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Effectiveness of Adjuvant Chemotherapy for Node-Positive Operable Breast Cancer in Older Women

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Abstract

Background—Randomized clinical trials have shown the efficacy of adjuvant chemotherapy in treating node-positive operable breast cancer in women aged ≤69 years, but the benefit of chemotherapy in women aged ≥70 is questionable. This study was to examine if adjuvant chemotherapy is effective for these women with breast cancer.

Methods—We studied a cohort of 5464 women diagnosed with node-positive operable breast cancer at age ≥65 in 1992 through 1996 with last follow-up of December 31, 1999 in five states and six metropolitan areas. Hazard ratio (HR) for all-cause mortality was used for survival analysis with adjustment for patient and tumor characteristics; propensity analysis was used to control for observed factors; and sensitivity analysis was used to estimate potential effects of unmeasured confounders.

Results—After adjusting for propensity to receive chemotherapy, the chemotherapy-treated and untreated groups were not statistically significantly different for covariates except for age and hormone receptor status. Mortality was significantly reduced in women aged 65–69 who received adjuvant chemotherapy compared to those who did not, after adjusting for patient and tumor characteristics (HR = 0.70, 95% confidence interval [CI], 0.57–0.88) or after adjusting for propensity scores (HR = 0.76, 95% CI, 0.62–0.94). HR did not significantly differ between the treated and untreated women aged ≥70 (HR = 0.96, 95% CI = 0.83–1.09, and HR = 0.99, 95% CI, 0.87–1.14). These results were relatively insensitive to changes in unmeasured confounders.

Conclusions—Adjuvant chemotherapy is associated with improved survival in women with node-positive operable breast cancer aged 65–69 living in the community, but not in women aged ≥70. These findings are consistent with those found in randomized controlled trials.

Over the past three decades, numerous randomized controlled trials have demonstrated that chemotherapy improves both recurrence-free survival and overall survival for women with early-stage breast cancer (1–5). However, the efficacy of adjuvant chemotherapy has been shown to decrease with age. For example, the pooled analysis of 47 randomized trials by the Early Breast Cancer Trialists' Collaborative Group showed that chemotherapy provided a 27% proportional reduction in 10-year mortality for women with early-stage operable breast cancer aged <50, 14% for women aged 50–59, and 8% for women aged 60–69 (3). This translates to an absolute benefit in 10-year survival of 7%–11% for those aged <50 and 2%–3% for those aged 50–69 years (3). This meta-analysis found no benefit of chemotherapy in women aged ≥70. Because of these findings, the recommendations for chemotherapy use in women aged

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≥70 are not clear cut, with most authorities stressing the need for decision making based on the particular condition of the individual patient (6–10).

Randomized controlled clinical trials are considered to be the gold standard for determining the efficacy of a therapy. However, participants in clinical trials do not represent a cross-section of patients in the community (11–14). Population-based observational studies can therefore be useful adjuncts to randomized controlled trials in determining whether efficacy under controlled conditions in special centers translates into real-world effectiveness in routine practice (11–13). Furthermore, in some circumstances where the randomized trials are not possible due to ethical or logistic issues, well-conducted observational studies could potentially function effectively in determining drug efficacy (11).

We used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry data, accounting for 14% of the total U.S. population, linked to Medicare data, to examine the effectiveness of adjuvant chemotherapy in older women with breast cancer. We hypothesized that chemotherapy is effective in treating node-positive operable breast cancer in women aged 65–69 years at diagnosis, consistent with what has been shown in clinical trials. Furthermore, given a large number of patients aged ≥70 in our study database, we wanted to assess whether adjuvant chemotherapy is effective in this population.

Methods

Data Sources

The SEER program, supported by the National Cancer Institute, includes population-based tumor registries in 11 selected geographic areas (15,16): the metropolitan areas of San Francisco/Oakland, Detroit, Atlanta, and Seattle; Los Angeles county; the San Jose–Monterey area; and the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii.

The Medicare Program covers hospital, physician, and outpatient medical services for more than 97% of persons aged ≥65 (17,18). These data were available for all beneficiaries starting in 1991, and their Medicare claims are available through 1999. Cases reported by the SEER registries from 1992 to 1996 were matched against the Medicare master enrollment file. Medicare eligibility could be identified for 94% of the persons aged ≥65 appearing in the SEER records. The method of linking these data has been described elsewhere (17,19). The Institutional Review Boards of the University of Texas Health Science Center at Houston and University of Texas Medical Branch at Galveston approved this study.

