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Breast Carcinoma in Women 35 Years of Age or Younger

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The relationship of the age at diagnosis and prognosis in breast carcinoma remains controversial. A widely held perception is that the disease has a particularly unfavorable prognosis in young women. To examine this question we have studied 166 women treated for primary operable breast carcinoma who were 35 years of age or younger at the time of diagnosis. Groups of patients treated consecutively in each of two time periods nearly a decade apart (1964–1970 and 1976–1979) have been studied. Differences between the patient groups in primary surgical treatment and postoperative adjuvant therapy were characterized in the 1970s by the increasing use of modified radical mastectomy and replacement of postoperative radiation therapy by systemic adjuvant chemotherapy. A trend to earlier stage of disease was found among patients treated in 1976 to 1979, but 5-year recurrence and survival rates were not significantly different from those of young women treated in the 1960s. Comparison of Stage II patients treated in 1964 to 1970 with postoperative radiotherapy with comparable women given adjuvant chemotherapy from 1976 to 1979 revealed no significant difference in disease-free survival in the first 3 years after surgery. It remains to be seen whether these changes in therapy will diminish the frequency of recurrences after 5 years, leading to an improvement in overall survival. When compared with historical controls from this and other institutions, the 5-year and 10-year survival rates of approximately 75% and 60%, respectively, found in this study of young women with primary operative disease were not appreciably different from those of women treated for breast cancer at a later age when the disease is more common.

CONTROVERSY SURROUNDS the relationship between age at diagnosis and prognosis in breast carcinoma.

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Particular interest has been focused on the extremes of age. One widely held perception is that the disease has an unfavorable prognosis in young women, especially those less than 35 years of age.[1-5] However, others[6-10] have reported that "cancer of the breast does not carry an unduly bad prognosis in the young.[11]" The present study was undertaken to assess clinical and pathological aspects of breast cancer in young women (≤35 years old at diagnosis) and their relationship to prognosis.

Materials and Methods

Patients Studied

Two groups of patients have been investigated, resulting in a total of 166 women available for analysis.

(1) Women first seen at Memorial Hospital between 1964 and 1970 have been included in a series of studies of prognostic factors in early stages of breast cancer.[12,13] For the present project, records of the Department of Pathology and Clinical Information Department were reviewed to identify every patient 35 years of age or younger whose initial diagnosis was made in that 8-year period, including those considered inoperable or referred for treatment of recurrence. A total of 158 women were found, including 101 treated for primary operable disease and 57 excluded from this category for reasons described below.

(2) The second group of patients was identified among women consecutively treated at Memorial Hospital from 1976 to 1979. During this interval, all patients with pri-

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mary operable disease were identified as part of a study of the pathology and epidemiology of breast cancer.[14,15] There were 65 patients 35 years of age or younger eligible for inclusion in this report.

Patient Records

For patients from the 1964–70 period, clinical data were abstracted from hospital charts. Histological sections were available in the hospital files for virtually all cases and these were reviewed. Follow-up information was obtained from hospital records, doctor's offices, death certificates, and from contact with patients or their families.

Virtually all patients treated from 1976–79 had been interviewed at the time of diagnosis and a concurrent review of pathology had been carried out. Information was obtained from these records and from an ongoing follow-up study. Whenever possible, recurrences have been confirmed by review of pathological material.

Data Analysis

Data were recorded on computerized forms and subjected to statistical analysis. Cross-classified categorical data were analyzed using the chi square or Fisher's exact test for contingency tables, as appropriate. Mean tumor sizes were compared using analysis of variance.

Comparisons of survival and time to recurrence distributions were made using the log rank test.[16] Cox's proportional hazard regression model[17] was used to analyze which factors alone or in combination were associated with survival. Survival distributions were estimated using the product limit method.[17] It should be pointed out that follow-up data derived from this study are presented in terms of follow-up category, based on each patient's status (*e.g.*, alive, dead of disease, dead of other cause, etc.) at the time the data were analyzed. This type of presentation was chosen due to the importance of emphasizing the actual status of patients. Therefore, while survival corresponding to the different variables was analyzed using methods of survival analysis, most of the data are presented in tabular form.

For all survival analyses, death due to breast cancer was the only end-point which was considered uncensored. All significance levels for survival analyses correspond to the log rank test, even where data are presented in tabular form.

Results

Excluded Patients

Fifty-seven patients with breast carcinoma diagnosed between 1964 and 1970 were excluded from the analysis. The age range in this group was from 23 to 35 years (mean 31 years).

The largest group consisted of women referred for management of metastatic or recurrent carcinoma after primary treatment elsewhere (30 women). All of these women died of metastatic carcinoma within 7 years of the date of recurrence with a median survival of 2.4 years.

