



Ettore "Ted" DeGrazia. *Free as the Wind*. Oil on canvas, 16" × 34". Courtesy of DeGrazia Foundation.

This study reports the frequency of use of adjuvant systemic therapy for early breast cancer among women 65 years of age and older in New Jersey.

Use of Adjuvant Systemic Therapy for Early Breast Cancer Among Women 65 Years of Age and Older

Bijal A. Balasubramanian, MBBS, MPH, Sampada K. Gandhi, MBBS, MPH, Kitaw Demissie, MD, PhD, David A. August, MD, Betsy Kohler, MPH, CTR, Omowunmi Y. Osinubi, MD, MSc, and George G. Rhoads, MD, MPH

Background: *The National Institutes of Health (NIH) consensus statement recommends adjuvant therapy for early breast cancer irrespective of age. However, the actual use of such therapy is not well documented among women over 65 years of age.*

Methods: *We studied the frequency of use of adjuvant therapy and report the receipt of this therapy among 200 women aged ≥ 65 years diagnosed with early breast cancer who were identified from the New Jersey State Cancer Registry.*

Results: *In this population, 28% of patients received chemotherapy alone or in combination with hormonal therapy, whereas 42% received hormonal therapy alone. Less than half of the women with estrogen receptor-negative tumors received chemotherapy alone or in combination with hormonal treatment. Adjuvant therapy was not prescribed in 30% of patients.*

Conclusions: *Despite NIH recommendations, the frequency of use of adjuvant therapy in New Jersey is low among women over 65 years of age, regardless of their receptor status.*

From the Department of Family Medicine, University of Medicine and Dentistry of New Jersey (UMDNJ), Robert Wood Johnson Medical School, Somerset, NJ (BAB), the Departments of Epidemiology (SKG, KD, GGR) and Environmental and Occupational Health (OYO), UMDNJ School of Public Health, Piscataway, NJ, the Cancer Institute of New Jersey, New Brunswick, NJ (KD, DAA, GGR), the Department of Surgery, UMDNJ Robert Wood Johnson Medical School and the Cancer Institute of New Jersey, New Brunswick, NJ (DAA), and the Cancer Control Program, Cancer Epidemiology Services, New Jersey Department of Health and Senior Services, Trenton, NJ (BK).

Submitted August 1, 2006; accepted November 1, 2006.

Address correspondence to Bijal A. Balasubramanian, MBBS, MPH,

Department of Family Medicine, UMDNJ Robert Wood Johnson Medical School, 1 World's Fair Drive, Somerset, NJ 08873. E-mail: balasuba@umdnj.edu

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

The editor of Cancer Control, John Horton, MB, ChB, FACP, has nothing to disclose.

Abbreviations used in this paper: NIH = National Institutes of Health, ER = estrogen receptor, PR = progesterone receptor, NJSCR = New Jersey State Cancer Registry, SEER = Surveillance, Epidemiology, and End Results.

Introduction

Because of the rapid growth of the elderly population and the higher mortality due to breast cancer in this age group, breast cancer in the elderly is a major public health problem. Initial adjuvant systemic therapy for breast cancer has been extensively evaluated in clinical trials, and its efficacy in prolonging survival has been established.¹ Based on these findings, the National Institutes of Health (NIH) Consensus Panel developed evidence-based guidelines for early-stage breast cancer treatment.² The consensus recommended that adjuvant systemic treatment for stage I or stage II breast cancer include (1) hormonal treatment for receptor-positive tumors of ≤ 1 cm regardless of involvement of axillary lymph nodes, (2) polychemotherapy (≥ 2 agents) for receptor-negative tumors > 1 cm (both node-negative and node-positive), and (3) hormonal treatment plus polychemotherapy (≥ 2 agents) for receptor-positive tumors > 1 cm (both node-negative and node-positive).²