Study Population and Sample Size Needed

Our study is based on the analytical SEER–Medicare files that excluded women who did not have full coverage of both Medicare Part A and Part B and those who were members of health maintenance organizations, because claims from these organizations may not be complete. The study population consisted of 6190 women aged ≥65 who were diagnosed with operable breast cancer (stage II or IIIA) and also with positive lymph nodes during the period from 1992 to 1996, identified from the 11 SEER areas. Of the total study population of 6190 women, 715 (11.6%) who had other primary cancers were excluded. Also excluded were 11 women who died within 3 months of breast cancer diagnosis. Thus, 5464 patients aged ≥65 remained for the final analyses. Assuming a difference of 8% in survival, the sample size needed to achieve 80% power at $p < .05$ is 1139 (aged 65–60 years) and 2904 (aged 70 or older) (20).

Study Variables

Chemotherapy—The details of the methods of identification of chemotherapy use through Medicare claims have been previously described (21,22). In brief, patients with breast cancer

were defined as having received chemotherapy if any of the Medicare procedure codes indicated so within 6 months of the diagnosis (21–24).

Comorbidity index—Comorbidity was ascertained from Medicare claims data through diagnoses or procedures made 1 year prior to and 1 month after the diagnosis of breast cancer, but not including the breast cancer diagnosis. We included claims for comorbid diseases made within 1 month of diagnosis because any comorbid diseases present at that time would be likely to affect the choice of chemotherapy. We adopted the comorbidity index created by Charlson and colleagues (25), and later validated by Romano and colleagues (26), using the *International Classification of Diseases*, 9th revision (ICD-9-CM) diagnosis and procedure codes. Women diagnosed with breast cancer at age 65 may have a shorter duration for identifying comorbid diseases in Medicare, but these women had similar comorbidity scores to those aged 66–69 years, and therefore were included in the analysis.

Mortality—For patients who died of any causes after diagnosis of breast cancer (all-cause mortality), information on months of survival from the date of diagnosis was provided in the SEER database. The last date of the follow-up for this cohort was December 31, 1999.

Other characteristics—Patient and tumor characteristics such as age, race/ethnicity, marital status, tumor stage, tumor size, tumor grade, hormone receptor status, surgery, radiotherapy, and geographic areas (11 SEER areas) were available from the SEER data. Information on household income at the level of the census tract in the SEER–Medicare database was obtained from the National Census Bureau.

Analyses

The Cox proportional hazard ratio (HR) of mortality was analyzed using the PHREG procedure after patients who were lost to follow-up or who were still alive at the last date of follow-up were censored, adjusting for patient and tumor characteristics that are shown and categorized in Table 1 (27,28).

A propensity score analysis was also conducted to minimize selection bias in this observational study (29,30). In observational studies, investigators have no control over the treatment assignment. Patients in the treated and untreated groups may have large differences in their observed covariates, and these differences can lead to biased estimates of treatment effects. Propensity score can be used to balance the covariates between the treated and untreated groups, and therefore reduce this bias (30). Propensity score was defined as the conditional probability of being treated, given the covariates. The probability that a patient would receive chemotherapy was generated from the logistic regression model that incorporated potential confounding factors listed in Table 1. Propensity score was then divided into five strata (quintiles) for all patients and stratified for age groups. It is estimated that five strata of propensity scores are able to remove over 90% of the unbalanced bias from confounding factors between the treated and untreated groups (30). In this study, the Mantel–Haenszel chi-square test was used to initially test for any significant differences in the distribution of confounding factors between the treated and untreated groups. The balances of confounding factors were tested again using the Cochran Mantel–Haenszel chi square, which adjusted for propensity scores (in quintiles). The covariates that were still significantly different between the treated and untreated groups were adjusted again, together with propensity score in the Cox proportional hazard models. In addition, survival analysis for the HR of mortality was also performed to show the effect of other factors on mortality.

Sensitivity analyses were performed to assess the potential effects of unmeasured confounders on the observed associations between chemotherapy and mortality. The unmeasured

confounders in our study could be patient level covariates, such as patient preference, and physician/clinic level covariates, such as oncologist clustering in preference to using chemotherapy. Sensitivity analyses were conducted using the method of Lin and colleagues (31). The prevalence of the unmeasured confounder was set to different levels within both the treated and untreated groups. Over the different prevalence levels, HR of the unmeasured confounder and mortality ranged from 1.25 to 2.50. The range for the prevalence estimates and for the HRs was obtained by inspection of the prevalence and hazard associated with the measured confounders in this study. The Cox regression parameter for chemotherapy was adjusted to determine the effect of the unknown confounder on HR in the treated group compared to the untreated group. All computer programming and analyses were completed using the SAS system (28).

