Dormancy of Mammary Carcinoma After Mastectomy

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Background: **The longest interval between primary treatment of breast cancer and tumor recurrence, i.e., the limit of breast cancer dormancy, defines the appropriate length of follow-up, the effectiveness of treatment, and curability (no excess mortality risk for patients relative to the general population) for the disease. To determine this limit, we analyzed long-term follow-up data from patients who underwent a radical mastectomy during a four-decade period at the University of Chicago Hospitals.** ***Methods:*** **For 1547 patients operated on during the period from 1945 through mid-1987, the number of recurrences and deaths occurring within each postoperative year were tabulated, and the hazard rate for first recurrence or death from breast cancer was estimated by use of the actuarial method. The excess mortality rate was calculated for successive 5-year intervals, beginning at the time of mastectomy, by use of U.S. life tables and matching on the basis of age, race, and sex.** ***Results:*** **Most recurrences occurred within the first 10 years after mastectomy. Recurrences were rare after 20 years; only one recurrence was reported among 192 patients followed for 26–45 years. Patients who had a recurrence within 5 years following mastectomy had shorter subsequent survival times than those whose recurrence appeared after 5 years (two-sided *P* = .0001). The excess death rate increased with pathologic stage of the primary tumor. Overall, there was evidence of excess mortality up to 20 years postsurgery (two-sided *P* = .009).** ***Conclusions:*** **The limit of breast cancer dormancy in this patient population appears to be between 20 and 25 years. After this time, recurrences were rare, and the mortality rate was no longer statistically significantly different from that of the general population. Patients surviving to this time without evidence of recurrence or contralateral breast cancer are probably cured. [J Natl Cancer Inst 1999;91:80–5]**

Dormancy of mammary carcinoma, the time after primary treatment during which cancer cells are undetected while likely to produce a clinical recurrence, can be measured by the time from first treatment to the recognition of recurrence. Early death from recurrence identifies the group of patients with the most virulent disease, including those with several factors that increase the risk of metastases, while later recurrences may reflect a different aspect of breast cancer *(1,2)*. Demicheli et al. *(3)*, in a retrospective study of more than 1100 patients entered into clinical trials between 1964 and 1980 at the Milan Cancer Institute in Italy, found an early peak in the hazard function for first treatment failure at 18 months after surgery and a second, smaller peak at 5 years, followed by a tapering off of the hazard rate that extended to 15 years. They concluded that the time distribution of recurrences was consistent with a tumor-dormancy hypothesis, which assumes that ''at the time of primary tumor removal micrometastatic foci may be in different biological steady states, most of which do not imply tumor growth.'' However, changes in the nature of the tumor or microenvironment could induce tumor growth at a later time.

The pathologic stage at which the patient is treated usually makes a larger difference in recurrence rate and survival than do variations in treatment. We have therefore stratified our analyses according to pathologic stage but have combined all types of radical mastectomy. (Given the retrospective nature of the data and the many potential confounding variables, we draw no conclusions regarding the benefits of any particular therapy.) The longest intervals between primary treatment and recurrence, the limits of dormancy, determine the length of follow-up required to establish curability. Better methods of detecting residual cancer cells and indicating their malignant potential may, in time, give more reliable signs than those already in use that an early or late recurrence is likely. Our data derive from clinical and radiologic recognition of recurrence, verified by microscopic pathology when indicated.

The limit of dormancy is related to but not identical with the statistical definition of curability, which addresses whether patients ever reach a point at which they no longer have an excess mortality risk relative to the general population *(4)*. This approach avoids the problems typically encountered in dating recurrences and, since estimates are based on all-cause mortality, also avoids the ambiguities and uncertainties involved in assigning causes of death *(5)*. This time point should occur several years after the majority of recurrences, depending upon the distribution of time to death from breast cancer following a recurrence. Recurrences after this point should be very rare, and the patient who survives to this time could reasonably be regarded as cured of her disease. Previous studies of curability in breast cancer have been performed by Brinkley and Haybittle *(6,7)*, Duncan and Kerr *(8)*, Easson and Russell *(9)*, and Pocock et al. *(4)*. These studies have generally found that there is significant excess mortality even 15–20 years after initial therapy, and thus long-term follow-up is required to establish curability. In this report, we analyze the recurrence and excess mortality rates of a large patient cohort undergoing mastectomy at the University of Chicago Hospitals over a period spanning four decades from 1945 through mid-1987. With the assistance of our tumor registry and through personal contact, we were able to maintain follow-up of 20 years or more in more than 350 patients and beyond 30 years in more than 100 patients.

