

Age-Related Patterns of Care: Evidence Against Ageism in the Treatment of Early-Stage Breast Cancer

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Purpose: To assess whether the use of adjuvant systemic therapy in postmenopausal women with early-stage breast cancer is influenced by patient age.

Methods: A retrospective cohort study based on data collected from medical records and from patients and their surgeons was performed among 746 postmenopausal patients diagnosed with early-stage breast cancer at 30 hospitals located throughout Minnesota. The adjusted odds of receiving hormonal therapy, chemotherapy, and both hormonal therapy and chemotherapy as a function of age was determined.

Results: Among women with negative lymph nodes, 62% received some form of adjuvant drug therapy. For these women, the likelihood of receiving hormonal therapy or both hormonal therapy and chemotherapy did not vary with patient age and the likelihood of receiving chemotherapy declined with age. Among women with positive lymph nodes, 92% received some form of adjuvant therapy. For these women, the likelihood of receiving

hormonal therapy increased with age and the likelihood of receiving chemotherapy declined with age, as did the likelihood of receiving both hormonal therapy and chemotherapy.

Conclusion: The observed associations between age and the use of adjuvant systemic therapy appear to reflect, in general, available information about treatment efficacy and do not suggest underuse among elderly women with early-stage breast cancer. The use of adjuvant therapy depends on clinical factors that predict the increased risk of metastases or the increased likelihood of response to treatment, rather than other sociodemographic factors. Our results also suggest that younger postmenopausal women with positive lymph nodes compared with older women may be undertreated with respect to tamoxifen because of the substitution of chemotherapy for hormonal therapy.

J Clin Oncol 15:2338-2344. © 1997 by American Society of Clinical Oncology.

ADJUVANT HORMONAL THERAPY prolongs the recurrence-free and overall survival of postmenopausal women with early-stage breast cancer. Two randomized controlled trials of women over age 65 years showed statistically significant improvements in relapse-free survival and a trend toward improved overall survival.¹⁻³ The Early Breast Cancer Trialists' Collaborative Group concluded from their meta-analysis that tamoxifen reduces the annual odds of breast cancer recurrence by 30% and the annual odds of death by 19% for postmenopausal women.⁴ Treatment benefits were of similar magnitude in cohorts of women aged 50 to 59, 60 to 69, and $\geq$ 70 years, and in node-negative and node-positive patients.

Compared with tamoxifen, the benefits of adjuvant chemotherapy are smaller in postmenopausal women. The

Early Breast Cancer Trialists' Collaborative Group reported a 13% reduction in mortality for women age 50 to 59 and a 10% reduction for women age 60 to 69.⁴ The benefits of adjuvant chemotherapy therapy could not be reliably assessed for women older than 70 years because of the small number of women in this age group who participated in clinical trials.

The value of combination chemotherapy and endocrine therapy is uncertain⁵ and trials are still ongoing.⁶ The Early Breast Cancer Trialists' Collaborative Group reported that the combination of chemotherapy and tamoxifen provided an advantage with respect to disease-free survival, but not overall survival.⁴ More work is needed to determine whether the benefits are justified given the increased toxicity associated with combination therapy.

Several studies have suggested that age bias exists in the selection of adjuvant therapy for women with breast cancer.⁷⁻¹¹ However, what may appear to be age-related differences in care may actually reflect our understanding of treatment efficacy. Therefore, we would hypothesize, for patients with negative nodes, no difference in the likelihood of hormonal therapy across age groups given that benefits are fairly consistent for younger and older patients (hypothesis I); however, we would expect the use of chemotherapy to decline with age given the paucity of data showing that older patients benefit from this treatment (hypothesis II). The use of both hormonal and chemotherapy is also likely to decline with age (hypothesis III). Among patients with positive nodes, we would hypothesize no difference in the use of hormonal therapy by age (hypothesis IV), and a decline in the use of chemo-

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Submitted September 16, 1996; accepted February 21, 1997.

Supported by grants no. CA59408 and CA57755 from the National Cancer Institute, Bethesda, MD.

