Jpn. J. Cancer Res. 81, 454–462, May 1990

Tumor Growth Rate and Prognosis of Breast Cancer Mainly Detected by Mass Screening

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To investigate the relationship between the tumor growth rate of the primary breast cancer and its prognosis, records for 122 breast cancer patients in 9 hospitals in Japan were retrospectively reviewed. These records contained at least two measurements of the same tumor mass in the breast. So the growth rate was estimated from these measurements taken at different points in time. The doubling time of the breast tumors showed an approximately log-normal distribution. The geometric mean of doubling times for all cases was 174 days. The solid-tubular histologic type of carcinoma had the shortest geometric mean of doubling time (126 days), the scirrhous carcinoma had the second shortest one (205 days), and the papillotubular carcinoma had the longest one (252 days). The patients with shorter doubling time of tumor tended to have a poorer prognosis. The Cox multiple regression analysis showed that the tumor growth rate was related significantly with survival, after adjusting for other covariates such as clinical stage, lymph node metastasis, age of patient, histological type, and year of treatment.

Key words: Breast cancer — Natural history — Tumor growth rate — Prognosis — Doubling time

Collins *et al.*[1] introduced the concept that the rate of doubling of a tumor mass reflects the rate of cell division and that volume-doubling time is constant, resulting in exponential growth. The gross doubling time of a tumor is influenced by (1) the duration of the mitotic cell cycle, (2) the fraction of proliferating cells vs. dormant cells, and (3) the rate of cell loss. The effective tumor growth is the net result of cell proliferation and cell loss. Although these effects influence tumor growth in clinically measurable tumors, constant exponential tumor growth, as reflected in a fixed tumor-doubling time, seems to be a basic pattern of neoplastic proliferation of a tumor throughout its clinical course.[2]

It is generally considered that a more rapidly growing breast tumor is more malignant, but little is known about the relationship between the growth rate of breast tumor and survival.

Kusama *et al.*[3] reported that the gross rates of growth of the primary tumor in the breast and various metastatic tumors determined by Collins' method correlate with the duration of survival after radical mastectomy among 199 American female breast cancer patients, diagnosed between 1940 and 1960, and that patients with more rapidly growing tumors tended to have the poorer prognosis.

We report here the relationship between the growth rate of primary breast tumor and its prognosis among Japanese female breast cancer patients.

SUBJECTS AND METHODS

The Research Group on the Study of Mass Screening for Breast Cancer, organized in 1987 with a Grant-in-Aid from the Ministry of Health and Welfare of Japan, conducted a collaborative study to investigate the relationship between the tumor growth rate of the primary breast cancer and its prognosis. The records of 122 female breast cancer patients treated between 1978 and 1988 in 9 hospitals in Japan were retrospectively reviewed. These records contained at least two measurements of the same tumor mass in the breast at different points in time, using direct measurement by palpation (63 cases at the latter point in time), findings of

mammography (33 cases) or ultrasonography (7 cases), or measurement of resected samples (19 cases). One hundred and two of the 122 tumors (84%), were measured at the latter point in time by the same method as the previous time. The precision of the measurement might be different from method to method. Overall, direct measurement by palpation, the accuracy of which is probably the worst, was the determinant of total accuracy.

The time interval between two measurements of the same tumor mass ranged from 2 weeks to 91 months; it was within 12 months in 50% (61/122 tumors), within 24 months in 82% (100/122), and within 36 months in 93% (114/122).

Out of the 122 records, 22 records contained almost invisible shadows (20) or vague shadows (2) on the previous mammography or ultrasonography. These cases were assumed to have already had a tumor of a detectable threshold size (5 mm) at the previous time. The growth rate was estimated from these measurements, and was expressed as a doubling time on the assumption of exponential tumor growth between elapsed times as in Collins' method.[1,2] The volume doubling time (Dt) is expressed by:

$$Dt=\frac{(t_1-t_2)\ln 2}{3\ln(S_1/S_2)}$$

where S_1 and S_2 are the tumor diameters at times t_1 and t_2, respectively. When the lesion was only roughly spherical, and the two-dimensional projection was not circular, the average of the longest diameter of the lesion and the one perpendicular to it in the two-dimensional projection, was used as S_1 or S_2.