Although side effects of chemotherapy can be more troublesome in older than in younger women, the majority of older women can tolerate hormonal or chemotherapy reasonably well.³ There is also evidence that medical care that does not adhere to consensus standard treatment is associated with a higher mortality rate in both older and younger women.⁴ Although the frequency of use of adjuvant systemic treatment in patients with early breast cancer is largely unknown, a recent study that used the New Mexico Tumor Registry data reported that only 11% of women with stage I, 47% with stage II, and 68% with stage IIIA received chemotherapy.⁵ Furthermore, across all tumor stages, the use of chemotherapy decreased substantially with increasing age. Overall, 66% of women younger than 45 years of age received chemotherapy compared with 44% of women between 50 and 54 years of age, 31% of women between 55 and 59 years of age, and 18% of women between 60 and 64 years of age.⁵ In that study, the decreasing pattern of chemotherapy use with age continued even after adjustment was made for prognostic factors.⁵

Cancer registry data are frequently obtained from hospital discharge abstracts. Since adjuvant systemic treatment is often administered in an outpatient setting, it is likely that such treatment may be underreported by cancer registries. The objective of this study was to report the frequency of use of adjuvant systemic therapy for early breast cancer among women ≥ 65 years of age in New Jersey.

Materials and Methods

Breast cancer cases used for this study were originally selected from the New Jersey State Cancer Registry

(NJSCR) for a pilot study of factors associated with breast cancer mortality in the elderly.

Selection of Fatal Cases

Fatal cases were women who died of breast cancer between 65 and 85 years of age in New Jersey during the period 1987–1998 and who were initially diagnosed with breast cancer that was either localized or with regional spread to lymph nodes as defined by the Surveillance Epidemiology and End Results (SEER) Summary Staging System. This corresponds to the American Joint Commission on Cancer (AJCC) stages I (T1-N0-M0), IIA (T1-N1-M0, T2-N0-M0), IIB (T2-N1-M0, T3-N0-M0) or IIIA (T1-N2-M0, T2-N2-M0, T3-N1-M0, T3-N2-M0).⁶ The tumor (T), node (N), and metastasis (M) in the above staging system are defined as follows: T1 = tumor ≤ 2.0 cm in greatest dimension, T2 = tumor > 2.0 cm but ≤ 5.0 cm in greatest dimension, T3 = tumor > 5.0 cm in greatest dimension, N0 = no regional lymph node metastasis, N1 = metastasis to movable ipsilateral axillary lymph node(s), N2 = metastasis to ipsilateral axillary lymph node(s) fixed or matted or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis, M0 = no distant metastasis, and M1 = distant metastasis.⁶

Cases were then stratified based on their receptor status into estrogen receptor (ER+) and estrogen negative (ER-) cases. Among all women meeting these criteria, we randomly selected 50 ER+ and 50 ER- breast cancer cases. Cases in which the ER status was not recorded in the registry were excluded.

Selection of Nonfatal Cases

Nonfatal cases were selected from breast cancer survivors who were alive at least until the date of death of the fatal case. One nonfatal case with no known recurrence of breast cancer was matched to each fatal case. These were randomly chosen from all women who matched the fatal cases on date of diagnosis (± 1 year), their age at diagnosis (5-year age groups), SEER Summary Stage of breast cancer (localized or regional spread to lymph nodes), and receptor status (ER+ or ER-). Fatal and nonfatal cases of women who were not New Jersey residents and nonfatal cases of women who, upon receipt of medical information from providers, were found to have probable evidence of recurrence in their breast cancer were excluded. In those cases, nonfatal cases were selected to match fatal cases from a back-up pool of nonfatal cases.

Construction of a Representative Sample of Elderly New Jersey Women With Breast Cancer

The case-control sampling method heavily represents cases (50% of our sample were cases). Thus, combining the nonfatal and fatal cases to determine the frequency of use of adjuvant systemic therapy is inappropriate. To

reconstruct a sample that was representative of the elderly NJ women with early breast cancer, we obtained the distribution of fatal and nonfatal cases of early breast cancer among women 65 to 84 years of age at diagnosis from the population-based NJSCR. To estimate the frequency of use of adjuvant systemic therapy in New Jersey, we calculated a weighted average using the proportion of fatal and nonfatal ER+ (6.6% and 93.4%) and ER- (13.3% and 86.7%) early breast cancer cases diagnosed during the years 1987 through 1998 from all records available in the NJSCR among women ≥ 65 years of age. On the basis of this information, we gave less weight to the fatal cases and more weight to the nonfatal cases in our sample. This enabled us to reconstruct a representative sample of elderly NJ breast cancer patients in the community.

