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Medical Comorbidities Predict Mortality in Women with a History of Early Stage Breast Cancer

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Abstract

Introduction—This analysis was conducted to determine whether comorbid medical conditions predict additional breast cancer events and all-cause mortality in women with a history of early stage breast cancer.

Methods—Women (n=2542) participating in a randomized diet trial completed a selfadministered questionnaire regarding whether they were currently being treated for a wide variety of diseases (cardiovascular, diabetes, gallbladder, gastrointestinal, arthritis, and osteoporosis) and conditions (high blood pressure, elevated cholesterol level). Height and weight were measured at baseline. Participants were followed for a median of 7.3 years (range 0.8 to 15.0). Cox regression analysis was performed to assess whether comorbidities predicted disease-free and overall survival; hazard ratio (HR) was the measure of association.

Results—Overall, there were 406 additional breast cancer events and 242 deaths. Participants with diabetes had over 2-fold the risk of additional breast cancer events (HR 2.1, 95% CI: 1.3, 3.4) and mortality (HR 2.5, 95% CI: 1.4, 4.4). The presence of multiple comorbidities did not statistically significantly predict additional breast cancer events. However, compared to no comorbidities, participants with 3 or more comorbidities had a HR of 2.1, 95% CI: 1.3, 3.3 for mortality.

Conclusion—Type 2 diabetes was associated with poor breast cancer prognosis. Given that 85 percent of deaths were caused by breast cancer, these findings suggest that multiple comorbidities may reduce the likelihood of surviving additional breast cancer events.

Keywords

comorbidities; breast cancer; mortality

INTRODUCTION

Advances in early detection and treatment have led to increasing survival rates following breast cancer, resulting in a burgeoning population of survivors [1]. As the US population ages and cancer survivorship increases, oncologists are increasingly being presented with patients with multiple threats to their longevity. Recent studies indicate that hypertension [2] and diabetes [3–5] are associated with reduced survival in women who have been diagnosed with breast cancer, although it is not clear whether these conditions increase the risk for breast cancer recurrence and breast cancer specific mortality or for competing diseases such as cardiovascular disease.

The mechanism by which comorbidities may affect risk of recurrent cancer is not well understood. It is likely that comorbidities are associated with poorer health-related quality of life, particularly with physical health. Low scores on physical health scales are associated with low levels of physical activity and obesity [6], both of which are associated with higher concentrations of circulating estradiol [7–9]. Not only has circulating estradiol concentration been associated with breast cancer recurrence in postmenopausal women [10], but it is the target for aromatase inhibitor therapy – a proven agent for prevention of breast cancer recurrence [11].

The most common approach to assessing comorbidity is through the use of indices that sum across multiple diseases and conditions [12,13]. The main endpoint explored has been mortality, with which comorbidity is reliably correlated [14]. Much less is known about the importance of comorbidities for specific disease outcomes.

The purpose of this analysis was to assess whether baseline comorbidities were predictive of additional breast cancer events or mortality in a sample of women with a history of breast cancer. Data were from the Women's Healthy Eating and Living (WHEL) Study, a randomized, controlled trial designed to test the effects of adoption of a diet that was very high in vegetables, fruit, and fiber and low in fat in women who had been diagnosed and treated for early stage breast cancer.

SUBJECTS AND METHODS

Study design and sample

Details of eligibility criteria, data collection, and assessment of outcomes in the WHEL trial have been reported previously [15]. Briefly, 3088 trial participants were enrolled at 7 study sites between 1995 and 2000. Major eligibility criteria included diagnosis within past 4 years of primary operable invasive stage I (≥ 1 cm), II, or IIIA breast carcinoma categorized using American Joint Committee on Cancer (edition IV); age 18–70 years at the time of diagnosis; no current or planned chemotherapy; no evidence of recurrent disease or new breast cancer since completion of initial treatment; and no other cancer in the past 10 years. Women were also excluded from participation if they required a diet or medication that contraindicated a high-fiber diet. WHEL Study participants were mailed a series of questionnaires for completion before or at their baseline clinic visit. At the baseline clinic visit, height and weight were measured. The Human Subjects Committee of the University of California, San Diego and all participating institutions approved the study procedures.