The survival rate for breast cancer patients was calculated by the actuarial life table method, and the test of significance of differences between survival rates was carried out based on the standard errors of survival rates estimated by using Greenwood's formula.

Univariate and multivariate analyses of factors related to survival were performed by means of the Cox regression model to investigate the single and the joint effect of factors such as growth rate, clinical stage, lymph-node metastasis, age at initial treatment, histology, and year of treatment.

RESULTS

Clinical characteristics of the subjects One hundred and two of the 122 patients were detected by mass screening for breast cancer, and 20 were detected in out-patient clinics. The frequency distributions of the clinical stage, T-classification, N-classification (macroscopic lymph node metastasis), and n-classification (histological lymph node metastasis) of the breast cancer are shown in Table I (UICC, 1978).

Stage II was the most common (44.3%) followed by stage I (36.1%). Among the breast cancers detected in out-patient clinics, Stage I was the most common (65.0%).

As a whole, T2 was the most common (45.9%), followed by T1 (38.5%). N1 (N1a+N1b) was the most common (51.6%), followed by N0 (42.6%).

No metastasis was observed histologically in the axillary lymph nodes in 58.2% of the 122 patients. No metastasis was observed in 54.9% of the patients detected by mass screening, and in 75.0% of the patients detected in out-patient clinics.

Table I. Distributions of the Breast Cancer Patients by Stage at Diagnosis and Detection Method

	No. of subjects (%)		
	Mass screening	Out-patient clinic	Total
Clinical stage			
Tis	0 (0.0)	1 (5.0)	1 (0.8)
I	31 (30.4)	13 (65.0)	44 (36.1)
II	52 (51.0)	3 (15.0)	54 (44.3)
IIIa, IIIb	19 (18.6)	2 (10.0)	22 (18.0)
Unspecified	0 (0.0)	1 (5.0)	1 (0.8)
Total	102 (100.0)	20 (100.0)	122 (100.0)
T-classification			
Tis, T0	0 (0.0)	1 (5.0)	1 (0.8)
T1	34 (33.3)	13 (65.0)	47 (38.5)
T2	53 (52.0)	3 (15.0)	56 (45.9)
T3	7 (6.9)	2 (10.0)	9 (7.4)
T4	8 (7.8)	0 (0.0)	8 (6.6)
Unspecified	0 (0.0)	1 (5.0)	1 (0.8)
Total	102 (100.0)	20 (100.0)	122 (100.0)
N-classification (macroscopic)			
N0	44 (43.1)	8 (40.0)	52 (42.6)
N1a, N1b	53 (52.0)	10 (50.0)	63 (51.6)
N2	4 (3.9)	1 (5.0)	5 (4.1)
N3	1 (1.0)	0 (0.0)	1 (0.8)
Unspecified	0 (0.0)	1 (5.0)	1 (0.8)
Total	102 (100.0)	20 (100.0)	122 (100.0)
n-classification (histological)			
n0	56 (54.9)	15 (75.0)	71 (58.2)
n1α	19 (18.6)	3 (15.0)	22 (18.0)
n1β	14 (13.7)	1 (5.0)	15 (12.3)
n2	8 (7.8)	0 (0.0)	8 (6.6)
n3	2 (2.0)	0 (0.0)	2 (1.6)
n4	0 (0.0)	0 (0.0)	0 (0.0)
Unspecified	3 (2.9)	1 (5.0)	4 (3.3)
Total	102 (100.0)	20 (100.0)	122 (100.0)

Frequency distribution of the doubling time of primary breast tumors The tumor doubling time for primary breast cancers exhibited an approximately log-normal distribution, as shown in Fig. 1 and Table II (the chi-square value of goodness of fit with 6 degrees of freedom was 1.36, $P>0.96$). The geometric mean of tumor doubling times was 174 days and the range was between 11 and 1293 days for 118 subjects excluding 4 cases with a doubling time of infinity (no growth). The geometric mean of doubling time for lobular carcinoma was the shortest (108 days), but this value may not be reliable because of the small sample size (only 3 cases). So, excluding these 3 cases of lobular carcinoma, the solid-tubular carcinoma had the shortest geometric mean of doubling time (126 days), followed by the scirrhous carcinoma (205 days), while the papillotubular carcinoma had the longest doubling time (252 days) (Table II).