Ascertainment of Adjuvant Systemic Treatment and Confounding Variables

The NJSCR computerized files provided information on subjects demographic characteristics (age, race, ethnicity, and marital status), tumor characteristics (date of diagnosis, stage, receptor status, grade, and histologic type), and treatment received (surgery, radiation therapy, chemotherapy, and hormonal therapy with tamoxifen). Additional information was sought from patients' treating physicians on adjuvant systemic treatment. Physicians of patients included in the study were mailed a questionnaire requesting that they verify existing information obtained from the NJSCR and provide information that was missing on the NJSCR file. In instances when information obtained from the NJSCR differed from that provided by the treating physicians, we considered the physician's information to be more accurate. Using this method, we were able to obtain information on use of adjuvant systemic therapy for 80% of the study population. Physicians were also requested to provide information on the presence of comorbid diseases for their patients. We used this information to calculate the Charlson's comorbidity index for each patient.⁷ This study was approved by the Institutional Review Boards of the University of Medicine and Dentistry of New Jersey and the New Jersey Department of Health and Senior Services.

Statistical Analysis

We examined the distribution of demographic and patient factors (age at diagnosis, race/ethnicity, marital status, and Charlson's comorbidity index) as well as tumor characteristics (ER status and progesterone receptor [PR] status, tumor

grade, histologic type, and SEER Summary Stage of the tumor) in the study population. We then determined the frequency of use of surgical therapy, hormonal therapy alone, chemotherapy alone, and hormonal therapy in combination with chemotherapy separately for subjects with ER+ and ER- tumors. Subjects with missing treatment information were not included in the calculation of this frequency. Multivariate logistic regression models were constructed with use of adjuvant hormonal and chemotherapy as dependent variables and ER status, PR status, stage, comorbidity index, patient age, and race as independent variables. All analyses were done using the SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC).

Table 1. — Patient and Tumor Characteristics of the Study Subjects

	Fatal Cases (n = 100)	Nonfatal Cases (n = 100)	Weighted Average*
Patient Characteristics			
Age at diagnosis			
65–69 yrs	23	21	21.2
70–74 yrs	28	31	30.7
75–79 yrs	33	32	32.1
80–85 yrs	16	16	16.0
Race/ethnicity			
White non-Hispanic	89	91	90.8
Black non-Hispanic	8	4	4.5
Hispanic	2	2	2.0
Unknown	1	3	2.8
Marital status			
Single	8	10	9.8
Married	39	38	38.1
Widowed	49	39	40.2
Separated/divorced	2	9	8.2
Unknown	2	4	3.8
Charlson's comorbidity index			
0	75	75	75.0
1	10	8	8.2
2	12	13	12.9
≥ 3	3	4	3.9
Tumor Characteristics			
Estrogen receptor status			
Positive	50	50	50.0
Negative	50	50	50.0
Progesterone receptor status			
Positive	39	42	41.7
Negative	43	39	39.5
Unknown	18	19	18.9
Tumor grade (%)			
Well/moderately differentiated	18.6	32	30.4
Poorly differentiated/anaplastic	43.3	37	37.7
Unknown	38.1	31	31.8
Tumor histology			
Infiltrating duct carcinoma	78	70	70.9
Lobular carcinoma	7	10	9.7
Adenocarcinoma	2	6	5.5
Mucinous adenocarcinoma	4	1	1.3
Other	9	13	12.5
SEER Summary Stage			
Localized	60	60	60.0
Regional spread to lymph nodes	40	40	40.0
* Percentages reported are calculated as a weighted average of the proportion of fatal (0.116) and nonfatal cases (0.884) having the specific characteristic.			

