Breast Surgery in the 'Arimidex, Tamoxifen Alone or in Combination' (ATAC) Trial

American Women Are More Likely than Women from the United Kingdom To Undergo Mastectomy

Gershon Y. Locker, M.D.[1]
J. Richard Sainsbury, M.D.[2]
Jack Cuzick, Ph.D.[3]

[1] Evanston Northwestern Healthcare, Northwestern University, Evanston, Illinois.

[2] Department of Surgery, University College London, London, United Kingdom.

[3] Cancer Research UK, Wolfson Institute of Preventive Medicine, London, United Kingdom.

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Performed on behalf of the ATAC Trialists' Group.

Address for reprints: Gershon Y. Locker, M.D., Evanston Northwestern Healthcare, 2650 Ridge Ave., Room 5134, Evanston, IL 60201; Fax: (847) 570-2336; E-mail: gylocker@northwestern.edu

Gershon Y. Locker has served as a consultant to and is a member of the speakers' bureau at AstraZeneca Pharmaceuticals.

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BACKGROUND. Various factors affect patients' decisions regarding whether to undergo surgery for the treatment of early-stage breast carcinoma. The 'Arimidex, Tamoxifen Alone or in Combination' (ATAC) trial, the largest multinational randomized trial of adjuvant therapy for patients with operable breast carcinoma to date, offers the opportunity to investigate whether nationality is one such factor.

METHODS. After receiving primary therapy for early-stage breast carcinoma, 9366 women (from a total of 21 countries) were randomized to receive anastrozole, tamoxifen, or anastrozole plus tamoxifen for 5 years. In the current study, mastectomy and breast conservation rates were compared among participating countries. The possibility that variations from country to country could be explained by inequalities in terms of pathologic, clinical, and hospital-related correlates of surgical choice was explored first on univariate analysis and then on multivariate logistic analysis.

RESULTS. National mastectomy rates ranged from 20% to 97%; 51% of the 2222 enrollees from the United States had undergone mastectomy, compared with 42% of the 3228 enrollees from the United Kingdom (odds ratio [OR], 1.43; 95% confidence interval [CI], 1.28–1.60; $P < 0.001$). On univariate analysis, larger tumor size, positive lymph node status, higher tumor grade, older age, and adjuvant chemotherapy use were found to be correlated with mastectomy use. In contrast, positive hormone receptor status, increased body weight, and enrollment at a center that had more than 40 enrollees were found to be associated with breast conservation. The same correlates were identified on multivariate logistic analysis ($P < 0.05$), except that the number of enrollees at a patient's treatment center no longer possessed predictive value. After correction for these correlated factors, residence in the United States (compared with residence in the United Kingdom) remained an independent predictor of mastectomy use (OR, 1.44; 95% CI, 1.26–1.64; $P < 0.001$).

CONCLUSIONS. American women enrolled in the ATAC trial were more likely to undergo aggressive surgery compared with their counterparts from the United Kingdom. More generally, nationality was found to be an independent determinant of surgical choice in the current study. ***Cancer*** **2004;101:735–40.**

KEYWORDS: anastrozole, tamoxifen, adjuvant, breast carcinoma, mastectomy.

Mastectomy and wide local excision with subsequent radiotherapy are both appropriate options for the management of patients with early-stage breast carcinoma. The long-term survival rates associated with both strategies are equivalent, although conservation therapy is associated with an increased rate of local recurrence when

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margins are not clear or when radiotherapy has been omitted.[1–4] Selection of treatment type is influenced by tumor size (relative to the size of the breast), tumor location, the presence of multifocal or multicentric disease,[3] and patient preference. Breast conservation has become the recommended treatment option in both the United States[3,5] and the United Kingdom,[6] with conservation rates often being considered indicative of quality of care.[7]

In the early 1990s, with the emergence of aromatase inhibitors for the systemic treatment of advanced breast carcinoma, the Cancer Research UK Breast Cancer Trials Group proposed that such agents be tested for use in the adjuvant treatment of early-stage disease. This proposal led to the multinational 'Arimidex, Tamoxifen Alone or in Combination' (ATAC) trial, which compared the efficacy and safety profiles of anastrozole (Arimidex; AstraZeneca, Wilmington, DE), tamoxifen, and anastrozole plus tamoxifen in the adjuvant setting for postmenopausal women who had received primary treatment for early-stage breast carcinoma. Using uniform eligibility criteria, 9366 women were enrolled in a total of 21 countries, and results favoring the use of anastrozole have recently been published.[8,9]