Nine patients were referred to Memorial Hospital for adjuvant radiotherapy in the immediate postoperative period after having had a mastectomy elsewhere. Two were alive and free of disease after follow-up of 11 years each. Axillary lymph nodes were reportedly negative in one long-term survivor; nodal status was not known in the other case. Among the other seven, one was lost to follow-up and six died of metastatic breast carcinoma within 5 years (mean 3 years). Axillary lymph nodes were known to be positive in four of the six cases with a fatal outcome.

Five women were inoperable when first evaluated. One had inflammatory carcinoma and four patients had systemic metastases. All died of disease with the patient who had inflammatory carcinoma surviving the longest period, 6 years.

Five patients were referred for clinical follow-up after primary therapy elsewhere. All had had infiltrating carcinoma treated by mastectomy. Three of these women with unilateral carcinoma and negative nodes were alive without recurrence at last follow-up 11, 14, and 18 years after diagnosis. One of the other two patients had been treated for bilateral carcinoma with negative lymph nodes and was free of disease after 15 years. The fifth woman had metastatic carcinoma in axillary lymph nodes on one side and was free of metastases 12 years later.

Four women did not undergo mastectomy after biopsy proven carcinoma. Two of these patients with infiltrating duct carcinoma who had radiation therapy to the breast and axilla after surgery each died of metastatic carcinoma 3.5 years after diagnosis. No follow-up is available for the other two patients.

Finally, four women came to Memorial Hospital for brief consultations after treatment elsewhere. Most were from foreign countries and lack review of the pathology material, clinical documentation, or follow-up.

Comparison of Patient Groups Included in Study

Findings were initially tabulated separately for patients treated in 1964–70 and 1976–79. Variables for which there were notable or statistically significant differences are shown in Table 1. More widespread use of oral contraceptives and other hormones in the past decade was evident in the comparison between groups. Known trends in treatment account for recent increased use of modified radical mastectomy and of adjuvant chemotherapy as well as for decreased frequency of postoperative radiotherapy. The higher frequency of multicentricity observed

TABLE 1. *Notable and Significant Differences Between Patients Treated in 1964–70 and 1976–79*

Variable	1964–70 #	1964–70 %	1976–79 #	1976–79 %
Hormone usage*				
Yes	21	25	40	64
No	64	75	22	36
Type of mastectomy†				
Simple	2	2	0	0
Modified radical	0	0	24	37
Radical	83	83	34	52
Extended radical	16	16	7	11
Multicentricity‡				
None	75	76	27	42
In situ only	11	11	32	49
Invasion	13	13	6	9
Adjuvant therapy§				
None	69	68	45	69
Radiation	22	22	1	2
Chemotherapy	10	10	19	29
Oophorectomy	10	10	0	0

* $p < 0.001$ Hormone usage unknown in 18 patients.
† $p < 0.001$ Simple and modified radical were grouped together.
‡ $p < 0.001$ Multicentricity unknown in two patients.
§ $p < 0.001$.

in the late 1970s reflects more extensive sampling of mastectomy specimens. Also of note was a higher death rate from causes other than breast cancer among women treated in the 1960s which can probably be explained by their longer follow-up. Variables for which no significant or notable differences were observed included: age distribution, number of children, parity, family history of breast carcinoma, prognosis at 5 years, axillary nodal status, histologic type of carcinoma, histologic grade of duct carcinoma, frequency of lymphatic invasion, tumor contour, location of primary in breast, intensity of lymphocytic reaction, and frequency of bilaterality.

Because of the lack of significant differences between the two sets of patients, in all but the few variables noted above, data in this study are presented for the combined group of 166 women. Where appropriate, separate analyses of the patient sets were obtained to determine whether known differences may have influenced the results.

TABLE 2. *Summary of Survival*

Patient Group	Survival Status* Alive NED #	Alive NED %	AWD #	AWD %	DOD #	DOD %	UNK or DOC #	UNK or DOC %
1964–70 (101 Patients)	55	55	4	4	36	36	6†	6
1976–1979 (65 Patients)	43	66	7	11	14	22	1‡	2

* These abbreviations also appear in subsequent Tables: NED = No evidence of disease; AWD = Alive with disease; DOD = Died of disease; UNK = Unknown survival status; and DOC = Died other cause.
† Dead other cause, 4; follow-up status unknown, 2.
‡ Follow-up status unknown.

Survival Analysis

Median length of follow-up was calculated separately for the 1964–69 and 1976–79 patients in each survival category. The results, expressed in months, were as follows (see Table 2 for abbreviation definitions): 1964–69 NED, 146; AWD, 142; DOD, 40; and DOC, 71; and for 1976–79 NED, 48; AWD, 42; DOD, 30; and DOC, 33. Survival status for each group appears in Table 2.

