Effect of Breast-Conserving Therapy versus Radical Mastectomy on Prognosis for Young Women with Breast Carcinoma

Niels Kroman, M.D.[1–3]
Helle Holtveg, M.D.[4]
Jan Wohlfahrt, M.Sc.[1]
Maj-Britt Jensen, M.Sc.[2]
Henning T. Mouridsen, M.D.[2]
Mogens Blichert-Toft, M.D.[3]
Mads Melbye, M.D.[1,5]

[1] Department of Epidemiology Research, Danish Epidemiology Science Center, Statens Serum Institut, Copenhagen, Denmark.

[2] Danish Breast Cancer Cooperative Group, Rigshospitalet, Copenhagen, Denmark.

[3] Department of Breast and Endocrine Surgery, Rigshospitalet, Copenhagen, Denmark.

[4] Department of Breast Surgery, Hørsholm Sygehus, Hørsholm, Denmark.

[5] Department of Medical Epidemiology, Karolinska Institute, Stockholm, Sweden.

BACKGROUND. Among middle-aged and older women with early breast carcinoma, breast-conserving therapy (BCT) has been shown to have an effect on survival that is similar to that of modified radical mastectomy (RM). Nonetheless, it remains to be established whether BCT also is the optimal treatment option for early breast carcinoma in young women, because these women generally have more aggressive disease and a higher frequency of local recurrence compared with older women.

METHODS. We investigated a cohort of 9285 premenopausal women with primary breast carcinoma who were age < 50 years at diagnosis. These women were identified from a population-based Danish breast carcinoma database containing detailed information on patient and tumor characteristics, predetermined treatment regimens, and survival.

RESULTS. In total, 7165 patients (77.2%) were treated with RM, and 2120 patients (22.8%) were treated with BCT. We calculated the relative risk of death within the first 10 years after diagnosis according to surgical treatment and age, both before and after adjustment for known prognostic factors. No increased risk of death was observed among women who received BCT compared with women who underwent RM, regardless of age at diagnosis (< 35 years, 35–39 years, 40–44 years, or 45–49 years), despite the increased risk of local recurrence among young women. Restricting the analysis to women with small tumors (size < 2 cm) yielded similar results.

CONCLUSIONS. Despite having a higher rate of local recurrence, young women with breast carcinoma who receive BCT are similar to young women treated with RM in terms of survival. *Cancer* 2004;100:688–93. © 2003 American Cancer Society.

KEYWORDS: breast carcinoma, breast conserving therapy, radical mastectomy, surgical treatment, young age.

Breast-conserving therapy (BCT), in which surgery is restricted to removal of the clinically apparent tumor, generally is accepted as a treatment whose effectiveness is equal to that of modified radical mastectomy (RM) in early-stage breast carcinoma.[1,2] Nonetheless, this conclusion is based primarily on data from middle-aged or older women rather than very young women. Several findings suggest that very young women with early breast carcinoma may have unique features. Studies have demonstrated that young age is a risk factor for local recurrence among women who receive BCT.[3–6] Among women age < 35 years at diagnosis who receive BCT, 10-year local recurrence rates of ≥ 30% have been reported, compared with local recurrence rates of < 10% among middle-aged and older women.[7,8] There is debate over whether local recurrence in this respect is an independent negative prognostic factor or simply an indicator of aggressive

disease.[9–15] In cases of local recurrence within the residual breast after BCT, women generally are offered RM.[16] It is unknown whether such a 'two-stage' procedure is as effective as primary RM in terms of overall survival. Thus, it remains to be determined whether BCT, compared with RM, is a safe treatment option for young women with breast carcinoma, who experience local recurrence more frequently than do their older counterparts.

We previously found that young age at diagnosis is an independent negative prognostic factor for patients with primary breast carcinoma, but this negative effect was restricted to women who did not receive adjuvant cytotoxic treatment.[17] In the current study, we examined the effect (adjusted for expected mortality) of age on breast carcinoma survival according to the type of surgical treatment used. Analysis was performed using a large, comprehensive, population-based Danish breast carcinoma registry, which contained detailed information on clinical presentation, surgical treatment, predetermined adjuvant therapy, and follow-up status.