Patients and Methods

All patients who were treated by any type of radical mastectomy (modified radical, radical, or extended radical mastectomy) for invasive mammary carcinoma between 1945, when the University of Chicago Tumor Registry was established, until July 1, 1987, when one of the authors (D. J. Ferguson) retired, are included. There were a total of 1578 such patients, 11 of whom lacked a pathologic diagnosis of invasive carcinoma and 20 of whom were at pathologic stage IV. The remaining 1547 patients, at pathologic stages I–III and at all ages, provide the basis of our analysis.

Demographic, medical history, and clinical/

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See ''Notes'' following ''References.''

pathologic data were abstracted from patient charts and maintained in a computerized database. Pathologic staging was according to the American Joint Commission 1988, TNM (tumor–node–metastasis) criteria *(10)*. Briefly, stage I includes patients with tumors 2 cm or less in diameter and who have no axillary lymph node involvement; stage IIA includes patients with tumors 2 cm or less in diameter and who have lymph node involvement or patients with tumors between 2 and 5 cm but who have no lymph node involvement; stage IIB consists of patients with tumors between 2 and 5 cm in diameter and who have lymph node involvement or patients with tumors larger than 5 cm in diameter and who have no node involvement; and stage III includes patients with tumors up to 5 cm in diameter and who have metastasis to axillary lymph nodes that are fixed to one another or other structures, patients with tumors larger than 5 cm and who have metastasis to either movable or fixed axillary lymph nodes, patients with tumors of any size that extend to the chest wall, or patients who have metastasis to internal mammary lymph nodes or the highest axillary lymph node. Patients with distant metastases are classified as stage IV and are not included. Follow-up information regarding tumor recurrences, life–death status, and cause of death was obtained with the assistance of the tumor registry as well as through personal contact with the patient or her local physician. Recurrence or its absence was diagnosed by query to the patient or physician, by biopsy, bone or liver scan, on x-ray, or at autopsy. When first recurrences were recorded in two loci, one was selected with the following priority: systemic, skeletal, internal mammary, supraclavicular, or local (i.e., within the field of the operation used for that patient). Follow-up for life–death status was complete (i.e., the patient was known to have died or was last contacted after January 1, 1996) for 1232 (80%) of the patients. The National Death Index *(11)* was searched to obtain additional information regarding the status of the patients lost to follow-up prior to 1996. Dates of death were thus determined for an additional 36 patients, bringing the completion rate to 82%. Among the 279 patients who were lost to follow-up, 70 were last known alive between 1.5 months and 10 years after their mastectomy, 108 between 10 and 20 years, 64 between 20 and 30 years, and 37 more than 30 years after surgery. Sixty-five of these patients were between 80 and 96 years old at the time of their last recorded examination.

About a quarter of the patients were given preventive radiation (6.2% of stage I, 19% of stage IIA, 32% of stage IIB, and 38% of stage III). Smaller numbers were given preventive chemotherapy (5.1%, 11%, 17%, and 28%, respectively) or endocrine treatment (4.8%, 18%, 23%, and 26%, respectively) according to the preferences of various oncologists. We include these women in all of the analyses. (A subgroup analysis of 832 women who underwent mastectomy without any other local or systemic therapy gave similar results.)