The total survival and disease-free survival curves overlap closely in the first 5 years (Figs. 1A and 1B). The overall higher frequency of recurrence and of death due to disease among patients treated in the 1960s reflects additional recurrences and deaths which occurred after the first 5 years of follow-up. The median time to recurrence of those who recurred in the 1964–70 group was 21 (range 3–162) months and the mean interval from recurrence to death was 10 (range 1–97) months. For

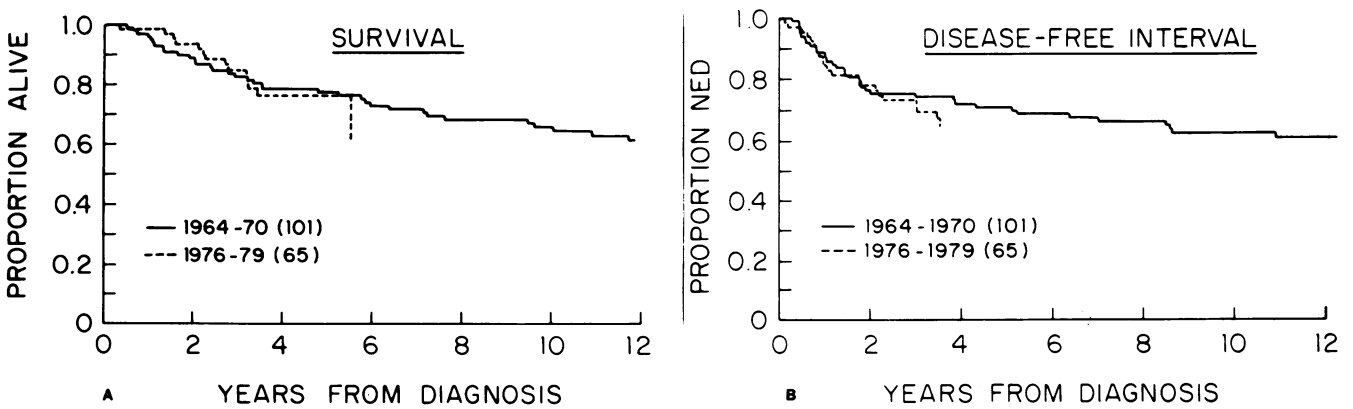

FIG. 1A. Breast cancer in young women. Comparison of time to death (A) and time to recurrence (B) for the two groups of patients studied. The curves are nearly identical for the first years of follow-up in each series.

TABLE 3. *Family History of Breast Carcinoma and Prognosis**

Relative Affected (Total)	Survival Status: Alive NED #	%	AWD #	%	DOD #	%	UNK or DOC #	%
None (119)	65	(54)	8	(7)	40	(34)	6	(6)
Mother only (7)	5	(71)	0		2	(29)	0	
Mother and other (5)	3	(60)	0		1	(20)	1	(20)
Sister (4)	3	(75)	1	(25)	0		0	
Aunt (13)	8	(62)	1	(8)	4	(31)	0	
Other (10)	7	(70)	1	(10)	2	(20)	0	

* Data available for 158 of 166 study cases.

women treated in the 1970s, mean intervals were 13 (15–42) months to recurrence and 16 (range 3–29) months to death.

Age

One hundred and twelve of the 166 patients (67%) were between 32 and 35 years of age at diagnosis with the single largest group (21%) being 35 years old. The youngest patient was 20 years old. Eight patients (5%) were between 20 and 25 years of age. 23 (14%) were 26 to 29 years old and 23 (14%) were 30 to 31 years of age. Within the age distribution of 20 to 35 years there was no significant association between age at diagnosis and prognosis.

Laterality of Primary Carcinoma

Carcinoma was more frequent in the left breast (97 cases, 58%) than in the right (69 cases, 42%). Prognosis and laterality were not significantly related.

Parity

The majority of women (121 or 73%) had had at least one child but only 13 of them (10% of parous patients) reported more than three children. Prognosis and parity were not significantly related.

TABLE 4. *Type of Primary Surgery and Prognosis*

Type of mastectomy	#	%	Survival Status: Alive NED #	%	AWD #	%	DOD #	%	UNK or DOC #	%
Simple	2	1	2	100	0		0		0	
Modified radical	24	15	17	71	3	13	3	13	1	4
Radical	117	71	65	56	6	5	40	34	6	5
Extended radical	23	14	14	61	2	9	7	30	0	
Total	166									

Most women (150 or 92%) were not pregnant when breast carcinoma was detected and did not become pregnant after treatment. Ten patients (6%) were pregnant at the time of diagnosis. Follow-up revealed recurrent disease in five of these patients, resulting in the death of four women. The other five women were alive and free of disease. Four additional women (2%) became pregnant after treatment of breast carcinoma. When last seen, three were alive and well while one patient died of recurrent carcinoma. Overall, no significant difference in prognosis was observed between patients pregnant at diagnosis or subsequently when compared with women who were nulliparous or parous prior to diagnosis.