MATERIALS AND METHODS
Registration of Patients with Breast Carcinoma
In 1977, the Danish Breast Cancer Cooperative Group (DBCG) initiated nationwide prospective studies on the effects of breast carcinoma treatment. To date, four generations of treatment programs have been launched, including DBCG 77 (patient accrual from 1977 to 1982), DBCG 82 (patient accrual from 1982 to 1989), DBCG 89 (patient accrual from 1989 to 1998), and DBCG 99 (patient accrual since 1999). Because BCT was introduced in 1982, we restricted the current study to patients from the DBCG 82 and DBCG 89 programs. Furthermore, our primary objective was to evaluate the prognosis of young patients; therefore, we limited the study to premenopausal women (defined as women who had experienced menstruation within the preceding 12 months) age < 50 years at diagnosis.

In all programs, the primary surgical treatment for patients who were assigned to treatment protocols included either total mastectomy plus axillary dissection or lumpectomy plus axillary dissection and radiotherapy against residual breast. Standard adjuvant cytotoxic chemotherapy was used in all three programs (Table 1).[17,18] Patients were classified as either low risk or high risk according to histopathologic criteria. High-risk criteria during the investigation period included positive lymph nodes, tumor size > 5 cm, and (after 1989) histologic Grade II or III disease (according to the Bloom and Richardson grading system). Treatment allocation, which was independent of pri-

TABLE 1
Overview of Postoperative Adjuvant Treatment Administered between 1982 and 1998 to Premenopausal, High-Risk Patients with Breast Carcinoma in Denmark

Treatment protocol	Treatment randomization
DBCG 82	CMF or CMF + radiotherapy; or CMF + tamoxifen
DBCG 89	
Patients with ER-positive disease	CMF or ovariectomy
Patients with ER-negative disease	CMF; or CEF; or CMF + pamidronate; or CEF + pamidronate

DBCG: Danish Breast Cancer Cooperative Group; CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; ER: estrogen receptor; CEF: cyclophosphamide, epirubicin, and 5-fluorouracil.

mary surgical treatment, is described in detail elsewhere.[17,18] In the 1980s, BCT was used only in a limited number of major departments as part of a randomized trial, whereas in the 1990s, BCT became a standard procedure.

Patients with bilateral breast carcinoma or inflammatory carcinoma, distant metastases, or contraindication against the planned postoperative therapy, as well as patients who were not treated according to the surgical guidelines, were not assigned to a protocol. These patients were known as the *miscellaneous group*.

Primary clinical and histopathologic data and data regarding postoperative adjuvant therapy and status at follow-up, including information on site of recurrence, have been registered by the DBCG secretariat based on specific case report forms submitted by departments of surgery, pathology, and oncology within Denmark. Comparison of the DBCG registry with the Danish Cancer Registry, which is considered nearly complete with respect to the reporting of breast carcinoma diagnoses among residents in Denmark, revealed a concordance rate of > 95% within the age group investigated in the current study.[19,20]

Registration of Vital Status
The Danish Civil Registration System (CRS) was established in 1968, and since then, a unique identification number has been assigned to each Danish resident. Individual information is kept using this personal identification number in all national registries, allowing accurate linkage of information between registries. The CRS registry maintains updated files on vital status. A detailed description of the information included in this registry is provided elsewhere.[21] Patient records in the DBCG registry were linked with records in the CRS registry to obtain complete information on vital status.

Statistical Analysis

Women with breast carcinoma diagnosed between January 1, 1982, and December 31, 1998, were included and followed for survival data until 10 years after diagnosis or until December 31, 2000 (whichever occurred first). The study was restricted to premenopausal women age < 50 years at diagnosis who had received either BCT or RM.

The overall death rate was modeled as a sum of two terms. The first term represented the age-and-calendar-specific expected mortality as a known time-dependent offset; expected mortality data was obtained from life tables for the overall female population in Denmark stratified by 5-year age groups and 5-year calendar periods.[22] The second term in the model was the exponential function of a linear expression that included the following categoric variables: an interaction term between surgical treatment type (BCT or RM) and age at diagnosis (by 5-year group); tumor size (≤ 2 cm, > 2 cm and ≤ 5 cm, or > 5 cm); number of positive lymph nodes (0, 1-3, 4-9, or ≥ 10); histologic grade (I, II, III, or nonductal carcinoma); protocol allocation (allocated, not treated according to surgical guidelines, or not allocated for other reasons); and year of diagnosis (1982-1988 or 1989-1998). This model can be viewed as a log-linear representation of the observed death rate minus the expected death rate—i.e., a log-linear model of the excess death rate. The expected number of deaths due to breast carcinoma accounts for only a small proportion of all expected deaths.[22] Therefore, the adjusted relative risks were interpreted as relative risks of death due to breast carcinoma. We chose to perform Poisson regression analysis, rather than Cox regression analysis, to facilitate additive adjustment for expected mortality.