Summary tabulations of the number of disease recurrences by site and deaths by cause (when available) are provided for each postoperative year. We estimated the hazard rate for first recurrence or death from breast cancer using the actuarial estimator *(12)*. For this analysis, patients who died from other or unknown causes without a known recurrence were censored at the time of death. Overall survival curves, for which the end point was death from all causes, were calculated using the Kaplan–Meier *(13)* product-limit estimator. The logrank test *(14)* and the Cox proportional hazards regression model *(15)* were used to compare survival rates among different groups. Plots of the log cumulative hazard functions indicated that the proportional hazards model provided an adequate fit to the data. Observed mortality rates were then compared with the expected mortality rates for an age-, race-, and sex-matched normal population using life tables obtained from U.S. Vital Statistics Reports encompassing the years during the period from 1945 through 1988 *(16–25)*. Statistical evaluation of observed and expected death rates was performed as described by Pocock et al. *(4)*. Specifically, the ratio of the observed number of deaths from all causes to the expected number of deaths in the general population was calculated for successive 5-year intervals, beginning at the time of mastectomy. We followed this by determination of the excess death rate, defined as the difference between the observed and expected number of deaths divided by the patient-years at risk. Ninety-five percent confidence intervals (95% CIs) for the true excess death rates were derived by assuming that the observed number of deaths follows a Poisson distribution. CIs that do not include zero indicate a death rate in the patients with breast cancer that differs from that in the general population at the $P<.05$ level of significance. All P values are two-sided.

RESULTS

The mean age of the patients at the time of mastectomy was 53.9 years (range, 21–91 years). Sixty-nine percent of the women were white, 30% were black, and 1% were of other races. Three hundred twenty-one (21%) of the patients had stage I disease, 500 (32%) had stage IIA disease, 408 (26%) had stage IIB disease, and 318 (21%) had stage III disease. Eighty-seven percent of the cancers were of the infiltrating ductal variety only. There were nine postoperative deaths.

The number of first recurrences by site (local, skeletal, visceral, supraclavicular, internal mammary, or site unknown), censored observations, and deaths by cause (breast cancer, other causes, or cause unknown) that occurred within each postoperative year are listed in Table 1. It is

Table 1. Number of first recurrences by site, censorings,* and deaths by cause in each postoperative year†

Year	No. at risk	Recurrences						Cens	Deaths		
		Local	Skel	Visc	SC	IM	Unk		BrCa	Oth	Unk
0–1	1547	17	38	39	11	3	19	1	53	15	3
2	1475	15	23	44	8	4	10	0	113	7	1
3	1354	10	17	37	12	2	9	1	89	12	7
4	1245	8	18	22	4	3	4	5	86	5	2
5	1147	2	9	12	5	3	1	3	51	15	0
6	1078	1	10	8	3	0	2	9	43	12	3
7	1011	0	3	14	0	0	0	11	32	11	3
8	954	2	0	6	1	0	0	13	45	16	6
9	874	2	3	6	0	1	1	11	21	13	1
10	828	3	1	1	1	0	2	31	15	6	6
11	770	0	3	3	0	0	2	24	12	11	1
12	722	0	3	4	1	1	1	37	14	10	5
13	656	0	1	1	0	0	0	18	12	19	2
14	605	1	2	2	0	0	1	29	9	8	7
15	552	0	3	1	0	0	0	19	10	10	3
16	510	0	1	0	1	0	0	17	6	13	6
17	468	0	0	3	0	0	1	17	7	8	4
18	432	0	0	1	0	0	1	18	5	10	4
19	395	1	0	0	0	0	0	15	5	5	4
20	366	0	1	0	0	1	0	20	4	11	1
21	330	0	0	0	0	0	0	19	4	8	2
22	297	0	1	0	0	0	0	15	3	10	0
23	269	0	1	1	1	0	1	18	2	5	4
24	240	0	0	1	0	0	0	15	2	8	2
25	213	0	0	0	0	0	1	14	1	3	3
26	192	0	0	0	0	0	0	15	0	6	2
27	169	0	1	0	0	0	0	12	2	6	3
28	146	0	0	0	0	0	0	3	0	4	4
29	135	0	0	0	0	0	0	6	1	2	3
30	123	0	0	0	0	0	0	17	0	3	0
30–35	103	0	0	0	0	0	0	33	0	18	11
35–40	41	0	0	0	0	0	0	20	0	4	7
40–50	10	0	0	0	0	0	0	5	0	2	3
Total		62	139	206	48	18	56	491	647	296	113

*Alive as of last contact.