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0732-183X/97/1506-0012\$3.00/0

therapy—alone or in combination with hormonal therapy—by age (hypotheses V and VI). We tested these hypotheses by examining the use of adjuvant systemic therapy in more than 700 postmenopausal women newly diagnosed with early-stage breast cancer during a 1-year period in the state of Minnesota.

METHODS

Subjects

We identified patients newly diagnosed with early-stage invasive breast cancer (stage I or II) between January and December 1993 at 30 hospitals located throughout Minnesota. The hospitals are participants in the Minnesota Clinical Comparison and Assessment Project administered through the Healthcare Education and Research Foundation located in St Paul, MN, and represent approximately two thirds of the hospital beds in the state. All patients had a histologically confirmed diagnosis of breast cancer and were over 21 years of age. We excluded patients with carcinoma-in-situ, bilateral synchronous carcinoma, or inflammatory carcinoma, and, for the present analysis, all premenopausal women. The study was approved by the Institutional Review Board of Harvard Medical School and informed consent was obtained from all patients.

Data Collection

Medical record data. For each patient, we collected information from the medical record associated with the visit (inpatient or outpatient) in which primary surgery occurred. We documented cancer history, tumor size, the result of axillary node dissection, the result of estrogen receptor protein testing, and the presence of lymphatic vessel invasion. We coded primary surgical therapy as mastectomy (modified radical mastectomy or total mastectomy) or breast conservation (partial mastectomy, segmental mastectomy, lumpectomy, quadrantectomy, tylectomy, wedge resection, or excisional biopsy) and documented whether adjuvant systemic therapy was planned or ordered. We used the Index of Coexistent Disease¹² to classify severity of comorbid disease as none, mild, moderate, or severe. Demographic characteristics collected were age, marital status (married v divorced, separated, or never married), and source of payment (health maintenance organization member v not a member).

Data collectors were either nurses or individuals with medical record abstraction training who completed the data collection form according to a standard protocol. A random sample of records completed by each data collector was reabstracted by a study nurse as a quality-control check.

Physician data. We mailed the surgeon of each patient a one-page form that asked him or her to indicate which type of adjuvant systemic therapy, if any, the patient received or planned to receive. We collected these data from surgeons because we considered them to be the physicians most responsible for managing the overall care of patients with early-stage breast cancer.

Patient interview data. Patients participated in a 30-minute telephone interview targeted to take place 2 months after primary therapy. Patients were asked whether they were currently receiving or had received adjuvant systemic therapy.

During March and April 1995, when most patients were 1 to 2 years' postsurgery, we recontacted patients to determine whether they either initiated or terminated drug therapy since we last spoke with them. The information collected at that time was combined with all information previously available to determine whether a patient received adjuvant systemic therapy.

Income and education data. We defined income for each patient as the median household income associated with the zip code of her residence. For each patient, an indicator for education was defined as the proportion of adults with a high school education residing in her zip code. The source of information for both variables was the 1990 United States Census. We used this source of data for income and education, because not all women completed the patient interview, and among those who did, a nontrivial proportion did not respond to the income and education questions.

Menopausal status. We documented each patient's menopausal status according to the following strategy: if she completed the interview, we coded her status based on her response to a question about whether she had gone through menopause; if she did not participate in the interview, we established her status based on data documented from the medical record; and if neither of these sources was available, we defined her as postmenopausal if her age was ≥ 55 years.

Adjuvant therapy status. We documented whether a patient received adjuvant systemic therapy—hormonal therapy only, chemotherapy only, or hormonal therapy and chemotherapy—according to the following strategy: if a patient completed the interview(s), we coded the status of drug therapy based on her responses to questions about treatment; if she did not participate in the interview, we used the responses provided by the surgeon on the treatment recommendation form; if both an interview and a treatment recommendation form were not available, we used adjuvant therapy information coded on the medical record abstract form. Finally, if information on adjuvant therapy was missing from the medical record, we attempted to get this information from the tumor registry located at the hospital where the patient underwent primary therapy or directly from her surgeon's office.

