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BODY SIZE AND MENOPAUSAL STATUS IN RELATION TO THE PATTERN OF SPREAD IN RECURRENT BREAST CANCER

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Abstract

The prognosis and pattern of spread were related to body size and menopausal status in 863 patients with recurrent breast cancer. These patients were all enrolled in the adjuvant protocols of the Danish Breast Cancer Cooperative Group. The pattern of spread was illustrated by the number of metastases, the anatomical location of recurrence, and the rate of progression. Body size was estimated as height, weight, Quetelet index (QI), and body surface area (BSA). The body size was unassociated with both recurrence-free interval (RFI) and survival after recurrence (SAR). The groups of patients with different body size had both the same number and the same location of metastases. The tumour growth rates were estimated as clinical rates of progression (i.e. the time elapsed from a single distant metastasis until dissemination). The progression rate was unaffected by body size. Postmenopausal patients had a significantly shorter RFI and SAR compared to premenopausal patients. The number of metastatic sites, the anatomical location of metastases, and the rate of progression were similar in pre- and postmenopausal patients. The study could not confirm most findings from the literature which report a poor prognosis for patients with large body size. Moreover, the results do not suggest interactions between body size, menopausal status, and the clinical course of recurrent breast cancer.

Key words: Breast cancer, recurrence, body size, menopausal status.

The most important prognostic factors in primary breast cancer are tumor characteristics such as stage, differentiation, status of regional lymph nodes, and presence of estrogen receptors. The body size may also have prognostic importance. Thus, in patients who have a body weight greater than the average a shorter survival has been reported (1–5). The status of the primary tumor characteristics and the body size could, however, be correlated. The influence of body size on survival could, therefore, work through the relation to these primary tumor factors (1, 6, 7). Using regression analyses, however, Greenberg et al. (3) showed that the prognostic effect of weight and, to a lesser extent, of height and Quetelet index (QI) was unassociated with stage. Moreover, others have found that overweight measured as body weight, body surface area (BSA), and QI, was unassociated with prognostic factors such as stage, tumor size, extent of axillary lymph node metastates, and ER status (8). Thus, body size parameters may be considered as independent prognostic factors.

In patients with recurrent breast cancer the duration of survival depends on factors such as the rate of progression, the tumor burden, and the anatomical location of metastases (9). Initial prognostic factors for the survival from the primary diagnosis may also be related to the duration of survival after recurrence (SAR) (9). Theoretically, these factors may influence SAR through a relation to either the progression rate or the extent or pattern of spread. We have investigated the relationship between body size and these manifestations in recurrent breast cancer. Since the effect of body size on the course of the disease may be mediated through endocrine mechanisms (6–8), we also analyzed the influence of menopausal status.

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Table 1

Progression rates and survival after recurrence according to body size. N indicates the total number of patients in each group, and percentages are 3 years actuarial rates

Variable		N[a]	ACP%[b]	p[c]	N[a]	SAR%[d]	p[c]
Height, cm							
Premenopausal	<160	29	22		49	36	
	160–164	45	52	0.65	78	25	0.48
	≥165	59	42		103	29	
Postmenopausal	<160	66	46		124	26	
	160–164	50	30	0.78	98	28	0.42
	≥165	49	42		95	30	
Weight, kg							
Premenopausal	< 60	57	36		93	32	
	60–69	43	49	0.96	78	30	0.30
	≥ 70	31	39		56	24	
Postmenopausal	< 60	45	26		94	30	
	60–69	61	60	0.64	110	28	0.91
	≥ 70	65	28		126	27	
Surface, m^2							
Premenopausal	< 1.7	71	32	0.33	129	32	0.06
	≥ 1.7	59	52		96	26	
Postmenopausal	< 1.7	79	45	0.39	154	27	0.43
	≥ 1.7	82	34		157	28	
Quetelet index, g/cm^2							
Premenopausal	< 2.4	81	40	0.99	139	30	0.78
	≥ 2.4	49	44		86	28	
Postmenopausal	< 2.4	59	35	0.73	116	29	0.83
	≥ 2.4	102	47		195	27	

[a] N: total number of patients.
[b] ACP%: actuarial cumulated proportion (i.e. the progression rates as defined in Material and Methods).
[c] p: probability, log rank test.
[d] SAR%: survival after recurrence.

Material and Methods

Assembly and selection of the patient population have been described in detail elsewhere (10, 11). All patients were registered, treated, and followed in accordance with the 1977–1982 protocols of the Danish Breast Cancer Cooperative Group (DBCG) for operable breast cancer (12). The primary treatment and follow-up took place at or in relation to one of the four participating oncological centres. The confirmative diagnosis of recurrent disease and the subsequent treatment were undertaken at the oncological centers according to uniform guidelines. Evaluation took place as of January 1st, 1984, and the median time of follow-up from primary diagnosis was 4.9 years (range: 2.0–7.0).

A total of 863 patients developed clinical recurrence. The files of these patients were reviewed in order to obtain information concerning the anatomical location of metastases, the number of metastatic sites, and the clinical course after recurrence (including therapy and subsequent metastases). When the number of sites was calculated the presence of recurrence in each anatomical location counts for one, irrespective of the number of tumor deposits within each site.

