (years)[a]	66–69	9690 (18.8)	9913 (19.2)
	70–74	13 469 (26.1)	12 451 (24.1)
	75–79	13 039 (25.3)	11 721 (22.7)
	≥ 80	15 392 (29.8)	17 505 (33.9)
Race/ethnicity	White	44 712 (86.7)	43 671 (84.7)
	Black	3345 (6.5)	3781 (7.3)
	Asian/Other	1843 (3.6)	2999 (5.8)
	Hispanic	1690 (3.3)	1139 (2.2)
SEER region	Georgia (Atlanta/Rural Georgia)	2027 (3.9)	2027 (3.9)
	California[b]	15 558 (30.2)	15 558 (30.2)
	Connecticut	4225 (8.2)	4225 (8.2)
	Hawaii	876 (1.7)	876 (1.7)
	Iowa	4544 (8.8)	4544 (8.8)
	Kentucky	3239 (6.3)	3239 (6.3)
	Louisiana	2731 (5.3)	2731 (5.3)
	Michigan (Detroit)	5013 (9.7)	5013 (9.7)
	New Jersey	6726 (13)	6726 (13)
	New Mexico	1408 (2.7)	1408 (2.7)
	Utah	1664 (3.2)	1664 (3.2)
	Washington (Seattle/Puget Sound)	3579 (6.9)	3579 (6.9)
NCI comorbidity score[c]	0	34 296 (68.6)	30 721 (63.3)
	1	10 844 (21.7)	10 797 (22.2)
	≥2	4833 (9.7)	7033 (14.5)
Stage at diagnosis[d]	*In situ*	7532 (14.6)	N/A
	I	22 235 (43.1)	
	II	14 753 (28.6)	
	III	2558 (5)	
	IV	2191 (4.3)	
	Unknown	2282 (4.4)	
Tumor grade at diagnosis	Well differentiated	9861 (19.1)	N/A
	Moderately differentiated	19 057 (26.9)	
	Poorly differentiated	12 564 (24.4)	
	Undifferentiated	1426 (2.8)	
	Other and unknown	8682 (16.8)	
ER/PR status	Positive	30 613 (59.3)	N/A
	Negative	5112 (9.9)	
	Unknown	15 865 (30.8)	
Year of diagnosis	1998	6412 (12.4)	N/A
	1999	6429 (12.5)	
	2000	12 915 (25)	
	2001	13 085 (25.4)	
	2002	12 749 (24.7)	

[a]Age at diagnosis index date.
[b]California includes Los Angeles, San Francisco/Oakland, San Jose/Monterey, and Greater California.
[c]Comorbidity index based on conditions identified in the 12 months before the diagnosis index date.
[d]Stage based on the American Joint Committee on Cancer's staging system (third edition).
ER, estrogen receptor; NCI, National Cancer Institute; PR, progesterone receptor; SEER, Surveillance, Epidemiology, and End Results.

first occurrence as the date of onset). For the subgroup of 10 conditions classified as adverse events, only claims associated with an inpatient or emergency department visit were counted, and, because 'rule-out' claims are less of a problem in the hospital setting, only a single diagnosis code was required. In this way, they align with the concept of 'serious adverse events' often used in clinical trials, although they may represent chronic conditions and/or be unrelated to cancer-directed therapy.

counts of physician encounters and diagnostic tests

As a simple approach to measuring interactions with the health system, we counted the number of physician encounters and the number of unique diagnostic tests carried out in the breast cancer and noncancer patient cohorts during the 12 months before, and after, the diagnosis index date. Physician encounters were defined as physician office visits using Healthcare Common Procedure Coding System (HCPCS) codes [18].

Unique diagnostic tests included claims with HCPCS codes for the following: radiology, pathology and laboratory, psychiatric diagnostics, gastroenterology diagnostics, echocardiography, intracardiac electrophysiology, cerebrovascular arterial studies, pulmonary testing, glucose monitoring, electroencephalography, and central nervous system assessments (see supplemental Appendix Table S2, available at *Annals of Oncology* online). One physician encounter per day per patient was counted, and one of each type of diagnostic test (HCPCS code) per patient was counted.

statistical analyses

For each condition, standardized rates were estimated for each of the three observation periods (before, 3 months after, and 12 months after the index date). These rates were estimated overall as well as within age, race/ethnicity, and stage-specific (for cancer patients) strata (data not shown). The cancer rates for each stratum were standardized to the age, race/ethnicity, and stage-specific characteristics of the total breast cancer cohort [19]. Rates in the noncancer patients were standardized to the age and race/ethnicity distribution of the total breast cancer cohort to facilitate comparisons.