All tests in the Poisson regression analyses were performed as likelihood ratio tests using Epicure software (Hirosoft International, Seattle, WA).[23] Tests for differences in the age-specific effects of surgical treatment between low-risk patients and high-risk patients receiving cytotoxic treatment were performed by including a three-way interaction term among surgical treatment (BCT or RM), age at diagnosis, and risk group. Associations between selected characteristics at diagnosis were analyzed using chi-square tests.

RESULTS

By January 1, 1999, 9285 premenopausal women age < 50 years with primary breast carcinoma were registered by the DBCG. The study cohort accounted for a total of 60,246 person-years of follow-up: 13,116 person-years in the BCT group and 47,130 person-years in the RM group. The median follow-up period was 7.1

TABLE 2
Distribution, According to Surgical Treatment Type, Age at Diagnosis, Tumor Characteristics, and Risk-Group Allocation, of 9285 Premenopausal Women with Primary Breast Carcinoma Who Underwent Surgery in Denmark between 1982 and 1998

Characteristic	Surgical treatment (%)	
	Mastectomy	Breast-conserving treatment
All patients	7165 (77.2)	2120 (22.8)
Age at diagnosis (yrs)		
< 35	500 (69.5)	219 (30.5)
35–39	1126 (75.9)	357 (24.1)
40–44	2355 (78.3)	654 (21.7)
45–49	3184 (78.2)	890 (21.8)
Tumor size (cm)		
≤ 2	3662 (69.5)	1611 (30.5)
> 2 and ≤ 5	2817 (86.1)	455 (13.9)
> 5	589 (97.8)	13 (2.2)
No information	97 (70.3)	41 (29.7)
Positive lymph nodes		
0	3516 (72.2)	1351 (27.8)
1–3	2147 (78.9)	574 (21.1)
4–9	1025 (91.3)	98 (8.7)
≥ 10	356 (93.2)	26 (6.8)
No information	121 (63.0)	71 (37.0)
Histologic grade		
I	1676 (74.3)	580 (25.7)
II/III	3962 (78.9)	1061 (21.1)
ND	1527 (76.1)	479 (23.9)
Estrogen receptor status		
Positive	3054 (74.7)	1036 (25.3)
Negative	1610 (75.7)	516 (24.3)
No information	2501 (81.5)	568 (18.5)
Protocol allocation		
1982 protocol	3450 (87.2)	506 (12.8)
1989 protocol	3715 (69.7)	1614 (30.3)
Risk group		
Low	3054 (72.5)	1156 (27.5)
High	3192 (84.1)	603 (15.9)
Not treated according to guidelines[a]	568 (64.4)	314 (35.6)
Not allocated for other reasons[b]	351 (88.2)	47 (11.8)

ND: patients with nonductal carcinoma or without available histologic grading information.
[a] Patients who were not allocated because surgical treatment did not follow guidelines.
[b] Patients who were not allocated due to medical contraindications, bilateral or inflammatory breast carcinoma, or distant metastases.

years, and 32.6% of all patients were followed for 10 years. The distribution of patients according to surgical treatment type, age at diagnosis, tumor characteristics, and protocol allocation is provided in Table 2. A total of 7165 patients (77.2%) were treated with RM, compared with 2120 patients (21.8%) treated with BCT. Until 1989, BCT was offered only in randomized trials; consequently, the overall rate of BCT use was relatively low. Compared with women age > 35 years at diagnosis, women age < 35 years were more likely to have tumors > 2 cm in size (P = 0.007) and lymph