Tumor growth rate: rapid, moderate, and slow growth As shown in Fig. 1, the doubling time of primary breast

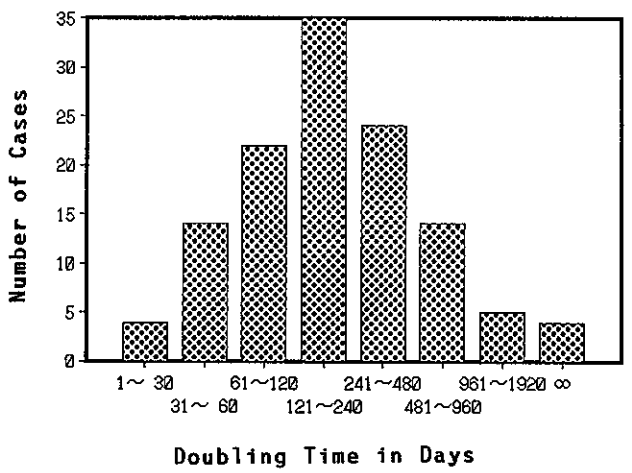

Fig. 1. Frequency distribution of the volume doubling time of 122 primary breast tumors.

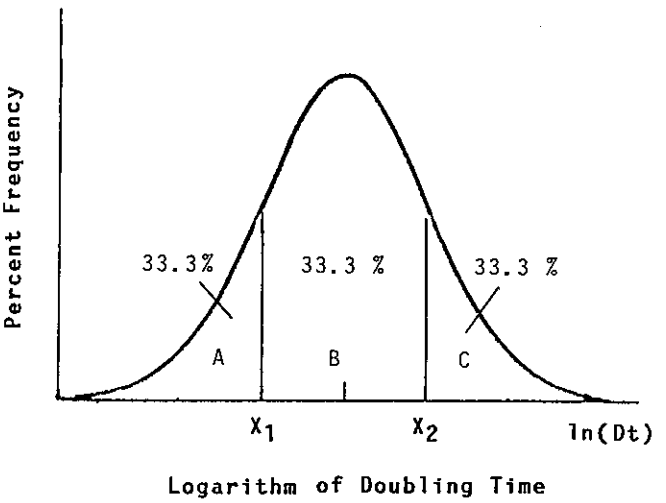

Fig. 2. Log-normal distribution of the doubling time of primary breast tumors.

Table II. Distribution of the Volume Doubling Time of Primary Breast Tumors by Histological Type

Doubling time (days)	No. of subjects by histological type					Total
	Papillo-tubular	Solid-tubular	Scirrhous	Lobular	Others	
1–30	0	3	0	1	0	4
31–60	2	9	1	0	2	14
61–120	7	11	3	0	0	22
121–240	11	12	7	2	3	35
241–480	6	10	3	0	5	24
481–960	8	3	3	0	0	14
961–1920	3	1	1	0	0	5
Infinity	1	1	1	0	1	4
Total	38	50	19	3	11	122
Geometric mean in days[a)]						
	252.1	126.1	204.6	107.7	189.0	173.6
95% Confidence limit (CL) in days						
Lower CL	187.9	93.5	133.9	5.4	105.0	145.4
Upper CL	338.4	170.1	312.7	2160.7	340.4	207.3

a) Mean was calculated excluding the 4 cases showing no growth.

tumors exhibited an approximately log-normal distribution. On the basis of a log-normal distribution, the cutting points (X_1, X_2) on the logarithmic scale of doubling time to obtain the tertiles were decided by using the mean (mean of $\ln(DT)=5.16$) and the standard deviation (SD of $\ln(DT)=0.98$) of the logarithm of doubling time calculated from observed/estimated values for 118 patients excluding 4 cases with no growth (Fig. 2). Thus,

Table III. Distribution of the Breast Cancers by Histological Type and Volume Doubling Time of Primary Breast Tumor

Histological type	No. of subjects (%)			
	Group by tumor doubling time			Total
	A (rapid-growing)	B (intermediate)	C (slow-growing)	
Papillotubular ca.	7 (18.9)	14 (33.3)	16 (41.0)	37 (31.4)
Solid-tubular ca.	23 (62.2)	14 (33.3)	12 (30.8)	49 (41.5)
Scirrhous ca.	4 (10.8)	8 (19.0)	6 (15.4)	18 (15.3)
Lobular ca.	1 (2.7)	2 (4.8)	0 (0.0)	3 (2.5)
Others	2 (5.4)	3 (7.1)	5 (12.8)	10 (8.5)
Unspecified	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)
Total	37 (100.0)	42 (100.0)	39 (100.0)	118 (100.0)

A, B, and C: refer to the text.