Hormone Usage

Information was available for 147 (89%) patients. As noted above, use of estrogenic hormones and/or oral contraceptives was considerably more frequent among women treated in the late 1970s when compared to patients from the 1960s. Overall, 86 (59%) of those with recorded data had not used these medications. Oral contraceptive use prior to or at the time of diagnosis was reported by 49 women (33%) and estrogen use by 10 (7%) others. Two patients (1%) reported using both medications. No significant relationship between hormone usage and prognosis was found when the patients were studied as a combined group or when the two sets were analyzed separately.

Family History of Breast Carcinoma

Information was reported in 158 (95%) cases and this is summarized in Table 3. Twenty-five per cent had one or more affected relatives. Recurrences were less frequent (12/39 or 31%) among patients with a positive family history but analysis did not reveal a statistically significant difference in the frequency of recurrences (48/119 or 40%) or in survival when compared with patients not reported to have relatives with breast carcinoma.

Type of Primary Surgery

The relationship between type of operation and prognosis is shown in Table 4 for the entire series of 166 patients. Death due to disease was more frequent among women treated by radical and extended radical mastectomy, although the difference did not prove to be statistically significant.

Size of Primary Tumor

Data relating to tumor size are shown in Table 5. Mean tumor size and standard deviation were virtually identical when patients in the 1964–70 and 1976–79 groups were compared. Patients with axillary nodal metastases and those with recurrence tended to have larger tumors than

TABLE 5. *Primary Tumor Size**

Patient Group	No. Pts.	Mean Size (cm)	S.D. Size (cm)
Treatment Interval†			
1964–70	79	2.6	1.9
1976–79	49	2.5	1.8
Nodal Status‡			
Negative	77	1.9	1.3
Positive	50	3.6	2.2
Follow-up Status§			
No recurrence	79	2.0	1.5
Recurrence	49	3.6	2.1

S.D. = standard deviation ±.
* Thirty-nine patients with *in situ* carcinoma or no recorded size excluded; nodal status unknown in one case.
† $p = 0.78$.
‡ $p < 0.001$.
§ $p < 0.001$.

those with negative nodes and those free of disease at last follow-up.

Histologic Type of Primary Carcinoma

Histologic sections were available for review in 159 cases. Slides could not be retrieved for seven patients who had a biopsy elsewhere. The distribution of tumor types is shown in Table 6. Twelve women (8%) had noninvasive carcinoma. The largest group (120 patients or 76%) had infiltrating duct carcinoma while 17 patients (11%) had medullary carcinoma.

Secondary histologic features were noted in a number of examples of duct carcinoma. These included the following: apocrine cytology (six cases); colloid component (three cases); and squamous metaplasia (one case).

TABLE 6. *Histologic Type of Primary Carcinoma*

			Survival Status							
			Alive NED		AWD		DOD		UNK or DOC	
Histologic Type*	#	%	#	%	#	%	#	%	#	%
Infiltrating duct	120	75	62	52	10	8	45	38	3†	3
Medullary	17	11	11	65	1	6	2	12	3‡	18
Intraductal	10	6	10	100	0		0		0	
Infiltrating lobular	4	3	2	50	0		1	25	1§	25
Lobular *in situ*	2	1	2	100	0		0		0	
Atypical medullary	2	1	2	100	0		0		0	
Colloid	2	1	1	50	0		1	50	0	
Tubular	2	1	2	100	0		0		0	
Total	159									

* Slides not available for review in seven cases.
† Two died other cause; one status unknown.
‡ Two died other cause; one status unknown.
§ Status unknown.

TABLE 7. *Level of Axillary Lymph Node Metastases and Prognosis**

		Survival Status							
		Alive NED		AWD		DOD		UNK or DOC	
Lymph Node Status*	(Total)	#	%	#	%	#	%	#	%
Negative	(101)	71†	(71)	6	(6)	18	(18)	6‡	(6)
Highest Positive Level									
I	(26)	15	(58)	3	(12)	7	(27)	1§	(4)
II	(20)	6	(30)	2	(10)	12	(60)	0	
III	(17)	4	(24)	0		13	(77)	0	
Total	164	96	(59)	11	(7)	50	(30)	7	(4)

* $p < 0.001$.
† Lymph node status unknown for two patients treated by simple mastectomy.
‡ Four patients DOC. Two patients UNK.
§ One patient UNK.

Axillary Lymph Nodes

Table 7 and Figure 2 show the distribution of axillary lymph node status in relation to prognosis. There was a highly significant relationship between stage of disease as determined by pathological examination of axillary lymph nodes and the risk of recurrence ($p = 0.001$). There was a trend to more frequent recurrence as involvement extended from level I to level III. This was related to the number of affected lymph nodes since patients with disease limited to level I tended to have fewer than four lymph nodes involved when compared to those with disease at level III. As might be expected there was a significant correlation between the number of lymph nodes with metastases and prognosis (Table 8) and with the time to recurrence (Table 9).