TABLE 3
Adjusted Estimates of Relative Risk of Death (with 95% Confidence Intervals) for Women Receiving Breast-Conserving Therapy Relative to Patients Undergoing Radical Mastectomy, by Age at Diagnosis, Tumor Size, and Protocol Allocation[a]

| | All patients (n = 9000)[b] | | | | Tumor size ≤ 2 cm (n = 5195) | | | | Protocol TM82 (n = 350)[c] | | | |
| | Mastectomy (n = 6971) | | BCT (n = 2029) | | Mastectomy (n = 3620) | | BCT (n = 1575) | | Mastectomy (n = 170) | | BCT (n = 180) | |
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Age at diagnosis (yrs)												
< 35	1 (ref.)	488	0.87 (0.64–1.19)	203	1 (ref.)	219	1.05 (0.71–1.54)	147	1 (ref.)	12	1.09 (0.35–3.40)	15
35–39	1 (ref.)	1094	1.02 (0.78–1.34)	343	1 (ref.)	598	0.77 (0.53–1.12)	254	1 (ref.)	31	1.37 (0.53–3.54)	36
40–44	1 (ref.)	2273	0.80 (0.62–1.04)	629	1 (ref.)	1197	0.72 (0.51–1.02)	496	1 (ref.)	50	2.07 (0.82–5.22)	66
45–49	1 (ref.)	3116	0.66 (0.50–0.88)[d]	854	1 (ref.)	1606	0.56 (0.38–0.83)	679	1 (ref.)	77	1.44 (0.60–3.49)	63

BCT: breast-conserving therapy; RR: relative risk; CI: confidence interval; ref.: referent group.

[a] Data from 9000 Danish women with primary breast carcinoma diagnosed between 1982 and 1988. Relative risk estimates are adjusted for tumor size, lymph node status, histologic grade, estrogen receptor status, year of treatment, and protocol allocation.

[b] Two hundred eighty-five patients were excluded because of missing information on tumor size or lymph node status.

[c] Patients randomized to breast-conserving therapy versus radical mastectomy.

[d] $P < 0.05$.

node–positive disease ($P = 0.002$). Younger patients also were more likely to receive BCT ($P < 0.001$). Overall, compared with women in the RM group, women in the BCT group were significantly more likely to have tumors < 2 cm in size ($P < 0.001$) and lymph node–negative disease ($P < 0.001$).

To evaluate the independent, age-specific effect of surgical treatment type on breast carcinoma–specific survival, we performed a multivariate analysis (with patients placed into 5-year age groups) that included surgical treatment, tumor size, axillary lymph node status, histologic grade, year of treatment, and protocol allocation (Table 3). Women who underwent RM were selected to be the reference group. All adjusted relative risk estimates for women receiving BCT were equal to or less than the reference values; this finding indicates that BCT was not associated with reduced survival. Among patients ages 45–49 years, the adjusted estimates of relative risk of death were significantly lower in the BCT group (relative risk, 0.66; 95% confidence interval [CI], 0.50–0.88) compared with the RM group. Restricting the analysis to small tumors (size < 2 cm) or to patients randomized to BCT versus RM (protocol TM82) did not change the results. Analysis of patients receiving BCT indicated a 5.2-fold greater incidence (15.4% vs. 3.0%) of local recurrence in the breast within 5 years of diagnosis among women age < 35 years compared with women ages 45–49 years.

To evaluate the effects of adjuvant cytotoxic therapy in relation to age at diagnosis and surgical treatment type, we allowed for an interaction between age at diagnosis and low-risk status (low-risk patients received no adjuvant systemic treatment; $n = 4210$)

TABLE 4
Adjusted Estimates of Relative Risk of Death (with 95% Confidence Intervals) for Patients Receiving Breast-Conserving Therapy Relative to Patients Undergoing Radical Mastectomy, by Age at Diagnosis and Adjuvant Treatment Use[a]

| | RR (95% CI) | | | |
| | Low-risk patients receiving no adjuvant treatment (n = 4210) | | High-risk patients receiving adjuvant cytotoxic treatment (n = 2935) | |
	Mastectomy (n = 3054)	BCT (n = 1156)	Mastectomy (n = 2486)	BCT (n = 449)
Age at diagnosis (yrs)				
< 35	1 (ref.)	1.31 (0.77–2.22)	1 (ref.)	0.73 (0.44–1.22)
35–39	1 (ref.)	1.18 (0.74–1.90)	1 (ref.)	0.69 (0.43–1.12)
40–44	1 (ref.)	0.94 (0.59–1.48)	1 (ref.)	0.81 (0.54–1.21)
45–49	1 (ref.)	0.63 (0.33–1.21)	1 (ref.)	0.64 (0.41–1.01)

RR: relative risk; CI: confidence interval; BCT: breast-conserving therapy; ref.: referent group.