Table IV. Distributions of the Breast Cancer Patients by Clinical Stage and Volume Doubling Time of Breast Tumor

	No. of subjects (%)			
	Group by tumor doubling time			Total
	A (rapid-growing)	B (intermediate)	C (slow-growing)	
Clinical stage				
Tis	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.8)
I	8 (21.6)	17 (40.5)	16 (41.0)	41 (34.7)
II	18 (48.6)	19 (45.2)	17 (43.6)	54 (45.8)
IIIa, IIIb	11 (29.7)	5 (11.9)	5 (12.8)	21 (17.8)
Unspecified	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)
Total	37 (100.0)	42 (100.0)	39 (100.0)	118 (100.0)
T-classification				
Tis, T0	0 (0.0)	0 (0.0)	1 (2.6)	1 (0.8)
T1	9 (24.3)	18 (42.9)	17 (43.6)	44 (37.3)
T2	21 (56.8)	19 (45.2)	16 (41.0)	56 (47.5)
T3	4 (10.8)	3 (7.1)	2 (5.1)	9 (7.6)
T4	3 (8.1)	1 (2.4)	3 (7.7)	7 (5.9)
Unspecified	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)
Total	37 (100.0)	42 (100.0)	39 (100.0)	118 (100.0)
N-classification (macroscopic)				
N0	13 (35.1)	17 (40.5)	20 (51.3)	50 (42.4)
N1a, N1b	19 (51.4)	23 (54.8)	19 (48.7)	61 (51.7)
N2	4 (10.8)	1 (2.4)	0 (0.0)	5 (4.2)
N3	1 (2.7)	0 (0.0)	0 (0.0)	1 (0.8)
Unspecified	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)
Total	37 (100.0)	42 (100.0)	39 (100.0)	118 (100.0)

A, B, and C: refer to the text.

primary breast tumors were classified into 3 groups. Group A consisted of the tumors with doubling times shorter than 114 days ($\exp(X_1)$), that is, the fast-growing tumors. Group C consisted of the tumors with doubling times longer than 266 days ($\exp(X_2)$), that is, the slow-growing tumors. Group B was an intermediate one.

Tumor growth rate and histological type The frequency distribution of the tumors with doubling time according to the previously mentioned group classification is shown by histological type in Table III. For the papillotubular carcinoma, tumors in group C (slow-growing) were the most frequent, while, for the solid-tubular carcinoma, tumors in group A (rapid-growing) were the most frequent.

Tumor growth rate and clinical stages The frequency distribution of the tumors according to the growth rate classification is shown by clinical stage, T-classification, and N-classification (UICC, 1978) in Table IV. Patients with rapid-growing tumors tended to be more advanced in clinical stage, T-classification, and N-classification.

Tumor growth rate and lymph node metastasis No clear association existed between the tumor growth rate and the lymph node metastasis (Table V).

Tumor growth rate and age at initial treatment The association of the growth rate with the age of the patients at initial treatment is shown in Table VI. Tumors in younger age groups tended to grow more rapidly than those in older age groups.

Tumor growth rate and prognosis The 5-year survival rates for the 37 patients of group A (rapid-growing), 43 patients of group B (intermediate), 38 patients of group C (slow-growing) were 74.3%, 97.4%, 100.0%, respectively. The 5-year survival rate for the patients of group A was statistically significantly different from that of group B ($P<0.05$), and from that of group C ($P<0.01$). The patients with a more rapidly growing tumor tended to have a poorer prognosis (Fig. 3).