†Skel = skeletal; Visc = visceral; SC = supraclavicular; IM = internal mammary; Unk = unknown; Cens = censorings; BrCa = breast cancer; Oth = other.

apparent that recurrences are concentrated in the first years after mastectomy and that they are rare after 20 years. The last known recurrence was detected 27 years after mastectomy and the last recorded death from breast cancer was 29 years after surgery. The patient dying of breast cancer at 29 years had a recurrence at 22 years and had also developed a contralateral tumor. In the two patients dying of breast cancer at 27 years, one had a recurrence at 16 years (as well as a contralateral tumor) and the other a recurrence at 25 years. Most of the 647 patients who died of breast cancer had a previously detected recurrence; however, 146 patients died of breast cancer without a previously identified recurrence. A recurrence was reported in only five of the patients who died of other or unknown causes. Among the 296 other causes of death, 48 were nonbreast cancers, 57 were cardiovascular related, and 191 were from other causes without a known recurrence from breast cancer.

Fig. 1 shows the estimated hazard rate for first recurrence or death from breast cancer, stratified by pathologic stage. The hazard rate was estimated using yearly intervals for the first 10 years and 2-year intervals for years 10–30. Values are plotted at the mid point of each interval with linear interpolation between the points. For stage I cases, the rate of recurrence or death from breast cancer was fairly low, peaking at about 3.5% per year in the third year after mastectomy, but generally remaining between 1% and 1.5% per year thereafter. For stage IIA, the hazard rate rose to nearly 6% in years 3 and 4 and then declined to less than 2% per year from year 10 onward. The initial hazard rate for patients with stage IIB disease was noticeably higher, reaching 14% per year in the second year after mastectomy; however, by 10 years, the hazard rate was similar to that for patients with stage IIA disease. As would be expected, the hazard rate for stage III cases was relatively high—nearly 28% per year in each of the first 2 years after mastectomy. The rate declined sharply to approximately 4% per year at 10 years, but remained at this level throughout most of the second decade.

Recurrence was usually followed by death from cancer within 5 years, but this depended to some extent on the time at which the recurrence first appeared. Fig. 2, A, shows the duration of survival after recurrence in patients who experienced a recurrence within 2 years of their mastectomy, between 2 and 5 years, between 5 and 10 years, between 10 and 15 years, and after 15 years, respectively. Corresponding 5-year, postrecurrence survival rates are 6.9% (95% CI = 3.6–10.2), 11.6% (95% CI = 6.9–16.3), 32.4% (95% CI = 21.1–43.6), 19.4% (95% CI = 4.4–34.5), and 23.5% (95% CI = 1.3–45.8), respectively. Thus, patients who recurred within the first 5 years had shorter subsequent survival times than those who recurred later ($P = .0001$ for the overall effect of time of recurrence, adjusted for pathologic stage, patient age, site of recurrence, and year of surgery [likelihood ratio test]). Not surprisingly, the site of recurrence also had an important influence on subsequent survival ($P = .0001$ [likelihood ratio test]). The death rate was 60% and 98% higher in patients with skeletal and visceral recurrences, respectively, than in those with local recurrences. The rates were not statistically significantly different among those with supraclavicular, internal mammary, or local recurrences.

Contralateral breast cancer remains a hazard, apparently, throughout the patient's lifetime. It occurred in 125 (8.1%) of our patients (including 23 who had bilateral cancer at the time of first diagnosis), although only two patients encountered it more than 25 years after the first cancer. As noted by Demicheli et al. *(3)* and others, these occur at a relatively low, constant rate and as such should be (and were) considered second primary cancers. Second cancers other than those discovered simultaneously may make measurement of dormancy impossible in such cases. Twelve contralateral preventive mastectomies were performed in others of our patients during the period from 1945 through mid-1987; four specimens obtained in this manner contained carcinoma *in situ.*

Overall survival curves for patients at pathologic stages I, IIA, IIB, and III are shown in Fig. 2, B. Differences in survival across the different pathologic stages were highly significant ($P = .0001$ [logrank test]). Patients at pathologic stage I had 10-, 20-, and 30-year survival rates of 78.9% (95% CI = 74.4–83.4), 52.8% (95% CI = 46.6–59.0), and 34.9% (95% CI = 27.9–41.8), respectively. At pathologic stage IIA, these were 63.6% (95% CI = 59.4–67.9), 42.4% (95% CI = 37.6–47.2), and 26.7% (95% CI = 21.3–32.1), respectively; at stage IIB, 47.6% (95% CI = 42.7–52.5), 29.9% (95% CI = 25.0–34.7), and 18.5% (95% CI = 13.8–23.3), respectively; and at stage III, 25.4% (95% CI = 20.6–30.3),