Prevalence was defined as the proportion of study subjects with a particular condition as of the index date using claims before the diagnosis index date. Binomial confidence intervals (CIs) were calculated for each prevalence proportion. Incidence rates were defined as new diagnoses after the index date in patients free of the condition at diagnosis. If the comorbid condition was not diagnosed, subjects were censored at death, the end of coverage according to the eligibility criteria, or the end of the observation period. Incidence rates per 1000 person-years were estimated. The 12-month and 3-month rates reflect overlapping time periods.

Zero-inflated negative binomial models were used to estimate the average number of visits or tests during the year before the index date by cancer stage at diagnosis in the breast cancer cohort and to compare the number of visits or tests between cancer and noncancer patients. These models were adjusted for age and race/ethnicity [20, 21].

All analyses were conducted in SAS (version 9.2; SAS Institute Inc., Cary, NC) and Stata (version 10; Stata Corporation, College Station, TX).

results

There were 51 950 women identified in both the breast cancer and the noncancer populations. See Table 1 for details on the cohorts.

The standardized prevalence rates for 27 of the 34 conditions were lower in women with cancer compared with women without cancer (Table 2). Certain comorbidities were exceptions to this pattern: atrial fibrillation, hypertension, diabetes, liver disease, osteoarthritis, thromboembolic events, and chronic obstructive pulmonary disease. In terms of incidence rates for all conditions, standardized 3-month and 12-month rates were, with the exception of the 12-month cardiac arrest rate, always higher in the women with breast cancer. See Table 3 for incidence rates.

When stratified by stage at breast cancer diagnosis, for many comorbid conditions, the prevalence rates were quite variable (Figure 1 and supplemental Appendix Table S3, available at *Annals of Oncology* online). In contrast, the incidence rates for most conditions increased with higher stage at breast cancer diagnosis (Figure 2 and supplemental Appendix Table S4, available at *Annals of Oncology* online).

Table 2. Prevalence proportions for Comorbid conditions in breast cancer patients and noncancer control patients

Comorbid condition	Breast cancer patients, % (95% CI)	Noncancer patients, % (95% CI)
Adverse events		
Anemia	6.09 (5.89–6.3)	7.59 (7.36–7.81)
Diarrhea	1.62 (1.51–1.73)	1.83 (1.71–1.94)
Electrolyte disorder	9.39 (9.15–9.64)	11.34 (11.07–11.61)
Infectious disease	11.95 (11.68–12.23)	14.39 (14.09–14.69)
Infusion reaction	0.43 (0.38–0.49)	0.46 (0.4–0.52)
Neutropenia	0.13 (0.1–0.16)	0.16 (0.13–0.2)
Oral mucositis	0.03 (0.01–0.04)	0.03 (0.01–0.04)
Skin rash (medication related)	0.13 (0.1–0.16)	0.21 (0.17–0.25)
Skin rash (other)	2.02 (1.9–2.14)	2.36 (2.23–2.49)
Thrombocytopenia	0.55 (0.49–0.62)	0.68 (0.6–0.75)
Cardiac/vascular		
Arrhythmia	7.24 (7.01–7.46)	7.41 (7.18–7.63)
Arterial thrombosis	0.29 (0.25–0.34)	0.47 (0.41–0.53)
Atrial fibrillation	9.19 (8.94–9.43)	8.61 (8.37–8.85)
Coronary artery disease	18.35 (18.02–18.68)	19.13 (18.8–19.47)
Congestive heart failure	10.69 (10.43–10.96)	11.6 (11.33–11.86)
Cerebrovascular disease	8.11 (7.88–8.34)	9.39 (9.14–9.64)
Cardiac arrest	0.09 (0.06–0.11)	0.11 (0.08–0.14)
Hypertension	50.74 (50.31–51.16)	42.93 (42.51–43.35)
Myocardial infarction	4.18 (4.01–4.35)	4.67 (4.48–4.85)
Peripheral vascular disease	2.86 (2.72–3.01)	3.47 (3.31–3.63)
Thromboembolism	2.12 (2–2.25)	2 (1.87–2.12)
Gastrointestinal/hepatic		
Cholecystitis	1.61 (1.5–1.72)	1.62 (1.51–1.73)
Gastric ulcers	0.74 (0.67–0.81)	0.94 (0.85–1.02)
Liver disease	0.49 (0.43–0.55)	0.39 (0.34–0.45)
Metabolic		
Diabetes	14.29 (13.99–14.59)	12.8 (12.51–13.1)
Hyperglycemia	0.09 (0.07–0.12)	0.11 (0.08–0.14)
Musculoskeletal/rheumatic		
Osteoarthritis	16.06 (15.74–16.37)	15.52 (15.2–15.83)
Rheumatalogic disease	2.08 (1.95–2.2)	2.38 (2.25–2.52)
Neurological/psychiatric		
Alzheimer's disease and dementia	3.79 (3.63–3.95)	6.67 (6.46–6.87)
Depression	5.56 (5.36–5.76)	6.27 (6.06–6.48)
Hemiplegia	0.94 (0.86–1.02)	1.27 (1.18–1.37)
Pulmonary		
Chronic obstructive pulmonary disease	9.83 (9.57–10.08)	9.77 (9.51–10.03)
Renal		
Nephrotic syndrome	0.06 (0.04–0.09)	0.08 (0.05–0.1)
Renal disease	1.33 (1.23–1.43)	1.49 (1.38–1.59)