Univariate analysis of factors related to overall survival for breast cancer patients through the Cox regression model showed that growth rate, clinical stage,

Table V. Distribution of the Breast Cancers by Lymph Nodes Metastasis and Volume Doubling Time of Breast Tumor

Lymph nodes metastasis	No. of subjects (%)			
	Group by tumor doubling time			Total
	A (rapid-growing)	B (intermediate)	C (slow-growing)	
n-classification (histological)				
n0	19 (51.4)	26 (61.9)	22 (56.4)	67 (56.8)
n1α	5 (13.5)	10 (23.8)	7 (17.9)	22 (18.6)
n1β	6 (16.2)	3 (7.1)	6 (15.4)	15 (12.7)
n2	6 (16.2)	1 (2.4)	1 (2.6)	8 (6.8)
n3	1 (2.7)	0 (0.0)	1 (2.6)	2 (1.7)
Unspecified	0 (0.0)	2 (4.8)	2 (5.1)	4 (3.4)
Total	37 (100.0)	42 (100.0)	39 (100.0)	118 (100.0)

A, B, and C: refer to the text.

Table VI. Distribution of the Breast Cancers by Age of Patient at Initial Treatment and Volume Doubling Time of Breast Tumor

Age at treatment (years)	No. of subjects (%)			
	Group by tumor doublimg time			Total
	A (rapid-growing)	B (intermediate)	C (slow-growing)	
–39	17 (45.9)	13 (31.0)	11 (28.2)	41 (34.7)
40–49	15 (40.5)	17 (40.5)	14 (35.9)	45 (39.0)
50–59	5 (13.5)	6 (14.3)	10 (25.6)	21 (17.8)
60–69	0 (0.0)	3 (7.1)	3 (7.7)	6 (5.1)
70+	0 (0.0)	3 (7.1)	1 (2.6)	4 (3.4)
Total	37 (100.0)	42 (100.0)	39 (100.0)	118 (100.0)

A, B, and C: refer to the text.

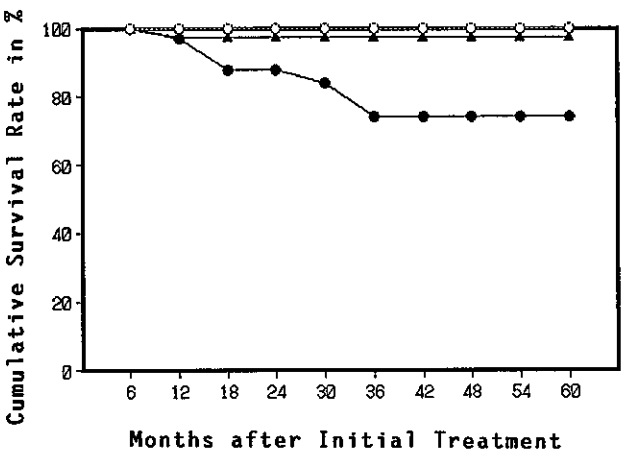

Fig. 3. Cumulative survival rates for primary breast cancers after initial treatment according to the volume doubling time of primary tumor: group A (●) consisted of patients with fast-growing tumors, group B (▲) those with intermediate-growing tumors and group C (○) those with slow-growing tumors, including 4 cases showing no growth. See the text for details.

lymph-node metastasis, and age at initial treatment significantly influence survival, when singly tested (Table VII and Table VIII).

Multivariate analysis of factors related to survival was performed by means of the Cox regression model to investigate the independence of the growth rate as a prognostic factor using all the variates listed in Table VII. The factor "growth rate" was shown to be signifi-

Table VII. Values/Scores of Variable Used in the Cox Regression Model

Factor	Values/Scores
Growth rate	1: A (rapid), 2: B (intermediate), 3: C (slow)[a]
Clinical stage	0: Tis, 1: I, 2: II, 3: IIIa, IIIb
Lymph node metastasis	0: Absent, 1: Present
Age at initial treatment	Age of each patient
Histology	1: Papillo-tubular ca., 0: Others
Year of treatment	1: 1978–1983, 2: 1984–1988

a) A, B, and C: refer to the text.