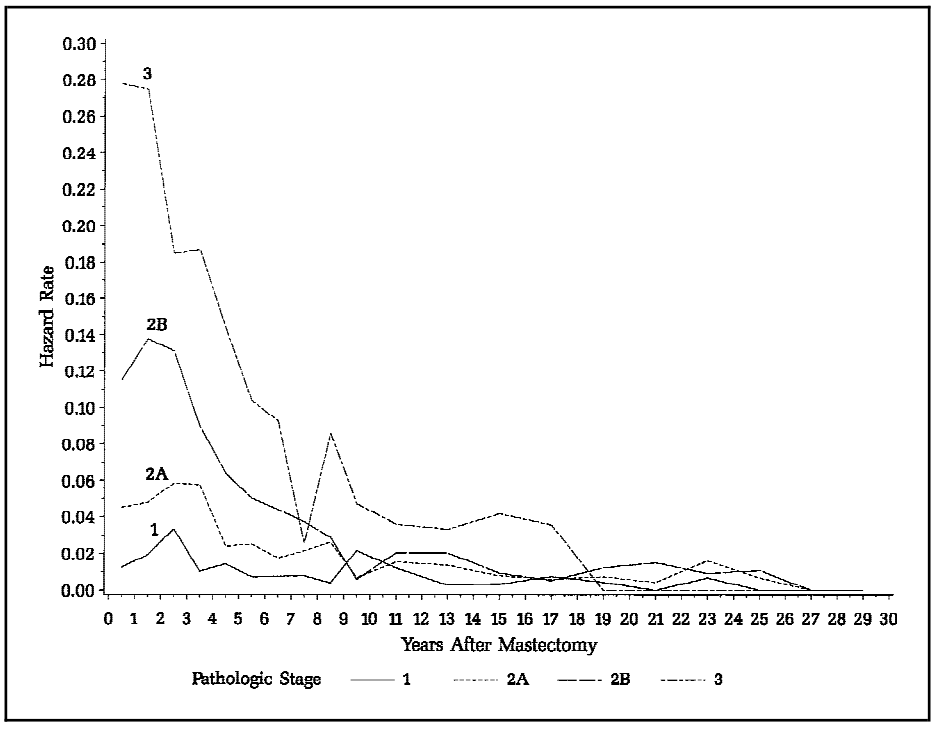

Fig. 1. Hazard rate for time to first recurrence or death from breast cancer among 1547 patients who underwent radical mastectomy, stratified by pathologic stage. Numbers at risk at 0, 5, 10, 15, 20, and 25 years were as follows: stage I—321, 275, 220, 152, 101, and 50; stage IIA—500, 367, 277, 189, 122, and 74; stage IIB—408, 226, 160, 105, 74, and 48; and stage III—318, 101, 61, 34, 21, and 13.