Noncancer women are matched to women with breast cancer by time and geographic area. All rates are standardized to the age and race/ethnicity distribution of the cancer population.
CI, confidence inteval.

Women with and without breast cancer had comparable numbers of physician encounters in the window of time beginning 12 months before the cancer diagnosis date and

Table 3. Estimates of 3-month and 12-month incidence of comorbid conditions in breast cancer and noncancer patients

Comorbid condition	Breast cancer patients 3-month rate/1000 (95% CI)	Noncancer patients 3-month rate/1000 (95% CI)	Breast cancer patients 12-month rate/1000 (95% CI)	Noncancer patients 12-month rate/1000 (95% CI)
Adverse events				
Anemia	105.65 (99.79–111.52)	34.66 (31.33–37.99)	63.63 (61.29–65.97)	34.51 (32.8–36.21)
Diarrhea	15.61 (13.43–17.8)	7.09 (5.63–8.55)	11.01 (10.07–11.95)	6.88 (6.14–7.62)
Electrolyte disorder	124.04 (117.59–130.49)	49.17 (45.12–53.21)	78.69 (76.04–81.34)	47.13 (45.1–49.16)
Infectious disease	149.82 (142.62–157.02)	55.02 (50.64–59.39)	94.64 (91.68–97.6)	56.78 (54.51–59.06)
Infusion reaction	5.71 (4.4–7.02)	1.12 (0.53–1.71)	3.16 (2.66–3.66)	1.64 (1.28–2.01)
Neutropenia	17.48 (15.19–19.77)	0.3 (0–0.6)	15.6 (14.49–16.71)	0.8 (0.55–1.04)
Oral mucositis	2.02 (1.27–2.77)	0.07 (0–0.2)	2.15 (1.73–2.56)	0.12 (0.02–0.21)
Skin rash (medication related)	2.34 (1.5–3.18)	0.56 (0.14–0.98)	1.17 (0.86–1.47)	0.63 (0.41–0.86)
Skin rash (other)	35.34 (32.04–38.63)	10.07 (8.32–11.82)	20.85 (19.55–22.15)	10.43 (9.53–11.34)
Thrombocytopenia	11.52 (9.66–13.38)	3.26 (2.26–4.26)	8.23 (7.43–9.04)	3.72 (3.18–4.27)
Cardiac/vascular				
Arrhythmia	52.25 (48.13–56.37)	15.69 (13.45–17.94)	25.56 (24.08–27.04)	16.28 (15.11–17.46)
Arterial thrombosis	2.73 (1.83–3.64)	1.3 (0.66–1.95)	1.97 (1.57–2.36)	1.41 (1.07–1.75)
Atrial fibrillation	58.73 (54.32–63.15)	21.34 (18.72–23.96)	30.45 (28.82–32.08)	21.66 (20.31–23.02)
Coronary artery disease	80.31 (74.85–85.77)	28.77 (25.48–32.07)	35.35 (33.49–37.21)	26.61 (24.99–28.22)
Congestive heart failure	64.58 (59.91–69.25)	32.49 (29.17–35.8)	37.71 (35.88–39.54)	28.61 (27.02–30.19)
Cerebrovascular disease	42.16 (38.45–45.88)	23.88 (21.08–26.68)	24.55 (23.09–26)	22.24 (20.85–23.62)
Cardiac arrest	2.42 (1.57–3.27)	1.99 (1.22–2.77)	1.84 (1.46–2.22)	2.24 (1.82–2.65)
Hypertension	252.56 (239.88–265.24)	50.75 (45.5–55.99)	94.51 (90.49–98.53)	43.54 (41.05–46.02)
Myocardial infarction	45.12 (41.36–48.89)	15.24 (13.04–17.43)	21.7 (20.36–23.04)	16.53 (15.37–17.69)
Peripheral vascular disease	18.15 (15.79–20.52)	9.38 (7.66–11.1)	9.83 (8.94–10.72)	8.68 (7.84–9.51)
Thromboembolism	26.17 (23.34–29)	5.53 (4.24–6.83)	20.75 (19.46–22.05)	6.32 (5.61–7.02)
Gastrointestinal/hepatic				
Cholecystitis	7.92 (6.37–9.47)	4.05 (2.9–5.2)	5.89 (5.2–6.57)	4.9 (4.26–5.53)
Gastric ulcers	4.63 (3.45–5.81)	2.93 (2.02–3.85)	3.29 (2.78–3.8)	3.42 (2.9–3.93)
Liver disease	3.13 (2.16–4.1)	1.04 (0.48–1.6)	1.7 (1.34–2.07)	1.25 (0.94–1.56)
Metabolic				
Diabetes	34.96 (31.46–38.46)	13.48 (11.32–15.64)	17.17 (15.91–18.43)	11.32 (10.31–12.33)
Hyperglycemia	1.48 (0.81–2.15)	0.35 (0.04–0.66)	0.69 (0.46–0.93)	0.33 (0.17–0.49)
Musculoskeletal/rheumatic				
Osteoarthritis	71.85 (66.76–76.93)	25.85 (22.83–28.87)	34.1 (32.29–35.9)	22.35 (20.91–23.79)
Rheumatalogic disease	8.99 (7.34–10.65)	2.73 (1.8–3.67)	3.97 (3.4–4.53)	2.66 (2.19–3.12)
Neurological/psychiatric				
Alzheimer's disease and dementia	37.9 (34.46–41.34)	19.02 (16.56–21.48)	20.78 (19.47–22.08)	21.3 (19.98–22.62)
Depression	44 (40.26–47.74)	14.27 (12.14–16.39)	23.55 (22.14–24.95)	14.59 (13.49–15.7)
Hemiplegia	7.79 (6.25–9.32)	4.53 (3.37–5.69)	4.74 (4.13–5.36)	4.41 (3.82–4.99)
Pulmonary				
Chronic obstructive pulmonary disease	78.02 (72.9–83.13)	19.08 (16.55–21.62)	33.06 (31.35–34.77)	18 (16.75–19.24)
Renal				
Nephrotic syndrome	0.55 (0.14–0.95)	0.29 (0–0.58)	0.31 (0.15–0.46)	0.3 (0.15–0.44)
Renal disease	8.45 (6.85–10.05)	5.27 (4.01–6.53)	5.57 (4.91–6.24)	5.14 (4.51–5.77)