Table VIII. Univariate Analysis of Factors Related to Survival in the Cox Regression Model

Factor	Regression coefficient (B)	Standard error of B	*t*-value	Statistical significance level (*P*)	Risk ratio (Fav./Unfav.)[a]
Growth rate	−2.65	1.01	−2.62	<0.01	0.005 (C(slow)/A(rapid))
Clinical stage	1.44	0.55	2.64	<0.01	0.056 (I/IIIa+IIIb)
Lymph node metastasis	2.63	1.09	2.42	<0.05	0.072 (absent/present)
Age at initial treatment	−0.11	0.05	−2.15	<0.05	0.032 (60 yr/30 yr)
Histology	−1.57	1.06	−1.48	NS	0.208 (papillo-tub./others)
Year of treatment	−1.09	0.82	−1.33	NS	0.336 (1984–1988/1978–1983)

a) Risk ratio for favorable characteristic versus unfavorable one.

Table IX. Multivariate Analysis of Factors Related to Survival in the Cox Regression Model

Factor	Regression coefficient (B)	Standard error of B	*t*-value	Statistical significance level (*P*)	Risk ratio (Fav./Unfav.)[a]
Growth rate	−2.30	1.01	−2.28	<0.05	0.010 (C(slow)/A(rapid))
Clinical stage	0.45	0.67	0.67	NS	0.408 (I/IIIa+IIIb)
Lymph node metastasis	2.04	1.11	1.84	NS	0.130 (absent/present)
Age at initial treatment	−0.02	0.05	−0.44	NS	0.491 (60 yr/30 yr)
Histology	−0.08	1.34	−0.06	NS	0.923 (papillo-tub./others)
Year of treatment	−0.99	0.88	−1.12	NS	0.372 (1984–1988/1978–1983)

a) Risk ratio for favorable characteristic versus unfavorable one.

Table X. Measurements of the Doubling Time of Breast Tumors

Study (Reference)	Year	Subjects	Doubling time
Gershon-Cohen *et al.* (6)	1963	American females, 18 primary ca.	Median 120 days Range 23–209 days
Philippe and Le Gal (7)	1968	French females, 78 recurrences	Mean 40 days Range 3–211 days
Kusama *et al.* (3)	1972	American females, 163 primary ca., 36 metastases	Median 3.5 months Range 0.2–18 months log-normal distr.
Lundgren (8)	1977	15 tumors in 13 Swedish patients	Mean 211 days Range 42–397 days
Heuser *et al.* (9)	1979	American females, 23 primary ca. 9 no growth	Mean 325 days Range 109–944 days
Kusama (10)	1980	Japanese females, 214 primary ca. 96 metastases.	Mean 3.4 months Range 0.2–69.7 months for primary ca. log-normal distr.
Fournier *et al.* (11)	1980	German females, 147 breast ca.	Mean 212 days Range 44–1869 days
Fournier *et al.* (5)	1985	200 German female ca. in 18 clinics 128 unmeasurable in previous screening	15% (< 100 days) 13% (101–149 days) 39% (150–299 days) 33% (>300 days)
Kuroishi *et al.* (present paper)	1990	Japanese females, 118 primary ca. in 9 hospitals 4 no growth	Geo. mean 174 days Range 11–1293 days

cantly related to survival, after adjusting for other covariates (Table IX).

DISCUSSION

Since Collins *et al.*[1] introduced the concept that the growth of a malignant tumor mass was exponential and that the rate of growth could be expressed by the constant volume-doubling time, many reports favoring exponential growth of tumors and metastases for grossly measurable neoplasms of various organs have been published, contributing to our understanding of the natural history of malignant neoplasms. In advanced experimental tumors the growth rate slows down as tumors reach a certain size. In these cases the growth of tumors is described by the Gompertz function.[4] But, in the early phase, the Gompertz function is identical to the exponential function.

Fournier *et al.*[5] showed the good fit of observed tumor growth as a function of time to the estimated exponential curves in 12 breast cancer cases with 5 or more serial mammograms per case, indicating the applicability of the exponential growth model for the observed periods of tumor life in most cases.

In the present study, we adopted the exponential growth model to describe the growth behavior of clinically measurable primary tumors of the breast.

The first gross measurements of the growth rates of primary breast cancers were provided by Gershon-Cohen *et al.*[6] in 1963. Since then, various investigators have obtained the doubling times of primary breast tumors or metastatic tumors. The results are summarized in Table X.