Results

Table 1 shows the percentage of women with node-positive operable breast cancer receiving adjuvant chemotherapy by various patient and tumor characteristics, and the comparison between patients who received chemotherapy and those who did not receive chemotherapy in terms of distribution of these characteristics, before and after adjusting for propensity score. Overall, 31% of women with node-positive operable breast cancer received adjuvant chemotherapy. The use of adjuvant chemotherapy decreased substantially with age, from 54% in women aged 65–69 to 3% in women aged ≥85. The distribution of cases between the treated and untreated groups varied significantly by potential confounding factors (except ethnicity) listed in the table. After adjusting for propensity to receive chemotherapy, the treated and untreated groups were not statistically significantly different in covariates except for age and hormone receptor status.

Table 2 presents HR for mortality associated with receipt of chemotherapy for all older women with breast cancer and for the five age groups. HR was statistically significantly reduced in women aged 65–69 years who received adjuvant chemotherapy compared to those who did not receive chemotherapy (0.70, 95% confidence interval [CI], 0.57–0.88), after adjusting for other factors that might affect survival. HR did not significantly differ between the treated and untreated groups in women aged ≥70.

Table 3 presents HR stratified for two separate age groups (65–69 and ≥70) to show the effects of chemotherapy and other potential confounders on mortality. As shown above, among the 1440 women aged 65–69, those who received adjuvant chemotherapy had a significantly reduced mortality when compared to those who did not receive chemotherapy. Mortality was also significantly associated with tumors of larger size, more positive lymph nodes, higher tumor grade, negative hormone receptor, higher comorbidity scores, and being unmarried. Among 4024 women aged ≥70, the effect of chemotherapy on mortality was not statistically significant.

We performed an analysis regarding the effect of chemotherapy on mortality by adjusting for propensity score. Those covariates (i.e., age and hormone receptor status) that remained statistically unbalanced between the treated and untreated groups as shown in Table 1 were also adjusted together with propensity score in the analysis. Mortality was still statistically significantly reduced in women aged 65–69 who received chemotherapy compared to those who did not (HR = 0.76, 95% CI, 0.62–0.94). Chemotherapy did not have a statistically significant effect on mortality in women with breast cancer aged ≥70 (HR = 0.99, 95% CI, 0.87–1.14).

We also conducted sensitivity analyses to estimate the potential effect of unknown confounders on the study results (Table 4). The estimated prevalence and HR of an unknown factor was

based on the prevalence and HR of measured variables shown in Table 1 and Table 3. For example, 53% of women receiving chemotherapy were married compared to 39% of those not receiving chemotherapy, a 14% difference between the treated and untreated groups (Table 1). HR of mortality was 1.36 (95% CI, 1.10–1.67) in unmarried women aged 65–69 compared to married women (Table 3). The highest HR associated with a measured confounder was about 2.50 for women with ≥10 positive nodes (Table 3). Based on these findings from measured variables, we set the prevalence of the unmeasured confounder up to 30% difference level between the treated and untreated groups. Over the different prevalence levels, the HR of the unmeasured confounder for mortality ranged from 1.25 to 2.50. These analyses show that an unmeasured confounder could be responsible for the results obtained if it has difference of approximately 30% in prevalence between the treated and nontreated groups and if it is associated with an HR of 2.00 or greater for patients aged 65–69 and those aged 70 or older.

Discussion

This study examined the effectiveness of adjuvant chemotherapy in 5464 women aged 65 or older with node-positive operable breast cancer. Mortality was significantly reduced in women aged 65–69 years who received adjuvant chemotherapy compared to those who did not, after adjusting for measured confounders and propensity score. However, chemotherapy failed to show significant effect on mortality in women aged ≥70.

There are several strengths to this study. First, the data were obtained from the National Cancer Institute's SEER program, which accounts for 14% of the U.S. population and ascertains nearly all cancer patients in the designated SEER areas (15). The advantage of this population coverage is that the data include all women residing in community-based settings, which avoids selection bias such as volunteer bias in randomized trials. Although 46% of incident breast cancer cases occur in women aged ≥65 and 32% of new cases are women aged ≥70 (15), only a small fraction of older women are enrolled in the randomized trials (1–3). For example, in the 47 trials on chemotherapy, 18,718 women were recruited, of whom only 609 (3.3%) were aged ≥70 (3).