Noncancer patients are matched to cancer patients on gender, index date, and geographic area. All rates are standardized to the age and race/ethnicity distribution of the cancer population. Rates are expressed per 1000 person-years.
CI, confidence interval.

ending 4 months prior, as seen in the unadjusted counts in Figure 3. For women with breast cancer, the counts of both physician encounters and new diagnostic tests during the 12-month precancer diagnosis period appeared to increase beginning 3 months before the cancer diagnosis date. Statistical models to estimate counts and rates in the precancer diagnosis period were consistent with these figures after adjusting for age and race/ethnicity, as well as accounting for censoring (i.e. losses to follow-up and death). When we excluded the 3-month pre-diagnosis period from the statistical models comparing utilization between women with and without breast cancer, most of the difference in physician encounters and virtually all of the difference in diagnostic testing were removed (Table 4).

Analyses of the numbers of physician encounters and unique diagnostic tests by stage showed that each measure was inversely related to the stage of breast cancer at diagnosis. This trend was consistent for both the entire 12-month period

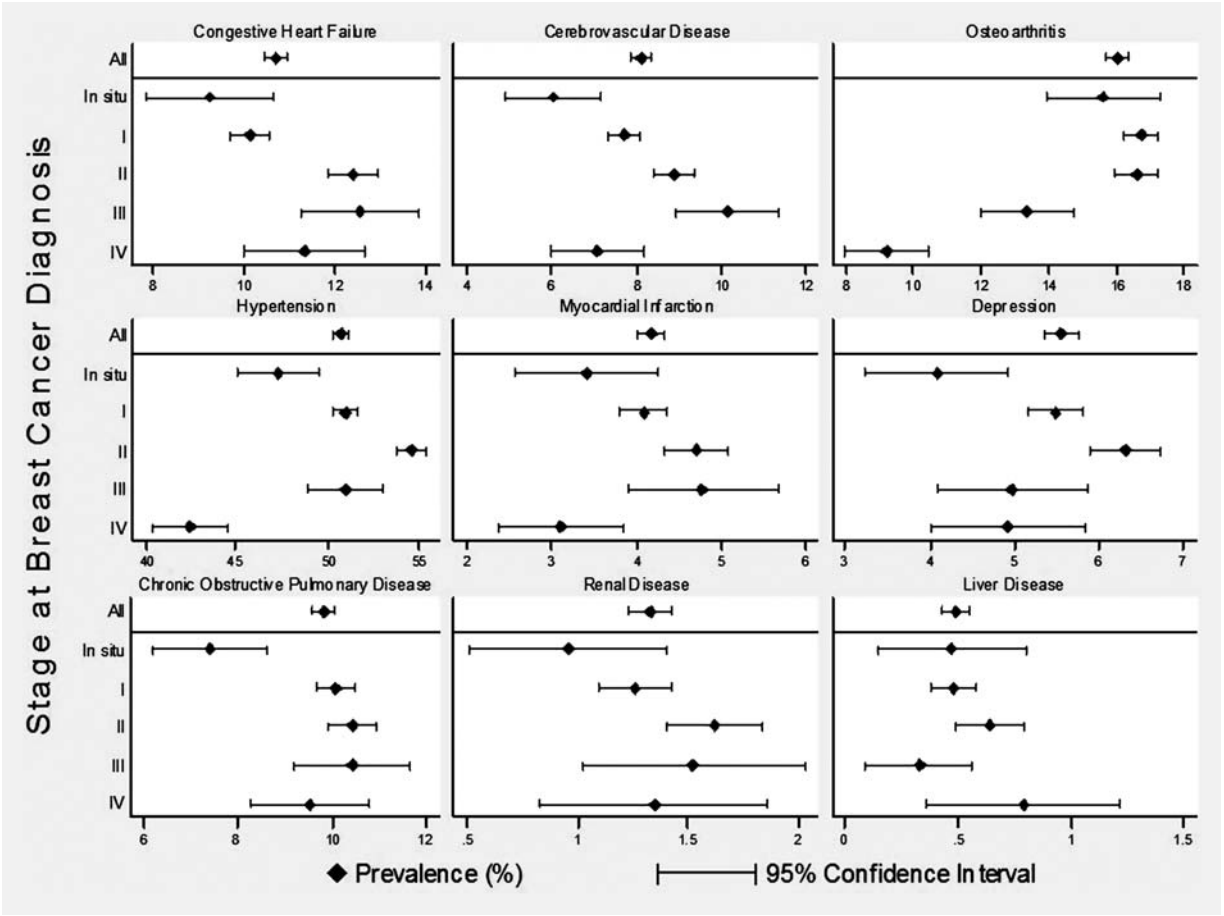

Figure 1. The prevalence of selected comorbid conditions in breast cancer patients by diagnosis stage. Comorbid conditions were selected to include a variety of systems. See supplemental Appendix materials (available at *Annals of Oncology* online) for data on other conditions.

before diagnosis, as well as the period excluding the 3-month pre-diagnosis period. In particular, patients presenting with stage IV disease had 41% (95% CI 38% to 43%) fewer physician encounters and 34% (95% CI 24% to 31%) fewer unique diagnostic tests than women diagnosed with carcinoma *in situ* when ignoring the 3-month pre-diagnosis period (Table 4).