In our study, the geometric mean of doubling times was 174 days and the range was between 11 and 1293 days in 118 primary breast tumors, and these values are within the range of the other observations mentioned above.

Very little is known about the relationship between the growth rate and the histological type of the breast tumor.

Spratt *et al.*[12] showed that papillary intraductal growth was associated with slow-growing breast cancers.

Our study also showed that the growth rate of the breast tumor was associated with histological type. The geometric mean of doubling time for the papillotubular carcinoma was the longest, and that for the solid-tubular carcinoma was the shortest; that for the scirrhous carcinoma was intermediate.

Watanabe and Kasumi[13] reported the relationship between the histologic type and the prognosis of 1,137 primary breast cancers operated from 1960 to 1969, in the Cancer Institute Hospital, Tokyo. The patients with papillotubular type of carcinoma had the most favorable prognosis (76% 10-year survival rate). The 10-year survival rates for those with scirrhous carcinoma and solid-tubular carcinoma were 62% and 60%, respectively. The proportions of lymph node metastases for papillotubular carcinoma, scirrhous carcinoma, and solid-tubular carcinoma was 32%, 54%, and 58%, respectively. These figures suggested that the determinant factor of the prognosis could be the lymph-node metastases. If the faster-growing cancers are likely to metastasize, then the trends of prognosis by histologic type could have a rational basis, as suggested from our study on the growth rate of tumors by histologic type.

A more rapid-growing breast tumor is generally considered to be more malignant, but few reports have been published on the relationship between the growth rate of breast tumor and survival.

Kusama *et al.*[3] reported that the doubling times for growth of the foci in 163 primary breast tumors and 36 various metastatic sites calculated in Collins' fashion correlated with the duration of survival after radical mastectomy performed at the Ellis Fischel State Cancer Hospital, United States, between 1940 and 1960. The 5-year cumulative survival rate after mastectomy varied from about 63% to 27% according to the doubling time of the tumors. They showed that a more rapidly growing tumor was associated with a poor prognosis and a more slowly growing tumor with a relatively favorable prognosis.

The present study also showed that the doubling time for growth of primary breast tumors in Japanese women was associated with the survival after initial treatment. However, among the 122 patients of the present study, the overall 5-year survival rate was much higher (91.6%) than that reported by Kusama *et al.*[3] The main reason for this difference may be the difference of detection method. The patients of our study were mainly detected by screening. On the other hand, the study by Kusama *et al.* was based on hospital cases.

Our study and Kusama's study showed that the clinically observed doubling time was associated with the prognosis of breast cancer patients. The findings that more rapidly growing tumors were more malignant, suggested that (a) cells of rapidly growing tumors may be more active in cell proliferation, and/or may have higher potential to metastasize, (b) the threshold size of the primary tumor at which metastasis could be established might be smaller in fast-growing tumors, so recurrence after mastectomy might happen earlier, (c) or even if the threshold size of the primary tumor at establishment of metastasis does not depend upon the growth rate of the primary tumor, the recurrence could happen earlier with rapidly growing tumors when the growth rate for the metastatic tumor corresponds to that of the primary tumor.[3]

A variable termed 'auxometry' proposed by Charlson and Feinstein[14] for the clinical growth rate of breast cancer was reported to influence the survival independently, indicating that this variable reflects unique information about the host-tumor relationship.[15, 16]

The prognostic role of cell kinetics, evaluated in terms of the thymidine labeling index (LI), was investigated for breast cancer patients. The results showed that rapid tumor cell proliferation is associated with a high probability of metastatic dissemination.[17-20]

More recent investigations have called attention to the possible prognostic relevance of oncogene amplification.[21, 22] The association of the amplification of c-*erbB*-2 was reported with shorter overall and disease-free survival time of human breast cancer. The degree of such oncogene amplification might be used as a prognostic indicator for cancer patients in the future.

ACKNOWLEDGMENTS

The present study was supported in part by Grants-in-Aid for Cancer Research (No. 62-34, No. 1-13) from the Ministry of Health and Welfare of Japan. We are indebted to all the members of the Research Group on the Study of Mass Screening for Breast Cancer.

(Received October 17, 1989/Accepted March 1, 1990)

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