Information on body size at the time of primary diagnosis was obtained from patient records. Since body size measurements were not compulsory for all patients entering the DBCG-study, information on both height and weight was available in only 62% (536 patients) of the 863 patients with clinical recurrence. The relation between the course of disease and height (H), weight (W), BSA, and QI was analyzed. The BSA and QI were calculated according to log BSA = 0.425 log W + 0.725 log H + 1.856 (13), and QI = H/(L) (14).

Groups of patients with different body sizes were compared using the following categorization: Height: <160, 160–164, and ≥165 cm. Weight: <60, 60–69, and ≥70 kg. BSA: <1.7 and ≥1.7 m^2. QI: <2.4 and ≥2.4 g/cm^2. The cut-off limits for differences in height and weight groups were chosen before data analyses to secure a sufficient number of patients in each group. Cut-off limits for the BSA and QI categorization were the median values. Information on menopausal status was obtained from the DBCG database. This was available in 3797 patients of the 3802 who were registered in the DBCG (cf. criteria of selection above). In accordance with the DBCG protocol, patients were considered postmenopausal at the time of primary diagnosis if more than 5 years have elapsed since the last menstrual bleeding. All the other patients were considered pre- or perimenopausal.

Preliminary explorative data analyses revealed that

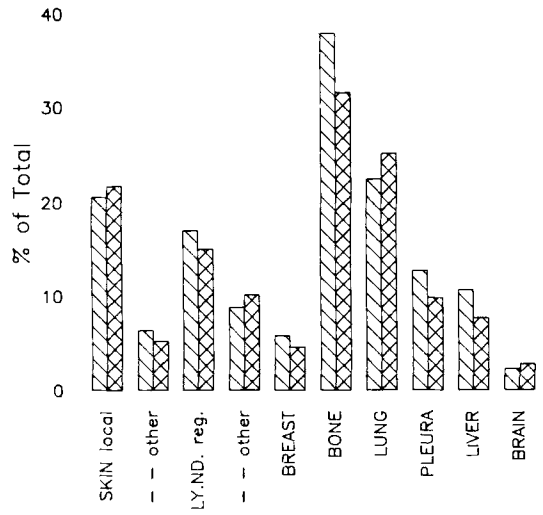

Figure. Anatomical distribution of metastases at first recurrence in patients with known and unknown body size. The heights of the columns reflect the percentage of total number of patients with recurrence in each stratum. ▨ body-size known (n=536). ▩ body-size unknown (n=327).

body size was known more often in stage II than in stage I patients. This was probably so, because many stage II patients were randomized to cytotoxic treatment, which required body surface area calculation before administration. Moreover, postmenopausal patients were both heavier and smaller than premenopausal patients. Patients with stage II were taller than patients with stage I disease. Therefore, the data were analyzed using the Mantel-Haenszel χ^2-test for stratified data (15) to control for the possible confounding effect of these differences. Thus, the prevalence of metastases in individual anatomical sites was analyzed according to body size when controlling for both stage and menopausal status. Analyses of the metastatic distributions according to menopausal status were performed with control for initial stage. As expression for the extent of metastasis the number of anatomical sites with metastases was used. Comparisons between different groups were made using the Kruskall-Wallis' or the Mann-Whitney rank t-test for ordered categories (16). The growth rate was evaluated as the progression time; i.e. the time from initial metastasis until the development of subsequent metastases. The progression time was determined in the subgroups of patients who recurred initially in a single distant site. This was done in order to eliminate the possible effect of variations in either extent of metastasis or therapy for recurrent disease. The life table method was used to estimate progression rates. The log rank test (17) was used to test the differences between both progression times and the durations of SAR. A p-value of less than 0.05 was considered significant.

Results

Among the 863 patients with recurrence, 74% had initial stage II disease and 63% were postmenopausal. Sixteen percent received adjuvant chemotherapy (mostly CMF), and 18% received adjuvant tamoxifen. Stage II disease occurred more often in postmenopausal patients, while systemic adjuvant therapy was given more often to premenopausal patients.

Body size. Information about height was available in 547 patients. The median height (range) was 162 cm (141–178 cm). Information about weight was available in 557 patients, median (range): 64 kg (43–150 kg). Calculations of BSA and QI were based on 536 patients, where both measurements were available. Eighty percent of the patients with known body size had initial stage II disease compared to 63% of the patients with unknown body size ($p<0.05$). Postmenopausal patients were smaller, had a greater weight, and consequently a higher QI than premenopausal patients ($p<0.05$). There was a tendency for patients with stage II to be taller than patients with stage I disease ($p=0.08$). Most patients developed recurrence within the first two years after mastectomy. The length of the disease-free intervals was unassociated with height ($p=0.99$), weight ($p=0.66$), BSA ($p=0.61$), and QI ($p=0.60$).

The median period of observation after first recurrence was 3.6 years (range: 0.8–6.4). Actuarially, 30% of the patients survived three years after first recurrence. There were no statistically significant differences in SAR between groups of patients with different body sizes (Table 1).