discussion

This study shows that older women, at the time of breast cancer diagnosis, have a comparable prevalence of comorbid conditions to women who do not have breast cancer. In addition, stage at diagnosis is associated with variability in the prevalence of many conditions, but the pattern of the association is quite heterogeneous. In contrast, the incidence rates of comorbid conditions, stratified by stage at diagnosis, show that more advanced cancer stage is associated with a greater likelihood of identifying new comorbid conditions. Most importantly from a public health perspective, more advanced stage at diagnosis is also associated with the degree of precancer health system interaction, as measured by office visits and unique diagnostic tests. Hence, there is evidence for a health care seeking behavioral component to the undiagnosed comorbidity burden in breast cancer patients.

Looking more closely, older women with breast cancer tended to have slightly lower prevalence rates for most comorbid conditions compared with women without cancer, even after accounting for age, race, time, and geographic area. Some of this is likely to be related to an under-diagnosis of conditions in women with later-stage disease, a gap that shrinks after the cancer diagnosis. However, the prevalence of several conditions was higher in women with breast cancer than in those without, in contrast to the overall pattern. For hypertension, diabetes, thromboembolic events, and osteoarthritis, there is an established association with higher body mass index (BMI), a confounder that could not be controlled through standardization in these data [22–28]. That is, because higher BMI is a risk factor for breast cancer, our breast cancer population may have been heavier, which may have increased the prevalence of conditions associated with higher BMI [29, 30]. Similar reasoning may apply to alcohol consumption and liver disease [31, 32].