The size of the ATAC trial and its international scope provide an opportunity to explore the way in which relative mastectomy rates vary from country to country. Because active research centers that enrolled patients in the trial might be expected to offer state-of-the-art treatment, it is likely that the surgical practices documented in the trial reflected best practices in each participating country. Thus, we were surprised to find marked differences in mastectomy rates from country to country. In the current study, we performed a multivariate analysis of the factors influencing mastectomy and breast conservation rates, with particular reference to the United States and the United Kingdom, to investigate why such differences existed.

MATERIALS AND METHODS

Postmenopausal women with operable early-stage breast carcinoma who were deemed to be candidates for adjuvant hormonal therapy were eligible for enrollment in the ATAC trial. The protocol was approved by local human subject protection committees in all participating countries, and written informed consent was obtained from all participants. Patients were randomized, after the completion of surgery ± radiotherapy ± chemotherapy, to receive anastrozole plus placebo, tamoxifen plus placebo, or anastrozole plus tamoxifen. The primary endpoints in this double-blind study were disease-free survival (defined as the time to locoregional or distant recurrence, development of contralateral breast carcinoma, or death due to any cause) and safety/toxicity. Nine thousand three hundred sixty-six women from a total of 21 countries were enrolled in the trial between August 1996 and March 2000.[8,9]

Information on primary breast surgery was available for 9365 patients, as was information regarding patient age, adjuvant chemotherapy use, and number of enrollees at the patient's treatment center. Data on patient ethnicity (99.3%), tumor size (99.3%), body weight (98.2%), and body mass index (95.6%) were also virtually complete. In addition, extensive data regarding lymph node status (94.8%), hormone receptor status (91.9%), and tumor grade (91.5%) were available.

Univariate and multivariate analyses were performed using the logistic regression procedure included in the STATA software package (Release 7.0; STATA Corp., College Station, TX). For each clinical factor, an odds ratio (OR) for receiving mastectomy, along with a 95% confidence interval (CI), was calculated. The multivariate analysis of national mastectomy rates (relative to mastectomy rates in the United Kingdom) included all available clinical variables. To correct for the high level of variability in national enrollment (which ranged from 14 patients to more than 3200 patients), shrinkage regression was performed.[10] Three countries in which mastectomy was almost universal were excluded from the analysis.

RESULTS

National levels of enrollment in the ATAC trial are summarized in Table 1, with mastectomy rates listed in parentheses. The overall mastectomy rate was 47.7% (breast conservation rate, 52.3%), with the same rate observed in each of the 3 treatment arms. National mastectomy rates varied from 20% to 97%. The United Kingdom had the largest number of enrollees (n = 3228; mastectomy rate, 42%), followed by the United States (n = 2222; mastectomy rate, 51%). The mastectomy OR for American patients relative to patients from the United Kingdom was 1.43 (95% CI, 1.28–1.60; $P < 0.001$). Thus, an analysis of factors correlated with surgical choice was performed to determine whether inequalities in terms of such factors could explain this difference in mastectomy use.

Table 2 summarizes the results of our univariate analysis of pathologic, clinical, and research center–related factors and their impact on surgical choice for study participants from all nations. The factors that were analyzed, which were selected from the pool of factors for which data were available for ATAC trial participants, had been identified in previous studies

TABLE 1
Enrollment in the ATAC Trial by Country

Country	Enrollment (% receiving mastectomy)
United Kingdom	3228 (42)
United States	2222 (51)
Italy	654 (50)
Canada	640 (47)
Spain	417 (60)
France	366 (33)
Sweden	291 (27)
Hungary	243 (49)
South Africa	201 (65)
Holland	195 (70)
Belgium	192 (36)
Australia	160 (36)
Germany	121 (38)
Poland	107 (97)
Czech Republic	84 (63)
Portugal	74 (91)
Turkey	53 (96)
Ireland	41 (56)
Slovakia	33 (48)
Argentina	30 (20)
New Zealand	14 (43)

ATAC: 'Arimidex, Tamoxifen Alone or in Combination.'