Intramammary Lymphatic Tumor Emboli

Analysis of lymphatic tumor emboli was limited to patients with invasive carcinoma. Recurrences were sig-

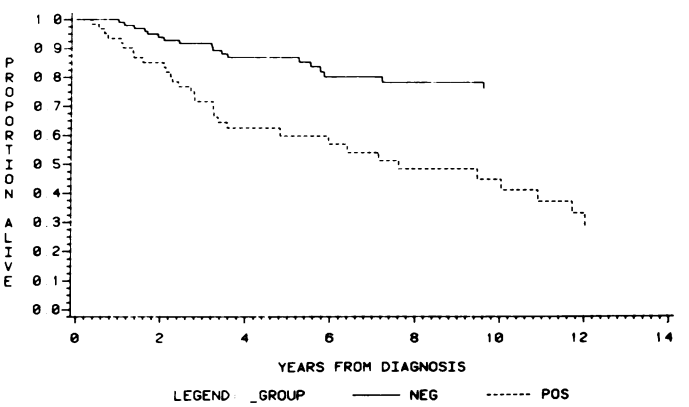

FIG. 2. Breast cancer in young women. Survival analysis for patients with and without axillary lymph node metastases. Patients from the two time intervals have been grouped together here since the curves were not significantly different in the first 4 years when analyzed separately.

TABLE 8. *Number of Axillary Lymph Node Metastases and Prognosis*

Number of Lymph Nodes with Metastases	Survival Status							
	NED		AWD		DOD		UNK or DOC	
	#	%	#	%	#	%	#	%
None	70	70	6	6	18	18	6	6
1-3	19	61	3	10	8	26	1	3
4 or more	9	26	2	6	24	64	0	0

$p < 0.001$.

nificantly (p = 0.01) more frequent when intralymphatic tumor emboli were present in the breast (59% recurrence) than when they were not found (32% recurrence). The majority (73%) of the patients with lymphatic emboli also had metastatic tumor in axillary lymph nodes, a factor which contributed appreciably to the high recurrence rate.

Intramammary lymphatic tumor emboli were found associated with 14 tumors that had not produced axillary metastases. There were three deaths (21%) due to disease in this group. Fourteen deaths (20%) due to breast carcinoma occurred among the 70 patients who had no lymphatic tumor emboli or nodal metastases. The combination of lymph mode metastases and lymphatic emboli resulted in more breast cancer fatalities (22/37 or 59%) than did nodal metastases in the absence of demonstrable emboli (10/26 or 38%).

Multicentricity

Slides of the mastectomy were available in 164 of the 166 cases. Multicentricity was defined as carcinoma in a quadrant other than the one which harbored the primary tumor. No multicentricity was found in 102 (62%) cases, 43 (26%) had one or more foci of *in situ* carcinoma, and 19 (12%) had multicentric invasive carcinoma.

Bilaterality

Throughout the period of the study, bilateral carcinoma was documented in 20 patients (12%). The carcinoma which occurred first in either period studied was regarded as ipsilateral and became the basis for analysis in this report.

Five women (3%) had been previously treated at another hospital for carcinoma of the opposite breast. Three previously treated carcinomas were infiltrating duct and there were single instances of infiltrating lobular and intraductal carcinoma.

Sixty-seven patients (40%) underwent a concurrent contralateral breast biopsy. Four (2%) proved to have carcinoma (infiltrating duct, three; intraductal, one) and the others were considered benign (38%).

Contralateral carcinoma is known to have developed subsequently in 11 of the 157 (7%) patients with a remaining contralateral breast.

The majority of bilateral carcinomas were histologically classified as infiltrating ductal. Individual instances of bilateral infiltrating lobular and bilateral intraductal carcinoma were noted. The following differences were found in tumor type between the breasts: intraductal-infiltrating ductal (three cases); infiltrating ductal-infiltrating lobular (2 cases); infiltrating duct-medullary (one case). Three patients with bilateral disease had unilateral axillary metastases. All other patients had no axillary metastases.

Five patients with bilateral carcinoma are known to have developed a recurrence, including three women who died of disease. Recurrence was considered due to ipsilateral breast cancer (as defined above) in four of these cases. In one instance, although laterality of the fatal carcinoma was indeterminate, death was nonetheless attributable to breast carcinoma.

TABLE 9. *Number of Axillary Lymph Node Metastases and Median Time to Recurrence**

Axillary Nodal Status	Median Time to Recurrence (mos.) Patient Group					
	1964-70		1976-79		Combined Patients	
	#	Time	#	Time	#	Time
Negative	15	18	10	26	25	21
Positive	26	22	11	12	37	16
1-3 Positive nodes	7	46	4	18	11	21
4 or more positive nodes	19	22	7	9	26	14

* Based only on patients with known recurrences.