Results

Patient Characteristics

The demographic characteristics of the study subjects are shown in Table 1. The study population was mostly composed of women aged 70–79 years who were predominantly non-Hispanic whites and were either married or widowed. A total of 75% of the women in the study had a Charlson's comorbidity score of zero. We also calculated the frequency of occurrence of specific comorbidity. Among subjects who were reported as having at least one comorbid condition, 62.4% suffered from various cardiovascular conditions including coronary artery disease, hypertension, congestive heart failure, myocardial infarction, and cerebrovascular accidents. Another 21.2% had a history of cancers other than their breast cancer. A further 12.9% of the study subjects suffered from respiratory conditions such as asthma, chronic emphysema, and bronchitis, and 10.6% had a history of diabetes mellitus. There were no substantial differences in demographic characteristics between fatal and nonfatal cases.

Tumor Characteristics

The distribution of tumor characteristics in the study population is displayed in Table 1. As a result of the stratification by ER status in the study design, the proportion of breast cancer patients with ER+ and ER- tumors was equal. The distribution of subjects with PR+ and PR- tumors was similar. Most women whose tumors expressed ERs were also PR+ (63%). Similarly, 73% of women with ER- tumors were also PR-. Breast cancer patients were diagnosed with poorly differentiated or anaplastic tumors more often than with well- or moderately differentiated tumors. When stratified by ER status, a higher percentage of women with well/moderately differentiated tumors expressed ERs (44%) vs 20% who were negative for ERs. Among those with poorly differentiated or anaplastic tumors, 54% were ER-, while only 20% were ER+. Infiltrating duct carcinoma was the most common histologic type observed among the study subjects. Other histologic types included lobular carcinoma, adenocarcinoma, and mucinous adenocarcinoma. More than half of the subjects had localized disease, with about 40% having regional spread to lymph nodes.

Table 2. — Receipt of Surgical and Adjuvant Systemic Therapy Among Study Subjects

	Frequency and Percentage of Women Receiving Adjuvant Systemic Therapy ^a		Weighted Average ^b
	Fatal Cases (n = 100)	Nonfatal Cases (n = 100)	
ER+ Subjects			
Surgical therapy			
Mastectomy	9 (21.4)	14 (29.2)	28.7
Lumpectomy	31 (73.8)	27 (56.3)	57.5
No surgery	2 (4.8)	7 (14.6)	14.0
Unknown ^c	8	2	
Adjuvant therapy			
Hormonal therapy only	15 (45.5)	23 (48.9)	48.7
Chemotherapy only	5 (15.2)	2 (4.3)	5.0
Hormonal plus chemotherapy	8 (24.2)	5 (10.6)	11.5
No adjuvant therapy	5 (15.2)	17 (36.2)	34.8
Unknown ^c	17	3	
ER- Subjects			
Surgical therapy			
Mastectomy	11 (22.0)	20 (40.0)	37.6
Lumpectomy	32 (64.0)	27 (54.0)	55.3
No surgery	7 (14.0)	3 (6.0)	7.1
Unknown ^c	0	0	
Adjuvant therapy			
Hormonal therapy only	8 (19.1)	14 (36.8)	34.4
Chemotherapy only	9 (21.4)	9 (23.7)	23.4
Hormonal plus chemotherapy	10 (23.8)	6 (15.8)	16.9
No adjuvant therapy	15 (35.7)	9 (23.7)	25.3
Unknown ^c	8	12	

^a Percentages are shown in parentheses.
^b Weighted average for ER+ subjects = (0.066 × proportion of fatal cases receiving specific adjuvant therapy) + (0.934 × proportion of nonfatal cases receiving specific adjuvant therapy). Weighted average for ER- subjects = (0.133 × proportion of fatal cases receiving specific adjuvant therapy) + (0.867 × proportion of nonfatal cases receiving specific adjuvant therapy).
^c In the calculation of percentages, subjects with unknown surgical, hormonal, and chemotherapy information were excluded.