Data Analysis

Sample characteristics. We compared the demographic characteristics, disease characteristics, and case-mix of patients by age using χ^2 tests.¹³

Influence of age on the use of adjuvant therapy by stage of disease. We compared the use of hormonal therapy only, chemotherapy only, both hormonal and chemotherapy therapy, and any adjuvant drug therapy by age, separately for patients with negative and positive lymph nodes, using χ^2 tests. We used logistic regression analysis¹⁴ to assess the influence of age on the likelihood of receiving each of these therapies, controlling for marital status, education, income, health maintenance organization membership, history of breast cancer, history of other cancer, severity of comorbid disease, tumor size, lymphatic vessel invasion, estrogen receptor status, poorly differentiated histologic grade (grade 3), and type of surgery. Regression analyses were performed separately for patients with positive and negative lymph nodes.

RESULTS

Sample Characteristics

We identified 746 postmenopausal women ≥ 50 years of age with early-stage breast cancer. Of these patients, we were not able to determine whether 19 patients received any form of drug therapy, and we identified 95 patients (13%) who did not undergo axillary node dissection. Those who did not undergo node dissection were more likely than those who did to be ≥ 85 years old (41% v 12%; $P < .001$) and to have a comorbid disease

Table 1. Demographic Characteristics, Disease, and Case-Mix Characteristics by Age for Postmenopausal Women Newly Diagnosed With Breast Cancer

Characteristic	Age, years										P
	50-59 (n = 154)		60-69 (n = 224)		70-79 (n = 180)		≥ 80 (n = 74)		Total (N = 632)		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Demographic											
Married	112	73	137	62	75	42	10	14	334	54	< .001
Education											
High school graduate*	86		87		85		86		86		.10
Income†											
< \$30,000	44	29	54	25	63	35	27	38	188	30	.039
\$30,000-\$39,999	54	36	90	41	71	40	31	44	246	40	
\$40,000-\$49,999	42	28	47	22	30	17	7	10	126	20	
≥ \$50,000	12	8	26	12	14	8	6	8	58	9	
HMO	84	55	87	39	48	27	17	23	236	37	< .001
Disease											
Tumor size (cm)											
≤ 1	52	35	74	35	56	33	18	25	200	33	.313
1-2	59	39	78	37	72	43	25	35	234	39	
> 2	39	26	60	28	41	24	28	39	168	28	
Negative lymph nodes	110	71	174	78	142	79	47	64	473	75	.036
Positive lymph nodes	44	29	50	22	38	21	27	36	159	25	
1-3 nodes	26	59	30	60	29	76	19	70	104	65	
> 3 nodes	18	41	20	40	9	24	8	30	55	35	
Poorly differentiated histologic Grade 3	34	22	59	26	30	17	17	23	140	22	.150
Lymphatic vessel invasion	15	10	26	12	14	8	5	7	60	9	.487
Estrogen receptor status, positive	95	62	143	64	120	67	48	65	406	64	.819
Case-Mix											
Mastectomy	98	63	139	62	128	71	63	85	428	68	< .001
Previous breast cancer	11	7	23	10	16	9	10	14	60	9	.455
History of other cancer	9	6	22	10	26	14	12	16	69	11	.032
Comorbid disease											
None	70	45	57	25	22	12	6	8	155	25	< .001
Mild	42	27	55	25	38	21	16	22	151	24	
Moderate	35	23	94	42	93	52	40	54	262	41	
Severe	7	5	18	8	27	15	12	16	64	10	

*Percent high school graduate in zip code.

†Median income for zip code of residence.

(85% v 75%; $P = .035$); they were less likely to be married (41% v 54%; $P = .026$), and to be insured by a health maintenance organization (21% v 37%; $P = .002$). We report results for patients with pathologically staged disease only.

The demographic, case-mix, and disease characteristics of patients are listed by age in Table 1. The proportion of married patients declined with age, as did income and health maintenance organization membership. Older patients were more likely to have had positive lymph nodes, to have had a mastectomy, to have had a history of cancer other than breast cancer, and to have more severe comorbid disease. The sample was predominantly white (98%).

Influence of age on the use of adjuvant therapy by stage of disease. We determined adjuvant therapy status

for the majority (71%) of women from the patient interview(s). For the remaining patients, we determined their status from information gathered from hospital tumor registries or physician offices (13%), from the surgeon (12%), or from the medical record (3%).