Other Pathology Variables (Table 10)

(a) *Histologic differentiation.* Grading was available for 130 infiltrating duct carcinomas. The distribution of grade was as follows: low—5 cases (4%); intermediate—51 cases (39%); high—64 cases (49%). None of the five patients with a low grade tumor developed recurrent carcinoma. No significant difference in the frequency of recurrence was found between those with moderately differentiated (47% recurrence) and poorly (46% recurrence) differentiated duct carcinomas. Recurrences were less frequent (14%) among the 36 women who had tumors other than infiltrating duct carcinoma.

(b) *Lymphocytic infiltrate in carcinoma.* The majority of tumors had a sparse lymphocytic infiltrate. The presence of a marked lymphocytic reaction did not affect prognosis significantly, regardless of whether medullary carcinomas were included.

(c) *Tumor contour.* Patients with a tumor that had a stellate configuration had a higher recurrence rate (53%) than those whose tumors had a rounded contour (27%) or a mixed contour with stellate and circumscribed features (29%).

(d) *Location of tumor in breast.* The primary site was known to be in a lateral quadrant in 105 cases and medial or central in 44. The position of 17 other tumors was unknown or bridged medial and lateral halves of the breast. Recurrence occurred in 34% of the cases with a medial or central tumor and 25% with a lateral lesion.

Multivariate Survival Analysis

Two multivariate analyses were carried out, using Cox's regression model, to determine which factors alone or in combination were associated with survival. The first analysis was based on selected independant variables: grouped year of diagnosis (1964–70 or 1976–79), nodal status (negative or positive), and measured tumor size. Only nodal status and tumor size proved to be significantly predictive of survival tissue (each $p < 0.001$).

The second analysis, limited to patients with infiltrating duct carcinoma, allowed for the effects of histologic grade and lymphatic invasion, in addition to the factors previously noted. Under these circumstances as well, only nodal status and tumor size were significant predictors of recurrence (each $p < 0.001$).

Estrogen Receptor Protein (ERP)

Analysis of estrogen receptor protein in the primary tumor was carried out for 46 of the 65 patients treated from 1976 to 1979. Fourteen tumors (30%) were positive, with the remainder either negative (24 or 52%) or borderline (8 or 17%). The median total binding level was 6.0 fmoles (range: 2–89 fmoles). Only six tumors had more than 30 fmoles of ERP.

Recurrences were observed more frequently among the patients with an ERP negative tumor (12/24, 50%) than in the groups with ERP positive (4/14, 30%) or ERP borderline (1/8, 13%) lesions. Relatively few of the patients with an ERP positive tumor who had a recurrence had died of their disease (1/4, 25%) at last follow-up, while among those with an ERP negative tumor the majority with a recurrence were dead (9/12, 75%).

TABLE 10. *Other Pathology Variables and Prognosis*

Pathology Variable	Survival Status: Alive NED #	%	AWD #	%	DOD #	%	UNK DOC #	%	Totals #	%
Grade*										
Low	4	(80)	0		0		1	(20)	5	(4)
Intermediate	26	(51)	6	(12)	17	(33)	2	(4)	51	(43)
High	32	(50)	4	(6)	27	(42)	1	(2)	64	(53)
							Total		120	
Lymphocytic Reaction†										
Sparse	57	(54)	9	(9)	35	(34)	4	(4)	105	(66)
Marked	35	(65)	2	(4)	14	(26)	3	(6)	54	(34)
							Total		159	
Tumor contour‡										
Stellate	35	(44)	9	(11)	33	(42)	2	(3)	79	(51)
Circumscribed	34	(63)	1	(3)	9	(24)	4	(11)	48	(31)
Mixed margin	19	(68)	1	(4)	7	(25)	1	(4)	28	(18)
							Total		155	
Location§										
Lateral	64	(61)	7	(7)	29	(28)	5	(5)	105	(71)
Medial-central	25	(57)	4	(9)	13	(30)	2	(5)	44	(30)
							Total		149	

* p = N.S. excludes 46 cases other than duct type.
† p = N.S. slides not available in seven cases.
‡ p = N.S. excludes two cases not evaluable or *in situ.*
§ p = N.S. location unknown or medial and lateral in 17 cases.

Discussion

Patients who develop breast carcinoma at the extremes of age are preceived as having a different prognosis than those afflicted in the middle range of age (45–65 years). Aged women have been thought to enjoy a more favorable prognosis while "breast cancer in young women is widely believed to be biologically less favorable than that occurring in the elderly."[18] For example, Ewing reported that "before 30 years of age mammary cancer is extremely fatal, so that some surgeons prefer not to operate during this period."[1] Upon investigation, the existing documentation for this perceived relationship of age and prognosis in breast cancer is contradictory and not entirely convincing. For this reason, two studies were undertaken to explore clinicopathologic aspects of breast carcinoma at the extremes of age. Analysis of a large series of patients treated in our institution indicated that 5% were 35 years of age or less while 5% were at least 75 years old. A detailed study of the elderly women has already been reported.[19]

Prognosis of Breast Cancer in Young Women

It is noteworthy that the survival curves for the two groups of young women chosen for the present study were nearly identical for the first 5 years of follow-up. This probably reflects the close similarity observed for most important prognostic factors. Overall, there was little difference in the actual proportions of recurrence between the two patient groups (40% at 10 years for 1964–70 patients and 33% at 5 years for 1976–79 patients). Taking into consideration differences in follow-up time, one may expect an increase of 5–10% in the total recurrence rate of the 1976–79 group.