Furthermore, because randomized clinical trials often have tight enrollment criteria and are conducted in motivated volunteers, one might expect that the effectiveness of chemotherapy in the community at large might be different from the efficacy of chemotherapy found in the controlled trials. In fact, to the best of our knowledge there is no study that has assessed the effectiveness of chemotherapy for breast cancer in routine practice.

Age has been demonstrated to be a major factor in determining cancer therapies, particularly for chemotherapy, because there are concerns about comorbidity and drug toxicity (21–23, 32–40). However, for women with breast cancer, there might be an additional reason for the declining use of chemotherapy with age, i.e., the decreasing efficacy of chemotherapy with age for breast cancer could have affected the knowledge and attitudes of oncologists and patients on the benefits and risks of chemotherapy (34). The decrease in both efficacy and effectiveness of chemotherapy with advanced age in women with breast cancer is not seen in men and women with colon cancer (34,35). In those persons with node-positive resectable colon cancer, chemotherapy seems equally efficacious and effective in patients aged ≥70 compared to those aged <70 (35).

It is important to note several weaknesses of this study. First, there is concern regarding whether the information on chemotherapy from Medicare claims is accurate and complete. However, a recent study comparing Medicare claims with medical chart reviews on the use of chemotherapy showed excellent agreement rates (ranging from 97.0% to 98.3%) (41). An additional limitation is that the study findings may only be applied to women aged ≥65 who

are not members of health maintenance organizations and have both Medicare Part A and Part B coverage. Furthermore, there was no information on the dose intensity of chemotherapy. Because of concern about lower tolerance of this therapy in older women, a lower dose of chemotherapy might have been given, which could have been less effective, thus confounding the results. In addition, we do not have information on adjuvant hormone therapy use, which may impact survival in older women with breast cancer. In a hospital-based study in several states across the United States, 59% of women with early-stage breast cancer aged 65 or older who received adjuvant chemotherapy also received adjuvant hormone therapy compared to 79% of women who did not receive adjuvant chemotherapy, a 20% difference (42). This difference of receiving hormone therapy among women who received chemotherapy and those who did not in the community setting was much smaller (33). Adjuvant tamoxifen therapy can achieve up to a 26% reduction in mortality (43). Our sensitivity analyses showed that the effect of adjuvant chemotherapy on mortality would not be much affected by confounding with above prevalence and magnitude of effect.

Women with breast cancer who received chemotherapy may have a different spectrum of prognostic indicators than those who did not. As shown in Table 1, women receiving chemotherapy had a higher percentage of large-sized tumors, more positive lymph nodes, and poorly differentiated tumors. These worse prognostic factors would have led to bias towards poorer survival. In contrast, women receiving chemotherapy had fewer coexisting diseases, were more likely to be married, and had a relatively higher socioeconomic status than those not receiving chemotherapy (Table 1); these factors would have led to better survival. Patients aged 65–69 had a higher percentage of anthracycline agent use (43%) than did those patients aged 70 or older (32%), but mortality was not affected because the HRs for anthracycline versus nonanthracycline agents were identical (HR = 0.99, 95% CI, 0.83–1.18) in our study. Although the differential distribution of these prognostic factors was minimized through propensity scores, there still might be some factors not linked to the measured confounders that affected the results. The sensitivity analyses suggested that such an unmeasured confounder would have to have a substantial effect on survival and a large difference in distribution between the chemotherapy and nonchemotherapy groups to affect the results. Also, it is difficult to envision how such a confounder or set of confounders could have produced the pattern of effectiveness in 65- to 69-year-olds with no effectiveness in those aged 70 or older. Because there are more diverse characteristics in older patients, adopting sensitivity analysis to estimate the potential effects of unmeasured or unknown factors are useful and should be encouraged in the studies of older individuals.