Just over half of all women with negative lymph nodes received hormonal therapy only and its use did not vary with age (Table 2). The proportion of patients who received chemotherapy only declined with age. Only 19 patients (4%) received both hormonal therapy and chemotherapy. Overall, 62% of women with negative lymph nodes received some form of adjuvant therapy and the use of therapy declined with age.

Forty percent of patients with positive lymph nodes received hormonal therapy and its use increased with age ($P < .001$; Table 2). The use of chemotherapy ($P < .05$)

Table 2. Adjuvant Therapy by Stage of Disease and Age for Postmenopausal Women Newly Diagnosed With Breast Cancer

Lymph Node Status	Age, years										P
	50-59		60-69		70-79		≥ 80		Total		
	No.	%	No.	%	No.	%	No.	%	No.	%	
Negative, no.	110		174		142		47		473		
Hormonal therapy only	57	52	96	55	72	51	16	34	241	51	.084
Chemotherapy only	16	15	15	9	1	1	0	0	32	7	< .001
Chemotherapy and hormonal therapy	7	6	5	3	6	4	1	2	19	4	.455
Any adjuvant systemic therapy	80	73	116	67	79	56	17	36	292	62	< .001
Positive, no.	44		50		38		27		159		
Hormonal therapy only	5	11	14	28	26	68	18	67	63	40	< .001
Chemotherapy only	14	32	13	26	3	8	3	11	33	21	.024
Chemotherapy and hormonal therapy	22	50	21	42	5	13	2	7	50	31	< .001
Any adjuvant systemic therapy	41	93	48	96	34	89	23	85	146	92	.371

and both hormonal therapy and chemotherapy ($P < .001$) declined with age. Overall, 92% of women with positive lymph nodes received some form of adjuvant therapy and the use of therapy did not vary with age.

Adjusted odds of undergoing treatment. Among patients with negative lymph nodes, the use of hormonal therapy only did not vary as a function of age controlling for demographic characteristics, disease characteristics, and case-mix (Table 3). Age was a strong predictor of the use of chemotherapy alone; patients over age 70 were 98% less likely than other patients to receive this therapy. The adjusted likelihood of receiving both hormonal therapy and chemotherapy did not vary with age. Overall, patients with negative lymph nodes over age 70 were 63% less likely than other patients to receive any form of adjuvant therapy.

The adjusted likelihood of receiving hormonal therapy among women with positive lymph nodes increased with age, with the odds of treatment greatest for women aged 70 to 79 (Table 4). The likelihood of receiving chemotherapy only declined with age, as did the likelihood of receiving both hormonal therapy and chemotherapy. A model to predict the likelihood of receiving any systemic drug

therapy was not generated because of the small proportion of women (8%) who did not receive any form of therapy.

Influence of other factors on the use of adjuvant systemic therapy: women with negative lymph nodes. Controlling for age and all other variables in our model, women with positive estrogen receptor status (odds ratio, 4.79; 95% confidence interval [CI] 3.09 to 7.44) were more likely than other women to receive hormonal therapy. Women who belonged to a health maintenance organization (odds ratio, .23; 95% CI, .08 to .62) and with positive estrogen receptor status (odds ratio, .12; 95% CI, .05 to .33) were less likely than other women to receive chemotherapy only; those with poorly differentiated histologic grade (odds ratio, 5.06; 95% CI, 1.84 to 13.91) were more likely than others to receive chemotherapy only. Women with tumors greater than 2 cm were more likely (odds ratio, 3.05; 95% CI, 1.10 to 8.45) than other women to receive both hormonal therapy and chemotherapy. Those with tumors greater than 2 cm (odds ratio, 1.82; 95% CI, 1.04 to 3.19), positive estrogen receptor status (odds ratio, 3.62; 95% CI, 2.32 to 5.65), and poorly differentiated histologic grade (odds ratio, 2.23; 95% CI, 1.23 to 4.06) were more likely than other women to receive any form of systemic drug therapy.