When compared with a number of historical controls from this institution, the 10-year survival of young women treated in 1964–70 does not appear to be especially poor. In an analysis of 262 patients of all ages with primary

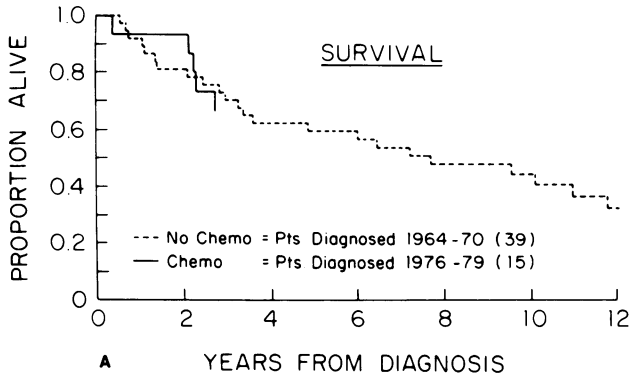

FIG. 3A. Breast cancer in young women. Survival analysis comparing patients with lymph node metastases from 1976–79 who received adjuvant chemotherapy and those from 1964–69 who did not have adjuvant chemotherapy.

operable breast cancer treated at Memorial Hospital, Urban[20] reported 60% 10-year survival with 56% disease-free. A comparable study of patients treated in 1960[21] yielded similar results at 10 years (56% disease-free and 60% total survival).

No appreciable differences from historical controls were apparent when young patients with Stage I disease were examined separately. In the present study, the 10-year survival for pathologic Stage I patients was 78%, a figure only slightly lower than the 82% result previously reported[21] for patients treated in the same time period not selected on the basis of age. For early Stage I ($T_1N_0M_0$) young patients, we found 80% to be disease-free after 10 years, a result not significantly different from the 84% result observed in an unselected series of women with the same stage of disease.[12]

As noted earlier, adjuvant chemotherapy was administered to almost all positive node patients treated in the 1976–79 period and to relatively few in the 1964–70 interval. On the other hand, a substantial proportion of the later group had regional postoperative therapy. The adjuvant chemotherapy consisted mainly of CMF, combined in some cases with levamisol. No significant differences

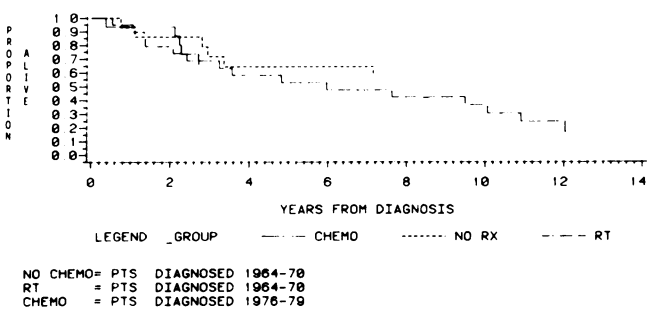

FIG. 3B. Breast cancer in young women. Survival analysis comparing three groups of patients stratified with respect to type of adjuvant therapy: patients diagnosed in 1964–70 who received adjuvant radiation therapy (RT); patients diagnosed in 1964–70 who received no adjuvant therapy (NO RX); patients diagnosed in 1976–79 who received adjuvant chemotherapy (CHEMO).

in disease-free survival were found in relation to type of adjuvant chemotherapy among women treated from 1976 to 1979. As shown in figure 3A, 5-year disease-free survival of positive node patients given adjuvant chemotherapy (1976–1979) was almost identical to that of patients with nodal metastases treated from 1964 to 1970 and not given adjuvant chemotherapy. Patients treated by oophorectomy alone in the 1964–70 period were excluded from this comparison. A more detailed analysis of adjuvant treatment was also undertaken comparing the following groups: adjuvant chemotherapy (15 cases); postoperative (adjuvant) radiation therapy only (21 cases); and no adjuvant treatment (14 cases). Survival up to 3 years was not significantly different among these groups (Fig. 3B), although somewhat lower among those treated with radiation.

Clinical Factors

Parity. Black et al.[27] observed a higher age adjusted survival among young multiparous patients, a finding not confirmed in our data. As might be expected among patients in this age group, a small number (6%) were pregnant at the time of diagnosis. This is a slightly lower proportion than has been reported in some other studies of young women with breast cancer. The data obtained from this series do not permit an independent assessment of the impact of concurrent pregnancy on prognosis. However, the finding that half of these women remained disease-free tends to support the conclusion of others[23,24] that breast carcinoma diagnosed during pregnancy is curable by conventional treatment.