Surgical and Radiation Therapy

Approximately 90% of the women in our study population underwent either a lumpectomy or a mastectomy for their breast cancers. Table 2 describes the use of surgical treatment for breast cancer by ER status. Among women with ER+ or ER- tumors, the use of mastectomy was higher among nonfatal cases, whereas lumpectomy was performed more often among fatal cases. Radiation therapy was administered to 35% of the women in the study.

Adjuvant Systemic Therapy

Overall, 42% and 14% of the study subjects received hormonal therapy alone and chemotherapy alone, respectively. Chemotherapy in combination with hormonal therapy was reported for another 14% of the subjects, and approximately 30% received no adjuvant systemic treatment. Table 2 shows the frequency of use of adjuvant systemic therapy separately for ER+ and ER- subjects. About 49% of the subjects whose tumors were ER+ received hormonal therapy alone, while 11% received hormonal therapy in combination with chemotherapy. On the other hand, 35% of women with ER+ tumors were not prescribed any adjuvant therapy. Among women whose tumors did not express ERs, the prevalence of use of chemotherapy alone or in combination with hormonal therapy was 23% and 17%, respectively. When the use of

adjuvant therapy was stratified by stage of breast cancer at diagnosis, we observed that hormonal therapy alone was prescribed more often for localized breast cancer (67.2% vs 37.5%). We also observed that a significantly higher percentage of subjects whose tumors had spread to regional lymph nodes compared to those that were localized (62.5% vs 32.8%, respectively, $P=.0015$) received chemotherapy alone or in combination with hormonal therapy. Thus, our results indicated a higher use of chemotherapy or combination therapy among those who had node-positive breast cancer.

Table 3 presents the results from multivariate logistic regression models with adjuvant hormonal and chemotherapy as dependent variables. Patients with cancers that had spread to regional lymph nodes were significantly more likely to receive adjuvant chemotherapy compared to those with localized tumors (odds ratio [OR] = 4.75; 95% confidence interval [CI] 2.10-10.78) as were patients with PR- tumors (OR = 3.27; 95% CI 1.08, 9.94). These estimates were adjusted for ER status, Charlson's comorbidity index, and patients' age and race/ethnicity.

Table 3. — Factors Related to Use of Adjuvant Systemic Therapy

Adjuvant Hormonal Therapy	Odds Ratio (95% CI)
Estrogen receptor status	
Positive	1.00
Negative	0.63 (0.25, 1.54)
Progesterone receptor status	
Positive	1.00
Negative	0.54 (0.21, 1.42)
Unknown	0.57 (0.20, 1.61)
Stage	
Localized	1.00
Regional spread to lymph nodes	1.33 (0.62, 2.83)
Charlson's comorbidity index	1.45 (0.98, 2.14)
Patients' age	1.03 (0.97, 1.11)
Race/ethnicity	
Non-Hispanic white	1.00
Non-Hispanic black	0.98 (0.24, 3.97)
Hispanic	0.64 (0.08, 5.35)
Unknown	0.73 (0.09, 5.73)
Adjuvant Chemotherapy	
Estrogen receptor status	
Positive	1.00
Negative	0.73 (0.25, 2.11)
Progesterone receptor status	
Positive	1.00
Negative	3.27 (1.08, 9.94)
Unknown	0.64 (0.17, 2.46)
Stage	
Localized	1.00
Regional spread to lymph nodes	4.75 (2.10, 10.78)
Charlson's comorbidity index	0.98 (0.71, 1.37)
Patients' age	0.88 (0.82, 0.96)
Race/ethnicity	
Non-Hispanic white	1.00
Non-Hispanic black	1.03 (0.22, 4.80)
Hispanic	0.81 (0.10, 6.68)
Unknown	0.77 (0.06, 9.33)

Contrary to the recommendations in the NIH consensus statement,² a significant proportion of women with ER- tumors (34%, $n = 22$) were prescribed hormonal therapy alone. A closer look at the data revealed that 8 women who were classified as ER- in the NJSCR files were subsequently reported to be ER+ by their physicians and/or hospitals. However, these cases were analyzed as per their original assignment at the design stage, and weights were calculated accordingly. In addition, 3 women were PR+. Data on use of adjuvant systemic treatment were not available for 20 ER+ and 20 ER- subjects. This was predominantly due to two reasons. First, for some patients, the NJSCR could not identify the treating physicians. Therefore, no additional information could be obtained. Second, the treating physicians could not locate the medical records of some of the patients, either because the medical records were destroyed or because the office staff could not find the necessary information.