Conclusion

Our study showed that adjuvant chemotherapy is associated with improved survival in women with node-positive operable breast cancer aged 65–69 living in the community, but there is no proof that adjuvant chemotherapy reduces the risk of mortality in women aged 70 or older. These findings were consistent with those found in pooled analyses of randomized controlled trials (1–3). Further study may be needed to determine whether these findings regarding the effectiveness of chemotherapy in routine practices remain the same in different populations and in various communities. Particularly because there is no proof that a 70-year-old woman is biologically different from a 68- or 69-year-old, further observational studies and randomized trials with sufficient sample size would be needed to generate the definitive answer and to identify those aged 70 or older who may benefit from adjuvant chemotherapy, if any. The answers to the above research questions would have important clinical implications for oncologists and physicians in treating older women with breast cancer, for the National Institutes of Health consensus conferences in developing clinical guidelines for chemotherapy, and for the benefit/risk assessment of this therapy by physicians and patients themselves.

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This study used the Linked SEER-Medicare Database.

The interpretation and reporting of these data are the sole responsibilities of the authors.

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Table 1

Comparison of Characteristics of Older Women With Node-Positive Operable Breast Cancer Who Received Adjuvant Chemotherapy Versus Those Who Did Not, Before and After Adjusting for Propensity Score

Patient and Tumor Characteristics	No. of Patients With Breast Cancer	Percentage of Women Receiving Adjuvant Chemotherapy	Comparison in Column Percentage Between Patients Receiving Chemotherapy and Those Not Receiving Chemotherapy			
			Patients Not Receiving Chemotherapy (*N* = 3774)	Patients Receiving Chemotherapy (*N* = 1690)	*p* Value Before Adjustment*	*p* Value After Adjusting for Propensity Score†
Age, y						
65–69	1440	53.5	17.7	45.6	<.001	.018
70–74	1590	36.1	26.9	34.0		
75–79	1275	20.1	27.0	15.2		
80–84	753	10.4	17.9	4.6		
≥85	406	2.7	10.5	0.7		
Race						
White	4916	30.7	90.3	89.2	.209	.995
Black	363	31.4	6.6	6.8		
Other	185	36.8	3.1	4.0		
Marital status						
Married	2365	38.1	38.8	53.4	<.001	.875
Unmarried	2998	24.9	59.7	44.1		
Unknown	101	41.6	1.6	2.5		
Tumor stage						
Stage II	4694	30.0	87.1	83.2	<.001	.058
Stage IIIA	770	36.9	12.9	16.8		
Tumor size, cm						
<1.0	311	31.2	5.7	5.7	<.001	.729
1.0–<2.0	1570	27.1	30.3	25.2		
2.0–<3.0	1527	31.2	27.9	28.2		
3.0–<4.0	820	32.2	14.7	15.6		
4.0+	1005	33.9	17.6	20.2		
Unknown size	231	37.7	3.8	5.2		
No. of positive nodes						
1	1939	22.5	41.3	22.5	<.001	.792
2–4	1908	32.8	35.9	32.8		
5–9	879	22.5	13.2	22.5		
10–43	668	20.4	8.6	20.4		
Unknown No., but positive	70	1.8	1.1	1.8		
Tumor grade						
Well differentiated	400	18.3	8.7	4.3	<.001	.782
Moderately differentiated	1836	25.7	36.1	27.9		
Poorly differentiated	1909	38.7	31.0	43.7		
Unknown	1319	30.8	24.2	24.0		
Hormone receptor status						
Positive	3786	25.9	74.3	58.1	<.001	.007
Negative	779	58.3	8.6	26.9		
Unknown	899	28.4	17.1	15.1		
Surgery and radiation						
BCS alone	290	33.8	5.1	5.8	<.001	.354
BCS with radiation	1001	30.6	18.4	18.1		
Mastectomy alone	3579	28.8	67.5	61.0		
Mastectomy with radiation	594	42.9	9.0	15.1		
Comorbidity scores						
0	3725	32.9	66.2	72.5	<.001	.489