TABLE 2
Correlates of Mastectomy Use on Univariate Analysis

	Mastectomy (%)		
Factor	No	Yes	Mastectomy OR (95% CI)
Tumor size > 2 cm	32	68	3.81 (3.48–4.17)
No. of positive lymph nodes			
1–3	42	58	1.89 (1.72–2.09)
≥ 4	26	74	3.94 (3.37–4.62)
Unknown lymph node status	81	19	0.31 (0.25–0.40)
Tumor grade			
Unknown	41	59	2.47 (2.09–2.92)
Poorly differentiated	45	55	2.14 (1.89–2.42)
Moderately differentiated	53	47	1.52 (1.37–1.70)
Positive ER or PR status	54	46	0.60 (0.52–0.70)
Age (yrs)			
60–69 (vs. < 60)	54	46	1.19 (1.08–1.31)
≥ 70	41	59	2.05 (1.85–2.28)
Body weight ≥ 70 kg	54	46	0.87 (0.80–0.94)
BMI ≥ 26.75 kg/m^2	52	48	0.97 (0.90–1.06)
Adjuvant chemotherapy use	40	60	1.90 (1.72–2.10)
No. of enrollees from treatment center			
40–80	55	45	0.77 (0.65–0.91)
> 80	54	46	0.81 (0.68–0.96)

OR: odds ratio; CI: confidence interval; ER: estrogen receptor; PR: progesterone receptor; BMI: body mass index.

as being related to either mastectomy use or breast conservation in the treatment of early-stage breast carcinoma. In the ATAC trial, larger tumor size, positive lymph node status, and higher (or unknown) pathologic grade were correlated with mastectomy use. Adjuvant chemotherapy use and older age also were associated with the use of more aggressive surgery, whereas greater body weight (but not body mass index), positive hormone receptor status, and unknown lymph node status were correlated with breast conservation. Patients treated at study centers that had more than 40 enrollees also were more likely to receive breast-conserving therapy.

TABLE 3
Correlative Factor Distributions for Patients from the United Kingdom, Patients from the United States, and Patients from the Rest of the World

	% of patients		
Factor	United Kingdom	United States	Rest of world
Tumor size > 2 cm	33.4	29.5	41.0
No. of positive lymph nodes			
1–3	27.4	27.4	43.2
≥ 4	6.3	7.7	13.3
Unknown lymph node status	5.3	5.8	4.8
Tumor grade			
Poorly differentiated	24.0	21.9	24.2
Unknown	4.6	8.9	11.6
Positive ER or PR status	76.8	93.6	83.7
Age ≥ 70 yrs	24.3	35.7	24.6
Body weight ≥ 70 kg	44.2	53.2	46.5
Adjuvant chemotherapy use	6.8	32.5	26.9
> 40 enrollees from treatment center	71.1	51.9	35.6

ER: estrogen receptor; PR: progesterone receptor.

The distributions of these correlates for patients from the United States, patients from the United Kingdom, and patients from other countries are summarized in Table 3. Compared with participants from the United Kingdom, participants from the United States tended to be older, more likely to have received chemotherapy, and more likely to be enrolled at a smaller center, and it was possible that the observed disparity in mastectomy rates was attributable to these differences. Nonetheless, with respect to other factors, there was no difference between patients from the United Kingdom and patients from the United States, or else there was a difference favoring increased breast conservation among American patients.

On multivariate logistic analysis (Table 4), the number of enrollees at the patient's treatment center was not identified as an independent determinant of surgical choice; however, all other factors tested were found to have independent predictive value. Larger tumor size exhibited the strongest correlation with mastectomy use, and unknown lymph node status exhibited the strongest correlation with breast conservation. Factors found to have predictive significance

TABLE 4
Multivariate Analysis of Correlates of Mastectomy Use

Factor	MastectomyOR (95% CI)
Tumor size > 2 cm	3.03 (2.74–3.35)
No. of positive lymph nodes	
≥ 4	2.41 (2.00–2.90)
1–3	1.51 (1.34–1.69)
Unknown lymph node status	0.25 (0.19–0.32)
Age (yrs)	
≥ 70	2.22 (1.95–2.52)
60–69 (vs. < 60)	1.28 (1.15–1.43)
Tumor grade	
Unknown	1.62 (1.33–1.97)
Poorly differentiated	1.35 (1.16–1.56)
Moderately differentiated	1.21 (1.07–1.36)
Adjuvant chemotherapy use	1.32 (1.15–1.52)
Body weight ≥ 70 kg	0.80 (0.70–0.91)
Positive ER or PR status	0.77 (0.65–0.92)
No. of enrollees from treatment center	
41–80	0.86 (0.71–1.05)
> 80	0.93 (0.76–1.14)
Enrollment in United States (vs. United Kingdom)	1.44 (1.26–1.64)

OR: odds ratio; CI: confidence interval; ER: estrogen receptor; PR: progesterone receptor.