Table 3. Adjusted Odds and 95% Confidence Intervals of Receiving Adjuvant Therapy by Age for Postmenopausal Women Newly Diagnosed With Negative Lymph Nodes

Age,* years	Adjuvant Therapy							
	Hormonal Therapy Only		Chemotherapy Only		Hormonal Therapy and Chemotherapy		Any Systemic Drug Therapy	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
50-59	—	—	—	—	—	—	—	—
60-69	1.28	.74-2.2	.38	.14-1.0	.32	.09-1.16	.73	.40-1.31
≥ 70	.82	.45-1.47	.02	.002-.18	.52	.14-1.98	.37	.19-.69

NOTE. Adjusted odds for marital status, education, income, health maintenance organization membership, tumor size, lymphatic invasion, estrogen receptor status, histologic grade, type of primary surgery, history of breast cancer, history of other cancer, and severity of comorbid disease.

*The ≥ 80 age category was combined with the 70 to 79 age category for all models because of the small number of women over age 80 who received treatment.

Table 4. Adjusted Odds and 95% Confidence Intervals of Receiving Adjuvant Therapy by Age for Postmenopausal Women Newly Diagnosed With Positive Lymph Nodes

Age, years	Adjuvant Therapy					
	Hormonal Therapy Only		Chemotherapy Only		Hormonal Therapy and Chemotherapy*	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
50-59	—	—	—	—	—	—
60-69	3.37	.81-14.05	.56	.16-1.90	.83	.29-2.36
70-79	38.52	7.04-210.90	.05	.01-.37	.23	.06-.93
≥ 80	19.62	3.33-115.72	.12	.02-.95	.09	.01-.93

NOTE. Adjusted odds for marital status, education, income, health maintenance organization membership, tumor size, lymphatic invasion, estrogen receptor status, histologic grade, type of primary surgery, history of breast cancer, history of other cancer, and severity of comorbid disease. A model for any systemic drug therapy was not generated because of the small number of women who did not receive any form of therapy.

*History of breast cancer deleted from the model to obtain convergence.

Influence of other factors on the use of adjuvant systemic therapy: women with positive lymph nodes. Women with positive estrogen receptor status (odds ratio, .15; 95% CI, .05 to .44) had a lower likelihood of receiving chemotherapy only, but women with tumor size greater than 2 cm (odds ratio, 10.18; 95% CI, 1.08 to 96.47) were more likely to receive chemotherapy. Married women (odds ratio, 2.97; 95% CI, 1.13 to 7.78) and women with positive estrogen receptor status (odds ratio, 3.87; 95% CI, 1.42 to 10.60) were more likely than other women to receive both hormonal therapy and chemotherapy.

DISCUSSION

We were not able to reject the majority of our proposed hypotheses and, therefore, it appears that use of adjuvant systemic therapy reflects what is known about treatment efficacy. Among women with negative lymph nodes, we observed no association between age and the use of hormonal therapy (hypothesis I) and a negative association between age and the use of chemotherapy alone (hypothesis II). Among women with positive lymph nodes, we observed a decline with patient age in the use of chemotherapy (hypothesis V), as well as a decline in the use of both hormonal therapy and chemotherapy (hypothesis VI).

Two of our hypotheses (hypotheses III and IV) were not supported; however, neither result suggested older women were less likely to receive therapy. We did not observe a decline with age in the use of both hormonal therapy and chemotherapy among women with negative lymph nodes, but rather we found no association between age and the use of this therapy. Among women with positive lymph nodes, we observed a positive association between age and the use of hormonal therapy, rather than the predicted lack of an association.

The decline with age in the frequency of adjuvant chemotherapy in our study is consistent with the diminished efficacy of the treatment in older patients and the uncer-

tainty about the indications for treatment in women over age 70 years. Overall, and in each age cohort, chemotherapy was used more frequently in node-positive patients than in node-negative patients. This suggests that the increased risks of systemic metastases in node-positive patients, irrespective of age, led to greater use of treatment.