Discussion

Our study documents the pattern of use of adjuvant systemic therapy among women ≥ 65 years of age with early breast cancer. Overall, 42% and 14% of the study subjects received hormonal therapy alone and chemotherapy alone, respectively. Chemotherapy in combination with hormonal therapy was reported for 14% of the subjects, and approximately 30% received no adjuvant systemic treatment. Hormonal therapy was the most frequently used treatment modality irrespective of hormonal receptor status. Chemotherapy alone or in combination with hormonal therapy was prescribed to less than half of the women with ER- tumors.

We found that approximately 42% of NJ women ≥ 65 years of age with early breast cancer received hormonal therapy alone. This is in line with the results obtained from other studies in which the use of this treatment ranged between 17% and 81% among this age group.^{5,8-12} Previous research has also demonstrated that the frequency of use of chemotherapy alone or in combination with hormonal therapy among elderly women with early breast cancer varies from as low as 2% to as high as 33%.^{5,8-12} In our study, about 28% of the subjects received adjuvant chemotherapy alone or in combination with hormonal therapy, which is consistent with previous research.

An interesting finding of this study was that, contrary to NIH guidelines,² a high proportion of ER- women received hormonal therapy alone (34%) or in combination with chemotherapy (17%). Data from several clinical trials published in the 1980s demonstrated an overall benefit of tamoxifen in reducing breast cancer mortality for both ER+ and ER- tumors.¹³⁻¹⁷ The increased use of adjuvant hormonal therapy for recep-

tor-negative tumors in our population of women diagnosed during 1988–1998 may reflect the evidence available to physicians at that time. However, with better assays available for ER and PR tests, recent research has shown no benefit of tamoxifen use among women with receptor-negative tumors.¹⁸ Also, it has been suggested that ER- women with a positive PR assay might benefit from tamoxifen.^{2,19} In our study, we found that 7 out of the 22 women with ER- tumors who received hormonal therapy alone were PR+. In such cases, the decision to prescribe hormonal treatment may have been driven by the patients' PR+ status.

In our study, we found that 8 women who were classified as ER- based on the NJSCR data were reported to be ER+ by their treating physicians and hospitals. Studies have reported considerable variability in techniques of measurement of ER status between laboratories^{20,21} as well as in the definitions for ER positivity.²² It has also been postulated that tamoxifen may have mechanisms of action other than its role of binding to ER protein. It has been suggested that tamoxifen may have an effect on insulin-like growth factor I levels, thus extending its therapeutic benefit to postmenopausal ER- women.²³ There is some evidence that women whose tumors express low but still detectable amounts of ER protein may show a favorable response to tamoxifen despite being reported as ER-.^{2,21}

Our study has its limitations, one of which is the lack of information on tumor characteristics and treatment for some patients. This was primarily due to three reasons. First, information on women diagnosed with breast cancer more than 7 years after diagnosis was not available from the physicians, either because their records were archived at an off-site location or were destroyed. Second, names and contact information of attending physicians and/or oncologists for some study subjects were not available from the registry data, thus making it impossible to obtain additional treatment information. Third, for some patients, the physicians identified from the registry had not contributed to the patients' breast cancer care and did not have any information on other physicians who may have evaluated the patient for their cancer treatment. Despite these limitations, the adjuvant treatment information obtained from the physicians was superior to that available in the registry data, thus providing a better estimate of the frequency of use of adjuvant systemic treatment for early breast cancer among women ≥ 65 years residing in New Jersey.