TABLE 5
Multivariate Analysis of Nationality as a Predictor of Mastectomy Use[a]

Country	Mastectomy OR[a] (95% CI)	OR after shrinkage correction[a]
Poland	32.67 (10.22–104.48)	—[b]
Turkey	29.87 (7.00–127.37)	—[b]
Portugal	12.58 (5.31–29.80)	—[b]
Czech Republic	2.11 (1.31–3.41)	1.87
South Africa	2.05 (1.47–2.86)	1.93
Holland	1.79 (1.26–2.55)	1.69
Spain	1.50 (1.18–1.92)	1.47
United States	1.44 (1.26–1.64)	1.43
Ireland	1.07 (0.52–2.20)	1.03
Canada	1.07 (0.88–1.30)	1.06
Italy	0.95 (0.78–1.17)	0.95
Hungary	0.92 (0.68–1.24)	0.92
Slovakia	0.87 (0.41–1.85)	0.89
Germany	0.71 (0.48–1.07)	0.73
Australia/New Zealand	0.64 (0.45–0.92)	0.67
Sweden	0.66 (0.49–0.89)	0.68
Belgium	0.58 (0.41–0.81)	0.60
France	0.45 (0.34–0.58)	0.46
Argentina	0.24 (0.09–0.62)	0.41

OR: odds ratio; CI: confidence interval.
[a] Relative to United Kingdom.
[b] Shrinkage correction was not applied, because mastectomy was performed in nearly all cases.

were included in a multivariate analysis of national mastectomy rates (which were referenced to the United Kingdom's mastectomy rate). In that analysis, the mastectomy OR for patients from the United States relative to patients from the United Kingdom increased marginally, to 1.44 (95% CI, 1.26–1.64; $P < 0.001$). Similar analyses were performed for all other participating nations; adjusted mastectomy ORs with 95% CIs and shrinkage regression corrections for enrollment size are presented in Table 5.

DISCUSSION

To our knowledge, the ATAC trial is the largest international prospective study of patients with early-stage breast carcinoma ever to be completed. The findings of the current analysis indicate that larger tumor size, positive lymph node status, higher tumor grade, and older age are correlated with mastectomy use, whereas positive hormone receptor status and greater body weight are correlated with breast conservation. These findings are consistent with those of numerous investigators who have reported that pathologic factors predicting poorer survival following treatment for early-stage breast carcinoma are correlated with mastectomy use and that favorable prognostic factors, in contrast, are associated with breast conservation.[11–16] Furthermore, the use of adjuvant chemotherapy, which generally is administered to women with a relatively poor prognosis, is also correlated with mastectomy use. Other than the possible cosmetic implications of breast-conserving treatment for a large tumor in a small breast, there is no objective explanation for these associations.

The presence of multicentric invasive carcinoma or ductal carcinoma in situ is predictive of increased in-breast recurrence and generally results in mastectomy use. Likewise, the mammographic observation of diffuse calcifications, which make postlumpectomy follow-up examination difficult, has been cited as a factor favoring mastectomy use.[3] Information regarding these two factors was unavailable for patients in the ATAC trial.

The high level of variability in mastectomy rates among participating nations was striking given the uniform entry criteria, although this variability may have been exaggerated by sampling errors resulting from low levels of enrollment in several nations (some of which had fewer than 100 enrollees). This potentially could affect the current analysis, because type of surgery was neither an entry criterion nor an outcome endpoint. Enrollment in the United Kingdom ($n = 3228$) and the United States ($n = 2222$), however, was substantial and allowed more reliable comparisons to be made. The most obvious finding yielded by these comparisons was that the mastectomy rate for American patients was greater than the corresponding rate

for patients from the United Kingdom, and enrollment in the United States remained an independent predictor of mastectomy use even after correction for the other prognostic factors described above. This finding does not appear to be attributable to an abnormally high mastectomy rate for American enrollees in the ATAC trial compared with other American patients, as the rate reported in the ATAC trial was the same as the overall rate in the United States at the start of the trial (according to the National Cancer Institute Surveillance, Epidemiology, and End Results [SEER] Program[17]). Nonetheless, the finding that the mastectomy rate was 9% greater among patients from the United States compared with patients from the United Kingdom must be viewed with consideration of the fact that 180,000 American women are diagnosed with breast carcinoma each year.[18]