As reported in 2007, among survivors of early stage breast cancer, adoption of a diet that was high in vegetables, fruit, and fiber and low in fat did not reduce additional breast cancer events or mortality during a 7.3-year follow-up period [16].

Comorbidity assessments

At baseline, subjects were asked to complete a self-administered questionnaire regarding whether they were currently being treated for a wide variety of diseases and conditions. These diseases/conditions were selected based on prevalence in this population and their potential to predict outcomes in breast cancer survivors. Specifically, they were asked about cardiovascular disease (angina, peripheral arterial disease, other heart conditions), diabetes, gallbladder/kidney/pancreas disease (gallbladder disease, kidney/bladder stones, pancreatitis), gastrointestinal disorders (ulcers, diverticulitis, colitis, intestinal removal, irritable bowel syndrome, and malabsorption syndrome), arthritis, and osteoporosis. The specific diseases were combined into general systems (such as cardiovascular disease) to mirror the well-validated Charlson index, to avoid the potential for double counting (e.g., intestinal removal and malabsorption syndrome), and to limit the problem of small sample sizes (e.g., peripheral arterial disease, $n=8$). Patients were also asked if they were being treated for hypertension and high blood cholesterol. Weight and height were measured at baseline with the participants wearing light clothing and no shoes; body mass index (BMI) was calculated and a cutpoint of 30 kg/m^2 was used to indicate obesity. An index was created by summing those comorbidities that were shown to be associated with poor outcomes.

Other assessments

Standardized questionnaires administered at baseline ascertained demographic, behavioral, and lifestyle characteristics. Variables assessed included age, race/ethnicity, educational achievement, employment and marital status, menopausal status, presence of hot flashes, smoking and alcohol intake.

Physical health was assessed using the Rand-36-item Health Survey (SF-36) that summarizes four physical subscales (general health perceptions, physical functioning, bodily pain, role limitations due to physical health problems). The RAND-36 uses the same questions as the SF-36, but with minor scoring differences. All subscales have been shown to be reliable (Cronbach's $\alpha=0.75$ to 0.91) and to have adequate construct validity in a variety of diseased populations [17]. The 4 subscales were summarized into the physical health summary score (range=0–100; higher scores indicate better health). Physical health was categorized as “Low” = quintiles 1–2 and “Moderate/High” = quintiles 3–5.

Data on the original tumor characteristics and treatment were abstracted from medical records. Specific variables include chemotherapy use (yes, no), anti-estrogen use (yes, no), tumor type (either or both lobular and ductal invasive, neither), tumor differentiation (well, moderate, poor), cancer stage (I, IIA, IIB, IIIA, and IIIC), and estrogen and progesterone receptor status.

Outcome ascertainment

The outcomes of interest were disease-free survival and overall survival. Disease-free survival is the time from WHEL Study enrollment (1995–2000) to development of an additional breast cancer event or the end of follow-up. An additional breast cancer event is defined as a recurrence from the original cancer or developing a new invasive breast cancer. Overall survival is the time from enrollment to reported/confirmed death from all causes (i.e., mortality). Participants could experience both an additional breast cancer event and death. Follow-up time for each outcome was censored at the time of an additional breast cancer event, a participant's death, the last documented staff contact date, or study completion (June 1, 2006). New breast cancer events or death were confirmed by medical record review and death records were collected from the National Death Index on an on-going basis to evaluate the cause of death among study participants.

Statistical analyses

The questionnaire on comorbidities was added to the WHEL baseline assessment protocol after recruitment had begun. Therefore, of the 3088 participants enrolled in WHEL, 546 women were missing data on baseline comorbidities (17.7%) so the size of the sample analyzed was 2542. We used a cohort analysis after verifying that comorbidities did not vary by intervention group or time period (over 6 years of baseline data collection), or show a group by time interaction. Cox proportional hazard regression was used to determine the association of comorbidities with disease free survival and overall survival, adjusting for cancer stage, grade, age, and education. The hazard ratio (HR) and the associated 95% confidence intervals were the measure of association.