There are a variety of conflicting studies evaluating the cross-sectional association between comorbidity burden and breast cancer stage at diagnosis. Yancik et al. [4] found no

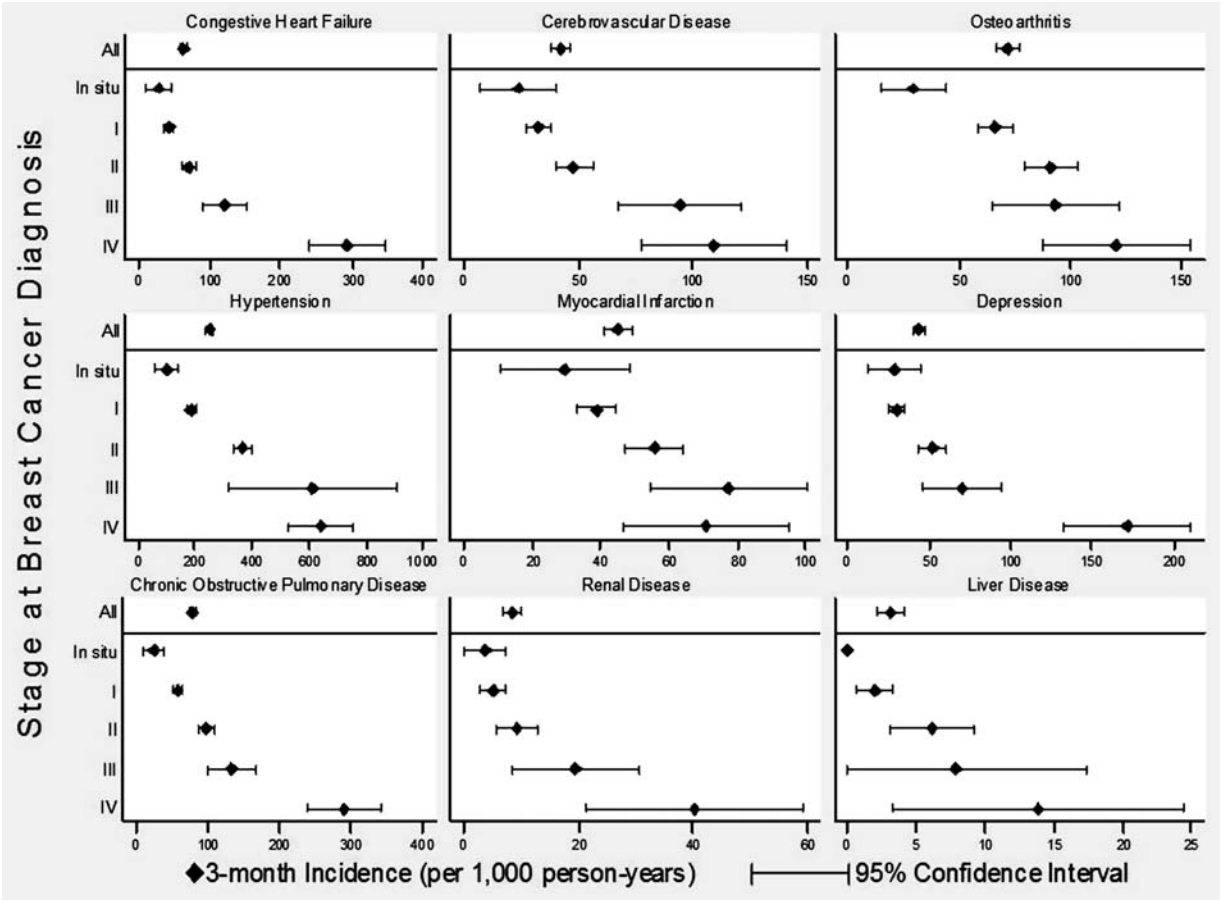

Figure 2. The 3-month incidence of selected comorbid conditions in breast cancer patients by diagnosis stage. Comorbid conditions were selected to include a variety of systems. See supplemental Appendix materials (available at *Annals of Oncology* online) for data on other conditions.

association between comorbidity and breast cancer stage. Fleming et al. [33] found that the association between comorbid conditions and advanced-stage diagnosis depended on the comorbid condition. Vaeth et al. [34] found that women with conditions causing functional limitations were half as likely to be diagnosed with advanced-stage breast cancer. Gonzalez et al. [35] found that a higher comorbidity index was associated with higher odds of advanced-stage breast cancer. In addition, similarly conflicting results exist for other tumors as well [36, 37]. The presence of undiagnosed conditions, many of which are found after cancer diagnosis, appears to confound associations at the time of diagnosis.