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Patient and Tumor Characteristics	No. of Patients With Breast Cancer	Percentage of Women Receiving Adjuvant Chemotherapy	Comparison in Column Percentage Between Patients Receiving Chemotherapy and Those Not Receiving Chemotherapy			
			Patients Not Receiving Chemotherapy (N = 3774)	Patients Receiving Chemotherapy (N = 1690)	p Value Before Adjustment*	p Value After Adjusting for Propensity Score†
1	658	27.5	12.6	10.7		
2	222	18.9	4.8	2.5		
≥3	859	28.2	16.4	14.3		
Household income						
1st quartile (≤ $27669)	1080	28.1	20.6	17.9	<.001	.796
2nd quartile ($27,670–$34,464)	1107	29.5	20.7	19.3		
3rd quartile ($34,465–$43,974)	1007	33.8	17.7	20.1		
4th quartile (>$43,974)	1002	35.1	17.2	20.8		
Unknown	1268	29.1	23.8	21.8		
SEER registry areas						
San Francisco, CA	465	26.9	9.0	7.4	<.001	.906
Connecticut	790	36.8	13.2	17.2		
Detroit, MI	896	33.9	15.7	18.0		
Hawaii	106	39.6	1.7	2.5		
Iowa	751	27.2	14.5	12.1		
New Mexico	212	22.6	4.4	2.8		
Seattle, WA	590	29.7	11.0	10.4		
Utah	270	30.4	5.0	4.9		
Atlanta, GA	307	32.3	5.5	5.9		
San Jose–Monterey, CA	259	32.1	4.7	4.9		
Los Angeles, CA	828	29.0	15.4	14.0		
Year of diagnosis						
1992	1203	27.9	23.0	19.9	<.01	.775
1993	1128	28.3	21.4	18.9		
1994	1114	31.7	20.2	20.9		
1995	1083	32.7	19.3	21.0		
1996	936	35.0	16.1	19.4		
Total	5464	30.9	100.0	100.0		

*p value was generated from the Mantel—Haenszel chi-square statistic.

†p value was generated from the Cochran Mantel–Haenszel chi-square statistic, adjusting for propensity score (categorized in quintiles).

BCS = breast-conserving surgery; SEER = The National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry.

Table 2

Effect of Chemotherapy on Mortality in Women With Node-Positive Operable Breast Cancer Diagnosed in 1992–1996 in SEER Areas

Age Group	Total No. of Patients (% of Patients Receiving Chemotherapy)	Risk (Cox Proportional HR and 95% CI)*	
		HR	95% CI
65–69 y	1440 (53.5)	0.70	0.57–0.88
70–74 y	1590 (36.1)	0.87	0.70–1.07
75–79 y	1275 (20.1)	1.06	0.84–1.34
80–84 y	753 (10.4)	0.90	0.63–1.29
≥85 y	406 (2.7)	1.21	0.53–2.74
All women aged ≥65	5464 (30.9)	0.90	0.80–1.01

* Cases who received chemotherapy vs those who did not. Cox proportional HR was adjusted for age (continuous), ethnicity (white, black, other), marital status (married, unmarried, unknown), tumor stage (II, IIIA), tumor size (<1, 1–<2, 2–<3, 3–<4, ≥4 cm, or unknown), hormone receptor status (positive, negative, or unknown), tumor grade (well, moderately or poorly differentiated, or undetermined), number of positive lymph nodes (1, 2–4, 5–9, 10–43, and positive nodes but unknown number), comorbidity index scores (0, 1, 2, or 3+), 11 SEER areas, other treatment (breast-conserving surgery alone, breast-conserving surgery plus radiotherapy, mastectomy alone, or mastectomy with radiation), and census tract household income in quartiles (four categories plus unknown one), and year of diagnosis (continuous).

SEER = The National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry; HR = hazard ratio; CI = confidence interval.

Table 3

Effect of Chemotherapy and Other Factors on Mortality in Women With Node-Positive Operable Breast Cancer Diagnosed in 1992–1996 in SEER Areas, by Age Groups (65–69 Years and 70+ Years)