Univariate associations were examined for the following variables known to affect disease-free and overall survival: (1) patient characteristics (age, BMI, race/ethnicity, education, marital and employment status), (2) lifestyle (physical activity, smoking and alcohol consumption), (3) reproductive (menopausal status, hot flash status) and (4) tumor characteristics (type, grade, stage, and tumor estrogen receptor [ER] and progesterone receptor status). Variables were included in the proportional hazards models if they were significantly associated with the comorbidity variables.

All tests were two-sided and analyses were conducted in SAS version 9.2 (Cary, NC).

RESULTS

In this sample of 2542 women with a history of breast cancer, the mean (SD) baseline age of participants was 52 (9) years and BMI was 27.2 (6.1) kg/m²; 54.7% were college graduates and 85.1% were non-Hispanic white. The majority of tumors were Stage I (37.7%) or Stage IIA (32.9%) and poorly (36.8%) or moderately (40.6%) differentiated. Most women received some form of adjuvant therapy as part of their post-surgical treatment (66.0% tamoxifen; 71.8% chemotherapy, and 62.7% radiation therapy). Finally, 74.5% of tumors were ER-positive. Mean follow-up time was 7.3 years (range 0.8 to 15.0 years). At the end of the trial (June 01, 2006), there were 406 (16.0%) additional invasive breast cancer events and 242 (9.5%) deaths from all causes. Among the deaths, 205 (84.7%) were caused by breast cancer.

The most common comorbidities in this cohort were obesity (26% of women) and arthritis (19% of women) (Table 1). To assess the face validity of these self-reported comorbidities, we compared comorbidities to physical health as assessed by the SF-36 questionnaire¹. In all cases, participants with a comorbidity were almost twice as likely to report poor physical health compared to participants without a comorbidity (all $p < 0.01$).

As shown in Table 2, participants who reported being treated for diabetes had over 2-fold the risk of additional breast cancer events (HR 2.1, 95% CI: 1.3, 3.4) and mortality (HR 2.5, 95% CI: 1.4, 4.4) compared to women without diabetes. With the exception of arthritis and osteoporosis, other comorbidities showed a trend toward increased risk of additional breast cancer events and mortality, none of which reached statistical significant. Given that arthritis and osteoporosis have some evidence of a protective effect, they were not included in the comorbidity index. When combining comorbidities into a summary (i.e., additive) index, there was no statistically significant association with additional breast cancer events. However, there was a significant trend for increased numbers of comorbidities to predict mortality ($p = 0.001$). For example, compared to no medical comorbidities, participants with 3 or more comorbidities had a HR of 2.1, 95% CI: 1.3, 3.3.

¹Note that 74 participants were excluded from this analysis because of missing physical health data.

DISCUSSION

In this cohort of breast cancer survivors, diabetes predicted increased risk of additional breast cancer events and mortality. A number of studies have reported that type 2 diabetes increased risk of incident breast cancer [3,18] and a recent meta-analysis indicated that diabetes was associated with increased mortality from breast cancer (HR, 1.61; 95% CI, 1.46–1.78) [19]. We found no publications regarding diabetes as a predictor of breast cancer recurrence. There are a number of explanations for how diabetes could increase the risk of breast cancer and/or death. Women with type 2 diabetes are frequently overweight or obese; which is associated with increased risk of postmenopausal breast cancer [20]. Mechanistically, type 2 diabetes is characterized by high levels of growth factors (insulin and insulin-like growth factor [IGF-1]) and inflammatory markers (C-reactive protein, IL-6, adiponectin, and VEGF); all of which have been associated with carcinogenesis [21,22]. Insulin and IGF-1 are growth factors and exhibit mitogenic effects that influence both premalignant and malignant stages of cell growth [23] and can promote tumor development by inhibiting apoptosis [23–25]. Inflammation-associated oxidative damage may initiate carcinogenesis by inactivating mutations in tumor-suppressor genes or post-translational modifications in proteins involved in DNA repair or apoptotic control [26]. In addition, inflammatory markers have been linked with a number of carcinogenic mechanisms, including angiogenesis, cell proliferation, metastasis, and alterations in sex-steroid hormone levels [27]. Pierce et al recently reported that in a cohort of 1183 breast cancer patients, 2 biomarkers of inflammation (C-reactive protein and serum amyloid A) were nonsignificantly associated with disease-free survival and statistically significantly associated with reduced overall survival (p trend <0.001) [28]. Finally, diabetes may affect response to treatment. In a SEER² study of older patients with breast cancer, diabetes was statistically significantly associated with chemotherapy toxicity, infection or fever, neutropenia, and anemia; as well as higher all cause mortality (HR 1.35, 95% CI: 1.31, 1.39) [29].