In addition to our study, others have suggested that interaction with the health system is a key factor in stage at diagnosis. Gornick et al. [7] showed that the use of preventive services was associated with a lower likelihood of late-stage diagnosis for breast cancer, colorectal cancer, and prostate cancer. Keating et al. [8] showed that women who saw a medical provider in the 2 years before diagnosis were significantly less likely to be diagnosed with advanced-stage disease. Furthermore, several studies have evaluated the use of mammography and have shown that its use is associated with a less-advanced stage at diagnosis [38, 39]. Our findings add additional evidence to support the idea that cancer can be identified early if women interact sufficiently, and appropriately, with the system.

Our findings extend this previous work in several ways. First, in the year before diagnosis (particularly when ignoring the 3-month pre-diagnosis period), the overall patterns of medical resource use for women with and without breast cancer were remarkably similar. Based on this, there does not appear to be any excess utilization in the year immediately preceding diagnosis. Second, the increase in resource use that occurs around diagnosis begins as early as 3 months before the month of diagnosis. Hence, the time it takes to diagnose a woman with breast cancer is variable, occurring over several months. Third, the rate of newly diagnosed conditions is very high in the 3-month period after the breast cancer diagnosis. These findings have implications for researchers as well as clinicians, particularly for researchers studying, or adjusting for, the effect of comorbidity on outcomes.

Studies of the comorbid conditions identified after breast cancer diagnosis are few. However, our results are comparable to those from a recent study of comorbid conditions in 1183 breast cancer patients in the Health, Eating, Activity, and Lifestyle Study (HEALS) [40]. In both HEALS and our study, hypertension was the most common comorbid condition at the time of diagnosis and also the most commonly identified new

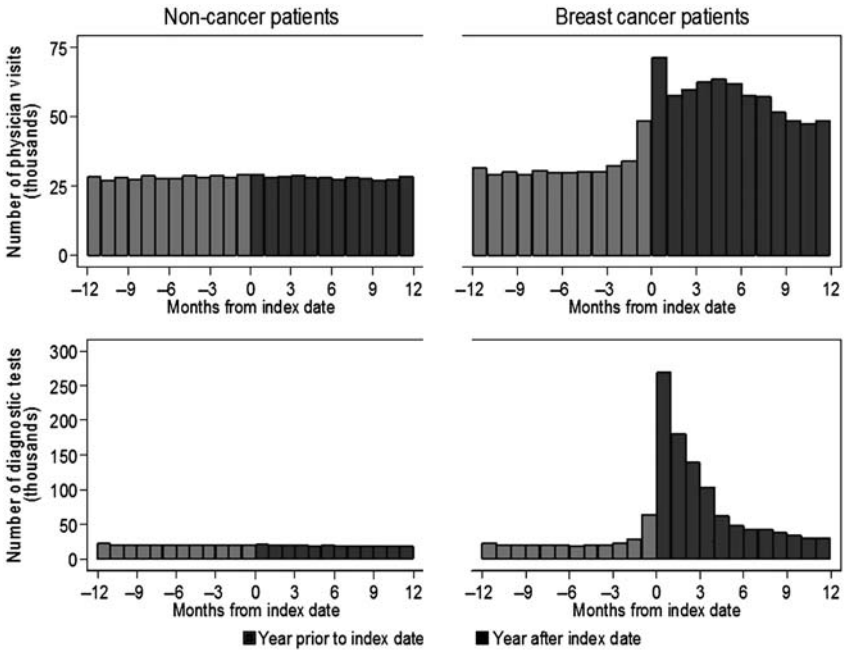

Figure 3. The unadjusted number of physician office visits and unique diagnostic tests before and after the diagnosis index date. Counts in the above figures do not show losses to follow-up after diagnosis. At 3 months the breast cancer and noncancer populations were 96% and 98% of the baseline total, respectively (51 590); at 6 months they were 94% and 96% of baseline, respectively; and at 12 months they were 90% and 93% of baseline, respectively.