Patient and Tumor Characteristics	Risk (Cox Proportional HR and 95% CI)*	
	Women Aged 65–69 Years (*N* = 1440)	Women Aged 70 Years or Older (*N* = 4024)
Chemotherapy		
No	1.00 (reference)	1.00 (reference)
Yes	0.70 (0.57–0.88)	0.96 (0.83–1.09)
Age (continuous)	0.96 (0.90–1.04)	1.06 (1.05–1.07)
Race		
White	1.00 (reference)	1.00 (reference)
Black	1.19 (0.85–1.67)	1.12 (0.90–1.39)
Other	1.56 (0.87–2.77)	0.85 (0.59–1.23)
Marital status		
Married	1.00 (reference)	1.00 (reference)
Unmarried	1.36 (1.10–1.67)	1.33 (1.19–1.49)
Unknown	1.29 (0.69–2.42)	1.44 (1.01–2.04)
Tumor stage		
II	1.00 (reference)	1.00 (reference)
IIIA	1.00 (0.73–1.37)	1.20 (1.04–1.39)
Tumor size, cm		
<1.0	1.00 (reference)	1.00 (reference)
1.0–<2.0	1.00 (0.61–1.63)	1.20 (0.89–1.62)
2.0–<3.0	1.26 (0.78–2.04)	1.58 (1.18–2.12)
3.0–<4.0	1.32 (0.79–2.21)	1.99 (1.47–2.69)
4.0+	2.00 (1.20–3.32)	1.91 (1.41–2.59)
Unknown size	1.35 (0.72–2.53)	1.34 (0.92–1.94)
Number of positive nodes		
1	1.00 (reference)	1.00 (reference)
2–4	1.30 (0.99–1.71)	1.11 (0.98–1.25)
5–9	2.07 (1.52–2.80)	1.38 (1.19–1.61)
10–43	2.56 (1.86–3.52)	1.94 (1.65–2.28)
Unknown no. but positive	2.12 (0.99–4.55)	1.72 (1.19–2.48)
Tumor grade		
Well differentiated	1.00 (reference)	1.00 (reference)
Moderately differentiated	1.38 (0.82–2.31)	0.99 (0.78–1.25)
Poorly differentiated	1.77 (1.06–2.97)	1.30 (1.03–1.65)
Unknown	1.46 (0.86–2.47)	1.14 (0.89–1.44)
Hormone receptor status		
Positive	1.00 (reference)	1.00 (reference)
Negative	2.13 (1.65–2.74)	1.76 (1.53–2.02)
Unknown	1.02 (0.76–1.36)	1.22 (1.07–1.39)
Surgery and radiation		
BCS alone	1.00 (reference)	1.00 (reference)
BCS with radiation	0.61 (0.38–1.00)	0.81 (0.62–1.05)
Mastectomy alone	0.79 (0.51–1.21)	0.94 (0.75–1.18)
Mastectomy with radiation	0.82 (0.50–1.34)	0.91 (0.70–1.19)
Comorbidity scores		
0	1.00 (reference)	1.00 (reference)
1	1.13 (0.81–1.57)	1.20 (1.03–1.38)
2	1.78 (1.06–2.96)	1.28 (1.03–1.58)
≥3	1.42 (1.08–1.86)	1.16 (1.02–1.31)
Household income		
1st quartile (≤$27,669)	1.00 (reference)	1.00 (reference)
2nd quartile ($27,670–$34,464)	1.20 (0.87–1.65)	0.98 (0.83–1.14)
3rd quartile ($34,465–$43,974)	1.06 (0.73–1.53)	0.93 (0.78–1.11)
4th quartile (>$43,974)	1.20 (0.81–1.76)	1.01 (0.83–1.23)
Unknown	1.52 (0.86–2.70)	1.22 (0.95–1.58)
Total		

* Mortality among women with node-positive operable breast cancer, by age. Cox proportional HR was adjusted for those variables listed, plus 11 SEER areas (categorized) and year of diagnosis (continuous).

SEER = The National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry; HR = hazard ratio; CI = confidence interval; BCS = breast-conserving surgery.

Table 4

Subset of Sensitivity Analyses of the Hazard Ratio of Mortality for Women Receiving Chemotherapy Compared to Those Receiving No Chemotherapy, Controlling for an Unmeasured Binary Confounder

Prevalence (%) of Unknown Confounder in the Chemotherapy Group	Prevalence (%) of Unknown Confounder in the Untreated Group	Unknown Confounder Hazard Ratio	Hazard Ratio of Mortality, Adjusted for Unmeasured Confounder (95% Confidence Interval)	
			Age 65–69 Years	Age 70 Years or Older
0	0	1.00	0.70 (0.56–0.88)	0.96 (0.83–1.09)
50	70	1.25	0.73 (0.59–0.92)	1.00 (0.87–1.14)
40	70	1.25	0.75 (0.60–0.94)	1.02 (0.89–1.17)
50	70	1.50	0.76 (0.61–0.95)	1.03 (0.90–1.18)
40	70	1.50	0.79 (0.64–0.99)	1.07 (0.94–1.23)
50	70	2.00	0.80 (0.64–0.99)	1.08 (0.95–1.24)
40	70	2.00	0.85 (0.69–1.06)	1.16 (1.01–1.33)
50	70	2.50	0.82 (0.66–1.03)	1.12 (0.98–1.28)
40	70	2.50	0.90 (0.72–1.12)	1.22 (1.07–1.40)