Racial and Social Characteristics

What, then, is the reason for the observed differences in mastectomy and breast conservation rates between the United States and the United Kingdom? Unrecognized inequalities in the incidence of multicentric tumors or diffuse mammographic calcifications are a possibility, but there is no reason to expect such inequalities, which would reflect basic differences in tumor biology. Of the nonpathologic factors that can vary from country to country, only one, racial distribution, was known to exhibit such variation in the current trial, and it has been suggested that race may play a role in therapeutic decision-making.[13,19–21] Only 9 enrollees (0.3%) from the United Kingdom were of African or Caribbean origin, whereas 108 enrollees (4.9%) from the United States were African American. There was no difference, however, in mastectomy rates between Caucasian Americans and African Americans in the ATAC trial (51% vs. 56%; $P = 0.26$).

Other individual factors that have been reported to affect surgical choice in the United States include level of education[19,22] and type of insurance.[12,15,22] Information on level of education was not available for participants in the current trial. With regard to insurance coverage, some studies have suggested that in the United States, women with private insurance are more likely to undergo breast conservation than are women with governmental coverage (i.e., Medicare/Medicaid).[12,23] In contrast, the National Health Service covers almost all patients in the United Kingdom, and therefore, such a bias is not likely to be present there. The validity of the association between insurance type and surgical choice is unclear outside of the United States and inconsistent within it.[12]

Regional Variation

Geographic variation in breast conservation rates is evident in both the United Kingdom[7] and the United States.[11,12] It has been reported that women from the southern and midwestern United States are more likely to undergo mastectomy than are women from the northeastern and western United States.[11,12] In the ATAC trial, 76.6% of American participants were from the South or the Midwest, and 23.4% were from the Northeast or the West Coast. Nonetheless, the overall breast conservation rate for American patients in the ATAC trial (49%) was comparable to the breast conservation rate calculated using 1995 SEER data (48%).[17] A second geographic consideration is the distance to or availability of radiotherapy for a patient in a given location[16]; however, although the United States population is more widely dispersed than the population of the United Kingdom, the vast majority of United States enrollees were from urban or suburban locations and had access to facilities that offered such treatment.

Conclusions

Of the possible explanations that were discussed, it is likely that cultural factors account for the observed differences in surgical preference between the United States and the United Kingdom. Breast conservation is the preferred treatment approach for early-stage breast carcinoma in both the United States and the United Kingdom. Nonetheless, it is possible that although surgical oncologists in the United States acknowledge breast conservation, at least in theory, as an acceptable alternative to mastectomy, they present this treatment option in a biased fashion or simply do not recommend it.[15,17] This practice may be influenced by the age of the physician, with older practitioners being more likely to recommend mastectomy,[23] or by surgical experience, with practitioners who handle fewer breast carcinoma cases being less likely to recommend conservation.[24,25] In the United Kingdom, efforts have been made by the National Health Service to standardize care and to promote multidisciplinary team meetings and peer review visits with the goal of minimizing the effects of individual physicians' opinions or biases.[26]

Education and experience may be the keys to further appropriate use of conservation therapy. Given that breast carcinoma affects 180,000 women in the United States each year, it would not be unreasonable to consider initiating mass public and professional education programs aimed at increasing general awareness of breast carcinoma treatment as well as screening options. Drawing on the collective experi-

ence of many practitioners is a common practice at many academic centers. As advocated by the American College of Surgeons, presentation of newly diagnosed cases to a multidisciplinary tumor board is desirable and may increase breast conservation rates.

It is difficult to comment on national mastectomy rates other than those for the United Kingdom and the United States in the ATAC trial. It is likely that some of the observed differences reflect cultural variations or ingrained biases. What is clear, however, is that many of the correlative factors associated with mastectomy, whether pathologic or age related, should not be considered in the selection of treatment; unfortunately, such correlations were transnational. The ATAC trial has raised novel possibilities for the treatment of early-stage breast carcinoma, but it also reminds us that there are long-standing treatment-related issues that have yet to be resolved.

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