Table 4. Outpatient visits and unique diagnostic tests in the year before the diagnosis index date for breast cancer and noncancer patients (both overall and by stage)

Population		Physician encounters		Unique diagnostic tests	
		Mean	Rate ratio (95% CI)	Mean	Rate ratio (95% CI)
Months −12 to −1 before diagnosis index date					
Noncancer (overall)		4.99	1.00 (ref)	4.83	1.00 (ref)
Breast cancer (overall)		7.43	1.49 (1.47–1.51)	5.73	1.17 (1.16–1.19)
By stage	*In situ*	8.26	1.00 (ref)	6.41	1.00 (ref)
	I	7.86	0.95 (0.93–0.97)	6.01	0.94 (0.91–0.97)
	II	7.14	0.86 (0.84–0.88)	5.39	0.84 (0.82–0.87)
	III	5.52	0.66 (0.63–0.68)	4.15	0.65 (0.62–0.68)
	IV	5.24	0.63 (0.60–0.65)	4.64	0.72 (0.69–0.76)
	Unknown	6.68	0.79 (0.76–0.82)	5.63	0.89 (0.84–0.93)
Months −12 to −4 before diagnosis index date					
Noncancer (overall)		4.87	1.00 (ref)	3.62	1.00 (ref)
Breast cancer (overall)		5.22	1.08 (1.06–1.09)	3.58	0.98 (0.96–1.00)
By stage	*In situ*	5.77	1.00 (ref)	3.96	1.00 (ref)
	I	5.54	0.95 (0.93–0.98)	3.76	0.95 (0.92–0.99)
	II	5.04	0.86 (0.84–0.88)	3.41	0.86 (0.83–0.89)
	III	3.92	0.66 (0.64–0.69)	2.70	0.68 (0.64–0.73)
	IV	3.48	0.59 (0.57–0.62)	2.62	0.66 (0.62–0.71)
	Unknown	4.72	0.80 (0.76–0.83)	3.57	0.91 (0.85–0.97)

Estimated by negative binomial regression and adjusted for age at diagnosis and race/ethnicity.
CI, confidence interval.

condition after cancer diagnosis. In contrast, our sample had higher rates of cardiovascular disease, which is not surprising given that our SEER–Medicare population was notably older.

In addition, our study shows that many of these newly identified conditions appear shortly after diagnosis (within 3 months), and in a period of time associated with a substantial

increase in the use of diagnostic tests and the initiation of interventions.

There are several key strengths to our analytic approach. The use of a noncancer control group has not been used in other related studies. Its inclusion is important because while claims data are limited in their ability to identify all clinically relevant disease, the control group facilitates internally consistent comparisons. Also, the calculation of both incidence and prevalence allows us to understand the complete picture of comorbidity around the time of diagnosis. The large sample size allows for more accurate rate estimation, particularly for less common conditions. Finally, matching by time and geographic area allows us to control for temporal trends and geographic variation (as well as socioeconomic factors to a limited degree), which can be difficult to adjust for, while allowing for analyses by race, stage, and age (not all of which are shown).

However, the limitations of these analyses also deserve discussion. The SEER–Medicare merged data lack certain variables (e.g. BMI) that would be useful for comparing women with and without breast cancer more precisely. In addition, we did not have complete medical histories for patients, particularly from their pre-Medicare coverage. Also, we were limited to diagnoses that are included in claims data. While studies have generally confirmed that claims data are reasonably sensitive and specific, there are limits to the reliability of claims data for identifying comorbid conditions [41, 42]. It is possible that some of the newly identified conditions are the result of cancer-directed therapy initiated shortly after diagnosis and are not previously undiagnosed conditions. On the other hand, the strong and consistent relationship across conditions between incidence and stage suggests otherwise, particularly in conditions that should not be related to breast cancer interventions (e.g. osteoarthritis). Finally, our measures of physician encounters and unique diagnostic testing are intentionally simplistic, and more sophisticated measures focusing on specific diagnostic tools and their utilization (as used by others) might provide improved insights into the nature of the interactions between providers and patients with respect to cancer diagnosis.

Even with these limitations, this study demonstrates that older women with breast cancer suffer from a myriad of comorbid conditions that may affect treatment and outcomes. Many of these are identified as a consequence of the cancer diagnosis. While some may result from common biological pathways, there is also an important contribution from health-seeking behavior before the cancer diagnosis. To the extent that this behavior is modifiable, particularly with screening-friendly reimbursement policies, it may be possible to find both cancer and comorbid conditions earlier and improve survival.

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Institutional Review Board (IRB) approval: At the time of study approval in July 2008, IRB approval was not required. Analyses of the SEER–Medicare data were considered to be exempt from the need for IRB review according to the National Institutes of Health's Office of Human Subjects Research.

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disclosures

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