The differential effectiveness of adjuvant chemotherapy might be related to biologic differences between breast cancers in younger and older women. This seems unlikely given that the response rates and survival of patients with metastatic breast cancer treated with chemotherapy are similar in younger and older patients.¹⁵ However, dose reductions may explain the reduced efficacy of adjuvant chemotherapy among older patients.¹⁶ Older patients may be treated with lower doses more frequently than younger patients, despite ample evidence that the physical and psychosocial effects of chemotherapy are similar in younger and older women.¹⁷⁻¹⁹ In sum, although the state of the art suggests that older patients are less likely than younger patients to benefit from chemotherapy, we may not yet have used the best designs to test the efficacy of this therapy in older patients.²⁰

Sixty-two percent of women with negative nodes received some form of adjuvant drug therapy. Women with negative nodes over age 70 were less likely to receive some form of therapy than younger women. This overall pattern is not unexpected given that the use of hormonal therapy alone did not vary with age and the use of chemotherapy alone declined with age. Because current treatment guidelines²¹ suggest that the patient should participate in the decision to have adjuvant treatment in the presence of negative nodes, we cannot evaluate whether 62% is an optimal rate of treatment for node-negative patients without knowing whether those who did not receive the treatment were offered it.

Nearly all women (92%) with positive lymph nodes received some form of adjuvant therapy. Although we did observe a decline in the use of any therapy with patient

age, the rate of decline was not statistically significant. The increased use of hormonal therapy with age and the decreased use of chemotherapy suggest that physicians may be substituting chemotherapy for hormonal therapy in younger patients. These results suggest that younger postmenopausal women may be undertreated compared with older women with respect to receiving hormonal therapy. Among the women with positive lymph nodes who received treatment, the proportion who received hormonal therapy (alone or in combination with chemotherapy) increased with age: 66%, 73%, 91%, and 87% for women aged 50 to 59, 60 to 69, 70 to 79, and ≥ 80 years (calculated from Table 2), respectively. Tamoxifen therapy has been shown to reduce the risk of contralateral breast cancer, whereas chemotherapy has not.²⁰ Moreover, tamoxifen therapy has been shown to have other benefits. It may prevent osteoporosis²² and lower cholesterol levels.²³ Recent reports from Europe suggest that tamoxifen reduces the risk of hospitalization for cardiovascular disease and for fatal myocardial infarction.^{24,25}

Prior studies have shown that breast cancer treatment varies with age.^{26,27} Older patients with breast cancer, especially those over age 70, were less likely to receive systemic adjuvant therapy than younger patients.⁷⁻¹¹ The precise reasons for age-related treatment variation are not fully understood, but age bias has been suggested as a possible contributor.¹² However, comparison of patterns of use of adjuvant treatment by age alone, or even by age and stage, may be misleading. Important variables such as tumor size and hormonal receptor status that routinely affect therapeutic decisions, especially in node-negative patients, were not included in some prior studies that focused primarily on age. The results from our logistic regression models reinforce the importance of hormone receptor status, histologic grade, and tumor size on treatment decisions.

We also found that members of health maintenance organizations with negative lymph nodes were less likely than nonmembers to receive chemotherapy and that married women with positive nodes were more likely to receive both hormonal therapy and chemotherapy. Further work is needed to understand the significance of these findings. Given that health maintenance organization membership and marital status did not demonstrate a consistent influence on the treatment indicators we examined, it is possible that they represent chance associations.

A strength of the study is the number of patients enrolled from a variety of treatment centers. However, our data describe practice in one state only. We cannot say with confidence that our results generalize to practice in other states.

In summary, the observed associations between age and use of adjuvant systemic therapy appear to reflect generally what we know about treatment efficacy and do not suggest underuse among elderly women with early-stage breast cancer. The use of adjuvant therapy depends on clinical factors that predict the increased risk of metastases or the increased likelihood of response to treatment, rather than other sociodemographic factors. Our results also suggest that younger postmenopausal women with positive lymph nodes may be undertreated with respect to tamoxifen compared with older women.

ACKNOWLEDGMENT

We thank Marilyn Sarnie, MA, Shera Gruen, Candace Zaiden, Nora Morris, MA, and Shirley Germann, RN, for their help in conducting the study, and Robert Wolf, MS, for statistical programming. Dr Gurwitz is the recipient of a Clinical Investigator Award (KO8 AG00510) from the National Institute on Aging. Dr Guadagnoli is a Picker/Commonwealth Scholar.

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