Conclusions

Only about a quarter of women ≥ 65 years of age in New Jersey received adjuvant chemotherapy. More significantly, less than half of the women with ER- tumors

were reported to have received adjuvant chemotherapy. Efforts in increasing the use of hormonal and adjuvant chemotherapy may help to reduce the excess mortality burden among elderly women with early breast cancer.

References

1. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1992;339:71-85.
2. Adjuvant Therapy for Breast Cancer. National Institutes of Health Consensus Development Conference Statement. November 1-3, 2000. Available at http://consensus.nih.gov/cons/114/114_intro.htm. Accessed November 12, 2006.
3. Cascinu S, Del Ferro E, Catalano G. Toxicity and therapeutic response to chemotherapy in patients aged 70 years or older with advanced cancer. *Am J Clin Oncol*. 1996;19:371-374.
4. Lash TL, Silliman RA, Guadagnoli E, et al. The effect of less than definitive care on breast carcinoma recurrence and mortality. *Cancer*. 2000; 89:1739-1747.
5. Du XL, Key CR, Osborne C, et al. Discrepancy between consensus recommendations and actual community use of adjuvant chemotherapy in women with breast cancer. *Ann Intern Med*. 2003;138:90-97.
6. Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer; 2002.
7. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.
8. de la Haba Rodriguez JR, Mendez Vidal MJ, Gomez Espana A, et al. Adjuvant treatment in elderly patients with breast cancer: critical review of clinical practice. *Am J Clin Oncol*. 2003;26:398-401.
9. Du X, Goodwin JS. Patterns of use of chemotherapy for breast cancer in older women: findings from Medicare claims data. *J Clin Oncol*. 2001; 19:1455-1461.
10. Guadagnoli E, Shapiro C, Gurwitz JH, et al. Age-related patterns of care: evidence against ageism in the treatment of early-stage breast cancer. *J Clin Oncol*. 1997;15:2338-2344.
11. Mandelblatt JS, Hadley J, Kerner JF, et al. Patterns of breast carcinoma treatment in older women: patient preference and clinical and physical influences. *Cancer*. 2000;89:561-573.
12. Merchant TE, McCormick B, Yahalom J, et al. The influence of older age on breast cancer treatment decisions and outcome. *Int J Radiat Oncol Biol Phys*. 1996;34:565-570.
13. Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer. Interim analysis at four years by Nolvadex Adjuvant Trial Organisation. *Lancet*. 1983;1:257-261.
14. Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years by Nolvadex Adjuvant Trial Organisation. *Lancet*. 1985;1:836-840.
15. Adjuvant tamoxifen in the management of operable breast cancer: the Scottish Trial. Report from the Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC), Edinburgh. *Lancet*. 1987;2:171-175.
16. Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer. "Nolvadex" Adjuvant Trial Organisation. *Br J Cancer*. 1988;57:608-611.
17. Delozier T, Spielmann M, Mace-Lesec'h J, et al. Tamoxifen adjuvant treatment duration in early breast cancer: initial results of a randomized study comparing short-term treatment with long-term treatment. Federation Nationale des Centres de Lutte Contre le Cancer Breast Group. *J Clin Oncol*. 2000;18:3507-3512.
18. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365:1687-1717.
19. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1998;351:1451-1467.
20. Rhodes A, Jasani B, Barnes DM, et al. Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. *J Clin Pathol*. 2000;53:125-130.
21. Smith RE, Good BC. Chemoprevention of breast cancer and the trials of the National Surgical Adjuvant Breast and Bowel Project and others. *Endocr Relat Cancer*. 2003;10:347-357.
22. Elwood JM, Godolphin W. Oestrogen receptors in breast tumours: associations with age, menopausal status and epidemiological and clinical features in 735 patients. *Br J Cancer*. 1980;42:635-644.
23. Mandala M, Moro C, Ferretti G, et al. Effect of tamoxifen on GH and IGF-1 serum level in stage I-II breast cancer patients. *Anticancer Res*. 2001; 21:585-588.