Overall, the presence of multiple medical comorbidities or conditions was not statistically significantly associated with additional breast cancer events. However, women with three or more comorbidities were at significantly higher risk of death, independent of stage and grade at baseline. This finding is consistent with the literature [4,30,31]. For example, a retrospective study of 799 breast cancer cases found that compared to patients without comorbid conditions, the hazard ratio of death was 2.3 (95% CI: 1.5–3.5) for a Satariano comorbidity index score $\geq$ 2. [31]. It is notable that 85% of the deaths among the WHEL Study participants were the result of breast cancer. It is possible that women with a number of comorbidities are more frail (as supported by the observed association with poor physical health) and therefore less likely to survive the challenges of recurrent breast cancer, such as additional surgeries and adjuvant treatments. In a population-based study of 2515 adults, Klein et al found that frailty was associated with greater likelihood of concurrent medical conditions and decreased survival [32].

Although based only on 5 cases, osteoporosis was associated with a statistically significant reduction in mortality. Lower estradiol concentrations are known to be associated with increased risk of osteoporosis [33] and decreased risk of breast cancer [34]. Therefore osteoporosis may be serving as a “bioassay” for low estrogen exposure. Additionally, women with osteoporosis are more likely to be of normal or low BMI [35]. Therefore BMI may explain some of the protective associations demonstrated for osteoporosis, although BMI was not associated with either additional cancer events or mortality in this sample.

²Surveillance, Epidemiology and End Results Program

This analysis has several strengths. Treatment and tumor characteristics of the original cancer were obtained from patients' medical reports and charts. Follow-up of outcomes in this sample was quite complete, with vital status known for 96% of participants and reported death was confirmed by a death certificate in almost all cases [16]. Other strengths include the long-term follow-up (median = 7.3 years) and extensive information on potential confounding characteristics, including demographic and lifestyle variables.

Limitations of this study include reliance on self-reported comorbidities, although research indicates that indices constructed from self-reported measures appear valid [36]. Nevertheless the relationships seen here are likely attenuated due to misclassification (e.g., undiagnosed diabetes). In addition, the WHEL Study questionnaire on comorbidities was not designed a priori for development of a summary index. Therefore we were unable to construct one of the validated indices, such as the Charlson Index or the Index of Coexisting Disease or to incorporate measures of comorbid severity [12].

WHEL participants were willing and able to be randomized to a dietary intervention that involved record keeping, blood draws, and regular clinic visits (i.e., healthy volunteers). The subset of participants with co-morbidity data at baseline included in this analysis were slightly younger and had somewhat fewer additional breast cancer events and lower death than women without co-morbidity data. As such, this sample had relatively few comorbidities, which limited our power and the ability to do subgroup analyses (e.g., stratification by race/ethnicity).

CONCLUSION

Among breast cancer survivors, diabetes appears to be an important risk factor for additional breast cancer events and mortality. Multiple comorbidities and adverse health conditions did not predict additional breast cancer even; there was a statistically significant trend for multiple comorbidities to predict mortality. Given that 85 percent of deaths were caused by breast cancer, these findings suggest that multiple comorbidities may reduce the likelihood of surviving additional breast cancer events.