A single distant metastasis was found in 54% of the patients. The location of these metastases was the same as for patients recurring in more than a single site (data not shown). Forty percent of the patients developed additional metastases within 3 years after first recurrence in a single distant site. There were no statistically significant differences in the rates of progression between groups of patients with different body sizes (Table 1).

The Figure shows the anatomical distribution of metastases. The most common sites of recurrences were bone (35%) and lung (23%), followed by local (21%) and regional recurrences (16%). The distribution of the metastases was the same in patients with known body size as in patients with unknown body size (Figure). More than 70% of the patients recurred only in a single anatomical site. There were no differences in the number of anatomical locations with metastases between groups of patients with different body sizes ($p=0.72$–0.98 for the 4 measurements of body size). The anatomical distribution of metastases was almost similar between the different groups and there was no statistically significant relation between the specific locations and the body size measurements.

Menopausal status. The 5-year actuarial rate of survival from primary diagnosis was 78% for premenopausal and 68% for postmenopausal patients ($p=0.001$). The longer survival of premenopausal patients applied to both a longer recurrence-free interval ($p=0.0001$) and a longer duration of SAR ($p=0.05$).

Table 2

Distribution of patients according to menopausal status, period of recurrence, and number of sites with metastases at the time of first recurrence. N (%) indicates the total number of patients in each group

	Pre-, perimenopausal		Postmenopausal	
	N	(%)	N	(%)
Period of recurrence after mastectomy, (year)				
1st	86	(27)	201	(37)
2nd	118	(37)	180	(33)
3rd	63	(20)	83	(15)
≥4th	52	(16)	80	(15)*
No. of metastatic sites				
1	218	(69)	400	(73)
2	68	(21)	88	(16)
3	23	(7)	42	(8)
≥4	10	(3)	14	(3)
Total No. of patients	319	(100)	544	(100)

*p=0.02.

Among the 863 patients with recurrence 544 were postmenopausal and 319 were premenopausal. 55% and 53% respectively of these patients had recurrence in only a single distant site. The rate of progression within 3 years was 35% and 45% respectively for pre- and postmenopausal patients (p=0.47).

Table 2 shows that among patients with recurrence, the postmenopausal group had recurrence earlier than the premenopausal group (p=0.02). However, the number of metastatic sites was the same in the two groups. The anatomical distribution of metastases was similar in pre- and postmenopausal patients.

Discussion

The present study was made in order to investigate whether variation in the parameters of body size is related to the clinical course of recurrent breast cancer. Body size has been identified as an independent prognostic factor for the duration of the survival after primary diagnosis (3). This influence on survival is supposed to apply to a relation of body size to the metastatic potential of the primary tumor. In patients with recurrent breast cancer the influence on prognosis might be related to the rate of progression and the extent and anatomical location of the metastases (18).

In this study it is not possible to calculate the influence of body size on survival from initial diagnosis, since information about height and weight was only available in patients with recurrence. These patients cannot be regarded as representative of an entire and unselected group of patients with primary breast cancer. The result might indicate, however, that the body size is unrelated to survival. Thus, both the recurrence-free interval and the SAR were unassociated with body size. This is in agreement with the findings of Sohrabi et al. (19).

We found no association with either the anatomical location of recurrence, the number of sites with metastases, or the rate of progression. Therefore, if there is a relation between body size and the survival of breast cancer, it might be ascribed to chronological rather than biological considerations. This means that patients with large body size may have older tumors calculated from inception. A long preclinical period may be associated with a greater risk of subclinical dissemination and, therefore, also a short duration of survival after primary diagnosis. The study supports the chronological concept, since patients with a large body size often had stage II disease, and since postmenopausal patients were more adipose than premenopausal patients. Thus, a lead time or a detection bias phenomenon may possibly apply as primary breast cancer is detected later (from tumor inception) in adipose and older patients than in (more) slender and younger patients.

Postmenopausal patients had a shorter survival than premenopausal patients. Menopausal status was not associated with either the metastatic pattern of spread, the number of metastatic sites, or the rate of progression. Moreover, the subgroup analyses of the pattern of spread in patients with different body sizes showed no differences between pre- and postmenopausal patients. Subgroup analyses might have shown differences, if body size influences the disease differently in pre- and postmenopausal patients. Therefore, the study does not support the idea that body size influences the course of breast cancer through endocrine mechanisms.

The median time of follow-up was only 4.9 years. Therefore, the present results are based on a group of patients with early recurrence. If body size has prognostic influence, obese women might be overrepresented among patients with recurrence. Non-obese patients with later recurrences might develop metastases in other locations than the ones found in adipose patients with early recurrence. The present study is not able to detect these possible late differences. However, there are no indications in the literature supporting the theory that metastatic distributions change with time after initial diagnosis (10). Therefore, we do not believe that longer follow-up would alter the present conclusions.

In conclusion, the study does not support the theory that body size influences breast cancer survival. Moreover, the basic clinical manifestations of recurrent disease—such as anatomical spread and rate of progression—were unassociated with both body size and menopausal status. The influence of body size on survival,

which is evident in most investigations; seems to be related to tumor chronology rather than to tumor biology.

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