The favorable outcome in three of four women who became pregnant after treatment of breast carcinoma is consistent with the conclusion of our earlier study which found that "no detrimental effect of subsequent pregnancy (on prognosis) could be demonstrated."[25]

Family history. Diagnosis at an early age has been associated with familial examples of breast carcinoma.[26] However, the frequency of positive family history in this series (25%) was consistent with a prior reported frequency of 31% from this institution[14] based on patients not selected on the basis of age. Maternal breast carcinoma was reported with the same frequency (8%) in the present study and in our prior analysis.[14]

The frequency of breast carcinoma among sisters in the present study was 3%. This was substantially lower than the 12% frequency among sisters in the earlier study,[14] but probably reflects the fact that the occurrence of breast cancer in a sister was significantly less frequent in patients who were premenopausal at diagnosis (8%) than it was among the sisters of postmenopausal women (15%).

Primary surgery. Recurrence and death due to disease were more frequent among women treated by radical or extended mastectomy although the differences were not

statistically significant. Several factors must be considered in an understanding of the relationship of primary surgery to prognosis. As noted in Table 1, none of the women treated in 1964–70 had a modified radical mastectomy; however, this operation was performed on 37% of patients operated on in the 1976–79 period. The shorter length of follow-up of those treated by the modified radical probably accounts in part for the higher proportion of patients alive with recurrence in this treatment group. In addition, the current tendency to select patients with earlier stages of disease for modified radical mastectomy has probably also contributed to the lower recurrence rate associated with this operation.

Pathologic Factors

Tumor type. The outstanding difference found in this series was a relatively high frequency of medullary carcinoma. An association of early age of diagnosis and medullary carcinoma had been noted previously.[15,27,28] When compared with other series of patients, not selected for age, the young patients appear to have a low frequency of *in situ* lobular carcinoma.

Axillary lymph nodes. Thirty-eight per cent of patients were found to have axillary metastases. This proportion is essentially the same as we observed in a consecutive series of patients of all ages treated between 1976 and 1979 at Memorial Hospital.[29] Others who have included patients with locally advanced and inoperable disease in their studies[29,30] have reported that axillary metastases were present in about two-thirds of young women. One author described positive nodes in 23% of 70 patients 35 years or younger treated by radical mastectomy.[8] In another series of 49 patients 30 years or less of age whose axillary lymph node status was documented, metastases were found in 17 or 35%.[31]

Tumor grade. Histologic grade was recorded for the 120 examples of infiltrating duct carcinoma. Well-differentiated tumors, other than tabular carcinoma, accounted for only 4% of this subgroup, a proportion lower than expected in a series of breast cancers not selected on the basis of age.[32] Slightly more than half of the tumors (53%) were classified as high grade. However, no difference in the frequency of recurrence was found when patients with high and intermediate grade were compared. Low grade tumors were noted to be infrequent in two other studies of breast cancer in young women.[8,27] Others[30] described a higher frequency of well-differentiated carcinomas but included "circumscribed" tumors, presumably medullary carcinomas, in this category.

Lymphocytic reaction. The lower recurrence rate observed for tumors with a marked lymphoid reaction reflects in part the inclusion of medullary carcinomas in this group. After exclusion of these 17 patients, the overall recurrence rate was 33% (3% AWD; 30% DOD).

Tumor contour. Tumors with a partly or completely rounded margin were associated with a lower recurrence rate than tumors with a stellate or infiltrating margin. After exclusion of medullary carcinomas, the recurrence rate among circumscribed tumors remained low (23%).

Bilaterality. Diagnosis of breast carcinoma at an early age has been associated with bilaterality.[33] In part, this probably reflects the relatively long period of risk for the contralateral breast among patients who survive the first carcinoma. Bilaterality in young women was reported in 14% of 29 patients,[34] and in four of 32 (13%) 5-year survivors.[32] A recent analysis of 880 women of all ages with invasive breast carcinoma revealed bilaterality due to previous or concurrent cancer in 14%.[35] Unfortunately, none of these data provide a full picture of the extent of bilaterality because extended follow-up is lacking. In the present series of 101 patients treated from 1964–70, with an average follow-up of nearly 10 years for survivors, subsequent carcinoma was documented in 8%. Including contralateral carcinomas treated concurrently (2%) and previously (3%), bilaterality has been found in 13%. Among 64 women treated in 1976–79, with follow-up averaging just under 5 years, there were two (3%) patients with previous, two (3%) with concurrent contralateral carcinoma, and three (5%) with subsequent disease.

Estrogen Receptors

The well-established relationship between age at diagnosis and estrogen receptors was confirmed in this study,[36] which revealed an exceptionally high proportion of estrogen receptor negative tumors. It is noteworthy that recurrences were more frequent among women with estrogen receptor negative tumors and that these lesions tended to be more rapidly fatal.

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