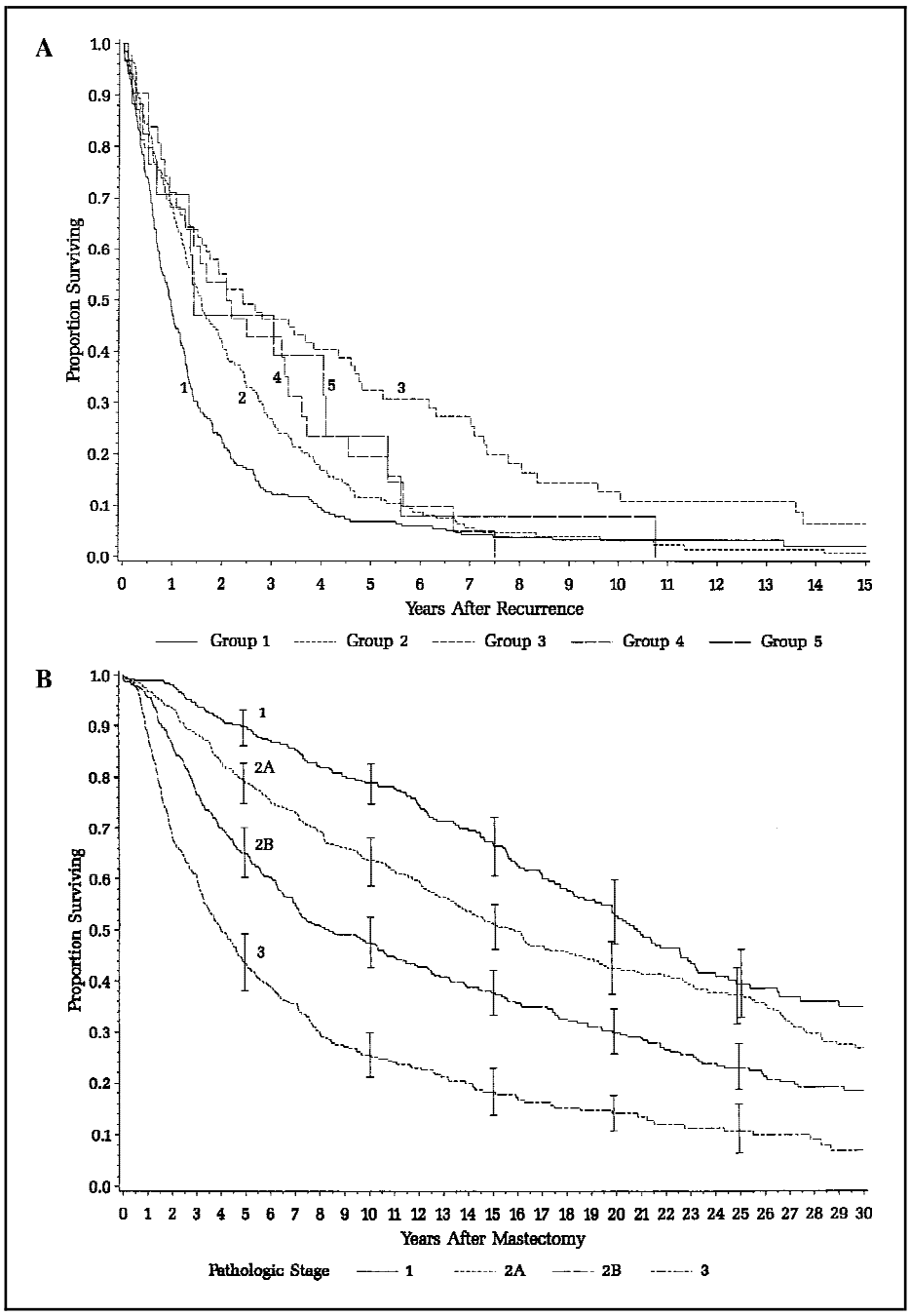

Fig. 2. A) Distribution of survival times following recurrences in 529 patients, stratified by time of recurrence. Group 1—less than or equal to 2 years; group 2—greater than 2–5 years; group 3— greater than 5–10 years; group 4—greater than 10–15 years; group 5—greater than 15 years. Numbers at risk at 0, 2, 5, and 10 years were as follows: group 1—232, 52, 16, and 6; group 2—179, 74, 20, and 4; group 3—69, 38, 19, and 7; group 4—31, 15, 5, and 0; and group 5—18, 6, 3, and 1. **B**) Overall survival rates by pathologic stage. For numbers at risk, *see* Table 2. Vertical bars = 95% confidence intervals.

14.2% (95% CI = 9.8–18.5), and 7.0% (95% CI = 3.0–11.1), respectively. There was no evidence of any racial differences in survival (P = .944, adjusting for pathologic stage and year of surgery [likelihood ratio test]). *See* Heimann et al. *(26)* for a more detailed analysis of this issue.

Table 2, A–D, compare the observed mortality rates in successive 5-year intervals with the expected mortality rates obtained from the U.S. life tables matched for age, race, sex (female), and year of surgery (within 5 years) for the four-stage strata. Of interest, for patients with stage I breast cancer, the observed death rate is not statistically significantly greater than the expected rate in any 5-year interval, including the initial period following mastectomy. This is in accord with the relatively low recurrence/breast cancer death rates seen in Fig. 1 and suggests that radical mastectomy is a curative surgery for most stage I cases. However, the observed number of deaths exceeds the expected number in all 5-year intervals except the last, and thus there may exist a small excess death rate in these early stage patients that is detectable only with a much larger sample size.