[a] Data from 7145 Danish women with primary breast carcinoma diagnosed between 1982 and 1998. Relative risk estimates are adjusted for tumor size, lymph node status, histologic grade, estrogen receptor status, year of treatment, and protocol allocation.

versus high-risk status + adjuvant cytotoxic treatment ($n = 2935$) (Table 4). We observed a nonsignificant trend toward reduced survival with decreasing age among patients in the BCT group who did not receive adjuvant cytotoxic treatment ($P = 0.26$). No trend was observed among patients who received adjuvant cytotoxic treatment.

DISCUSSION
Among younger women, we found that long-term survival was similar for those who received BCT and

those who underwent RM. Previous studies evaluating these treatment regimens have reported similar results, but these studies included a very limited number of women age < 40 years and consequently are not as conclusive in their findings on younger women.[1,2] The current study included more than 9000 women age < 50 years who received either BCT or RM; 1483 of these women were diagnosed at ages 35–39 years, and 719 were diagnosed at age < 35 years.

Our finding is reassuring since young women with breast carcinoma generally have a particularly poor prognosis.[24–26] Specifically, young women who receive BCT are more likely to experience local recurrence, as also noted in the current study, in which younger patients who received BCT were more than five times as likely to experience local recurrence compared with their middle-aged counterparts. Although this finding could be explained in part by the failure to control for the increased frequency of advanced disease among younger patients,[27–29] we previously found young age to be an independent negative prognostic factor.[17]

Despite efforts to adjust for differences in prognostic factor profiles between the BCT and RM groups, residual confounding cannot be ruled out. As expected, women who received BCT had a significantly lower incidence of advanced disease as measured by tumor size and lymph node status. This finding may explain why superior survival was observed in the BCT group regardless of age at diagnosis. Nonetheless, the results remained unchanged when the analysis was restricted to women with tumors < 2 cm in size; in this group of women, the risk of selection bias is expected to be reduced, and therefore, the credibility of the result is enhanced. Furthermore, an updated analysis of patients randomized to either RM or BCT[30] revealed no trend toward decreased survival among the youngest patients.

Bias would be introduced if the surgeon changed the criteria for offering BCT based on patient age. Thus, residual confounding may explain the apparent survival advantage observed among women ages 45–49 years who received BCT, because the proportion of women receiving BCT was smallest in this age group. However, women age < 35 years at diagnosis were less likely to have small tumors and negative lymph node status, and the proportion of women who received BCT was largest in this age group. Thus, selection bias (and, consequently, residual confounding) should not be any more apparent in this group. Nonetheless, BCT was found to be as beneficial as RM among young patients, indicating that young patients have similar survival irrespective of treatment type.

We performed additional stratified analyses that focused on the adjusted relative risk of death according to surgical method among women who did or did not receive adjuvant therapy. Among women who did not receive adjuvant therapy, the risk of death was not significantly greater for patients who received BCT compared with patients who underwent RM in any of the age categories; however, overall, there was a nonsignificant trend toward poorer prognosis with decreasing age. In theory, if substantial residual confounding were present in the BCT group, then the observed trend toward reduced survival among younger patients who received BCT could hide true risks for very young patients who received BCT without adjuvant treatment. Among women who received BCT with adjuvant cytotoxic treatment, no association between age and survival was found. We previously observed decreased survival among young women who did not receive adjuvant cytotoxic therapy,[17] and the International Consensus Panel on the Treatment of Primary Breast Cancer recently changed its recommendation to include age < 35 years as a sufficient criterion for systemic chemotherapy, irrespective of disease stage.[31] Such treatment reduces the risk of distant metastases and disease recurrence and thus must be expected to decrease the likelihood of observing any trend toward diminished survival among very young women with BCT-treated early breast carcinoma in the future.

The use of BCT has steadily become more common over the last few decades. As might be expected, younger patients typically choose BCT more often than do older patients. Although the high frequency of local recurrence among younger patients represents a problem in itself, the current study did not find survival to be significantly different for young women who received BCT compared with those who underwent RM. Based on the results of the current study, however, adherence to the international recommendation of systemic chemotherapy in addition to surgery for very young women does appear to be justified.

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