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Table 1

Self-reported medical comorbidities by physical health¹ in a cohort of US breast cancer survivors followed for a median of 7.3 years (n = 2468²)

	Overall N (%)	Poor physical health N (%)	Moderate/high physical health N (%)
Cardiovascular disease ³	141 (5.7%)	79 (8.0%)	62 (4.2%)
Diabetes	54 (2.2%)	33 (3.3%)	21 (1.4%)
Gallbladder/Kidney/Pancreas ⁴	109 (4.4%)	57 (5.7%)	52 (3.5%)
Gastrointestinal ⁵	201 (8.1%)	117 (11.8%)	84 (5.7%)
Hypertension	353 (14.3%)	178 (17.9%)	175 (11.9%)
High blood cholesterol	152 (6.2%)	79 (8.0%)	73 (5.0%)
Obesity (≥ 30 kg/m ²)	634 (25.7%)	370 (37.2%)	264 (17.9%)
Arthritis	476 (19.3%)	285 (28.7%)	191 (13.0%)
Osteoporosis	130 (5.3%)	68 (6.8%)	62 (4.2%)

¹ As assessed by the Rand SF-36.

² 74 participants were excluded from this analysis because of missing physical health data.

³ Angina (n=15), peripheral arterial disease (n=5), other heart conditions (n=115), multiple cardiovascular comorbidities (n=6).

⁴ Gallbladder disease (n=75), kidney/bladder stones (n=22), pancreatitis (n=2), multiple comorbidities of gallbladder, kidney, bladder or pancreas (n=10).

⁵ Ulcers (n=15), diverticulitis (n=67), colitis (n=6), intestinal removal (n=4), irritable bowel syndrome (n=78), malabsorption syndrome (n=1), multiple gastrointestinal comorbidities (n=30).

Adjusted¹ hazard ratios (HR) of disease-free and overall survival in relation to comorbidities in a cohort of US breast cancer survivors followed for a median of 7.3 years (n = 2542)

Table 2

	Additional Breast Cancer Event			Mortality	
	Event n	HR (95%CI)	Event n	HR (95%CI)	
Individual Comorbidities					
Cardiovascular ²	145	25	1.11 (0.74, 1.67)	17	1.13 (0.69, 1.86)
Diabetes	56	16	2.06 (1.25, 3.41)	13	2.50 (1.42, 4.39)
Gallbladder/Kidney/Pancreas ³	109	22	1.47 (0.95, 2.27)	15	1.46 (0.86, 2.49)
Gastrointestinal ⁴	204	33	1.13 (0.79, 1.62)	24	1.30 (0.85, 2.00)
Hypertension	365	56	1.04 (0.78, 1.39)	44	1.23 (0.88, 1.72)
High blood cholesterol	153	22	1.01 (0.65,1.56)	17	1.08 (0.66, 1.79)
Obesity (>30 kg/m ²)	647	112	1.14 (0.92, 1.42)	77	1.28 (0.97, 1.68)
Arthritis	483	77	1.12 (0.86, 1.45)	46	0.92 (0.66, 1.29)
Osteoporosis	133	14	0.74 (0.43, 1.26)	5	0.37 (0.15, 0.90)
Women with Multiple Comorbidities					
0	1436	224	1.0	123	1.0
1	704	113	1.01 (0.81–1.27)	63	0.97 (0.71–1.32)
2	270	42	1.03 (0.74–1.43)	32	1.26 (0.84–1.88)
3 or more	132	27	1.45 (0.98–2.17)	24	2.09 (1.32–3.29)
P Trend			0.32		0.001

¹ Adjusted for stage, grade, age, and education.

² Angina (n=15), peripheral arterial disease (n=5), other heart conditions (n=119), multiple cardiovascular comorbidities (n=6).

³ Gallbladder disease (n=75), kidney/bladder stones (n=22), pancreatitis (n=2), multiple comorbidities of gallbladder, kidney, bladder or pancreas (n=10).

⁴ Ulcers (n=15), diverticulitis (n=68), colitis (n=6), intestinal removal (n=5), irritable bowel syndrome (n=78), malabsorption syndrome (n=1), multiple gastrointestinal comorbidities (n=31).