For patients with pathologic stage IIA cancer, there is statistically significant excess mortality out to 15 years, amounting to approximately 2%–3% per year. The excess death rate is also high in the 25–30-year interval but does not reach statistical significance. For stage IIB cases, the excess mortality is also statistically significant out to 15 years, exceeding 7% per year in the first 5 years, and then declining to a little more than 2% per year between 10 and 15 years. The excess death rate remains at about 2% per year during the 15–20- and 20–25-year intervals, although these are not statistically significant.

Finally, for patients with stage III cancer, the excess death rate is very high—15% per year in the first 5 years after surgery and more than 9% per year in years 5–10, before falling to a little less than 4% per year between years 10 and 15. After 15 years, the difference is no longer statistically significant, but again the numbers are small and consequently the CIs are fairly broad.

Based on these analyses, there is strong evidence for excess mortality throughout the first 15 years after mastectomy in patients with stage II and III cancers. Furthermore, examination of excess mortality on a yearly basis after year 15 reveals differences that are fairly consistently positive over the ensuing 5–10 years in all pathologic stage groups. Although not statistically significant, this suggests that excess mortality may continue to exist beyond year 15. Pathologic stage had a major effect on the death rate during the first 15 years, but after 15 years, the observed death rates were actually fairly similar—between about 3% and 7% per year—across the different pathologic stages, in agreement with the findings reported in Pocock et al. *(4)*. Pooling the data after 15 years over the four pathologic stage groupings, we detected a statistically significant excess death rate of 1.2% per year (95% CI = 0.28–2.12 per year; P = .009) in the 15–20-year interval and, again, examination of the yearly data revealed nonstatistically

Table 2. Observed and expected death rates by 5-year intervals*

Years	No. at risk†	Obs	Exp	Ratio	Pt-Yrs	Obs death rate‡	Exp death rate‡	Excess death rate (95% CI)‡
				A) Pathologic stage I§				
0–5	321	32	26.3	1.22	1526	2.10	1.72	0.38 (−0.37 to 1.12)
5–10	284	34	31.0	1.10	1282	2.65	2.41	0.24 (−0.67 to 1.15)
10–15	228	31	28.7	1.08	963	3.22	2.98	0.24 (−0.92 to 1.39)
15–20	159	31	24.8	1.25	652	4.75	3.79	0.94 (−0.75 to 2.67)
20–25	104	23	17.6	1.30	385	5.98	4.59	1.39 (−1.10 to 3.89)
25–30	50	5	10.4	0.48	202	2.47	5.15	−2.68 (−4.89 to −0.47)
				B) Pathologic stage IIA§				
0–5	500	106	33.1	3.21	2256	4.70	1.47	3.23 (2.32 to 4.15)
5–10	391	73	31.4	2.32	1714	4.26	1.83	2.43 (1.43 to 3.42)
10–15	291	52	28.7	1.81	1211	4.29	2.36	1.93 (0.74 to 3.12)
15–20	197	30	23.6	1.27	797	3.76	2.95	0.81 (−0.57 to 2.18)
20–25	125	13	18.3	0.71	502	2.59	3.64	−1.05 (−2.49 to 0.38)
25–30	78	19	12.3	1.55	279	6.81	4.41	2.40 (−0.72 to 5.53)
				C) Pathologic stage IIB§				
0–5	408	143	23.0	6.21	1681	8.51	1.37	7.14 (5.72 to 8.56)
5–10	265	69	20.4	3.38	1067	6.47	1.91	4.56 (3.00 to 6.11)
10–15	178	34	17.4	1.95	712	4.77	2.44	2.33 (0.69 to 3.96)
15–20	114	22	13.2	1.67	471	4.67	2.80	1.87 (−0.12 to 3.86)
20–25	77	16	9.9	1.62	294	5.44	3.36	2.08 (−0.64 to 4.80)
25–30	49	8	7.5	1.07	183	4.38	4.11	0.27 (−2.82 to 3.37)
				D) Pathologic stage III§				
0–5	318	179	14.3	12.52	1078	16.60	1.33	15.27 (12.79 to 17.76)
5–10	138	56	8.8	6.38	508	11.03	1.73	9.30 (6.35 to 12.25)
10–15	73	18	7.0	2.59	279	6.46	2.50	3.96 (0.92 to 7.00)
15–20	40	8	4.6	1.75	152	5.27	3.01	2.26 (−1.47 to 5.99)
20–25	24	5	3.0	1.65	90	5.56	3.38	2.18 (−2.79 to 7.15)
25–30	15	4	1.7	2.31	52	7.65	3.31	4.34 (−3.31 to 11.99)

*Obs = observed; Exp = expected; Pt-Yrs = patient-years; CI = confidence interval.
†At start of interval.
‡Percent per year.
§Pathologic stage of the primary tumor.

significant, but continuing, excess mortality in each of years 21, 22, 23, and 24.

Discussion

Pocock et al. *(4)* also found excess death rates extending 15–20 years after treatment of breast cancer. Friedl and Herfarth *(27)* presented survival data and conclusions similar to ours, although they lacked data on recurrences. We did not see evidence for a second peak in the hazard curve as reported by Demicheli et al. *(3)*. (The increase between 7.5 and 8.5 years in Fig. 1 for the stage III cases is not statistically significant.) The evidence for tumor dormancy in our data arises not from a second peak in the hazard curve but rather in the elevation of the mortality rates out to 20 years and the detection of new recurrences even after this time. It is also possible that some late recurrences were missed due to incomplete follow-up.

Metastatic cells may be present after surgery but remain dormant for several reasons. They may be unable to invade blood or lymph node vessels; they may be unable to induce angiogenesis and/or revascularization *(28,29)* with the balance between angiogenic and antiangiogenic stimuli favoring antiangiogenesis; apoptosis predominates; cell cycle regulatory proteins function normally so that there is no loss of cell cycle control *(30);* or a balance between growth-inducing and growth-inhibiting factors in the tumor microenvironment favors inhibition. Changes in any of these factors could result in tumor growth at a later time.

When mastectomy patients die without any evidence of recurrence, apparently of other causes, a search for persisting cancer is not usually made, and in any case it is difficult to rule out. Indeed, one popular theory has it that all breast cancers contain dormant as well as active cancer cells, although the dormant cells may never become overt *(31)*. Evidence qualifying this idea is provided by follow-up beyond 25 years, after which time clinically apparent recurrences, being nearly absent in our study and that by Friedl and Herfarth are probably very rare. There is little excess mortality in the pathologic stage I cases even in the first years after surgery, which suggests that local treatment eliminated the tumor and that no cells had metastasized. We also did not find a significant excess rate of deaths after 20 years based on nearly 2000 cumulative years of follow-up. A limitation of our data, however, is the lack of complete follow-up in 18% of the cases. If individuals lost to follow-up were at increased risk of death, then our estimates of excess risk would be too low. On the basis of our CIs, we cannot rule out the possibility that a small excess mortality exists even into the third decade after mastectomy. Nonetheless, at least some of the patients must have had no persisting disease or disease that remained localized. Interestingly, the high hazard rate for recurrence or death from breast cancer in patients with stage IIB and stage III disease drops substantially after the first several years (Fig. 1), but for the latter group remains relatively high throughout most of the second decade.

Recurrences that appear after radical mastectomy—except if they are small, local lesions—are usually followed by death from cancer within a few years. Only 49 (9.3%) of 529 recurrences were first observed more than 10 years after mastectomy, as shown in Table 1. No death from breast cancer has been observed in our series after 25 years, except among patients who had a recurrence or a contralateral cancer within that 25-year period.

The quality and the extent of surgical treatment need to be taken into account when evaluating recurrence and survival of patients with mammary cancer *(32)*. A diagnosis of recurrence is difficult to establish after partial mastectomy because the procedure may miss part of a multicentric cancer. We did not attempt analysis of dormancy in these patients.

In conclusion, recurrence of mammary carcinoma after various types of radical mastectomy occurred only rarely after 20 years, and the mortality rate after 20 years was not significantly different from that of the nondiseased population. The limit of dormancy appears to be between 20 and 25 years, and the patient surviving that long without recurrence or contralateral cancer is probably cured. Although the period of dormancy may be quite long, patients with very early stage disease have an excellent prognosis, and most recurrences and ex-

cess deaths in patients with stage II–III tumors occur within the first 10 years after mastectomy.

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