The relationship of body weight to response to endocrine therapy, steroid hormone receptors and survival of patients with advanced cancer of the breast

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Summary  High body weight is associated with increased production of oestrogens which may influence the clinical behaviour of breast cancer. We have examined the influence of body weight on the response to endocrine therapy, steroid hormone receptor content and survival in 227 women who either presented with or developed advanced cancer of the breast. One hundred and thirty-three (59%) patients presented with operable disease and 94 (41%) with locally advanced tumours. Two hundred (88%) were treated by tamoxifen and 27 (12%) by ovarian ablation.

In postmenopausal women high body weight was correlated with advanced tumour stage (P=0.002) and progesterone receptor (PR) positivity (P=0.01), but not with the presence of oestrogen receptor (ER P=0.21). The association between high body weight and PR positivity was particularly noticeable among ER positive tumours. There was no significant relationship between the nature of the response to therapy and weight (P=0.57). There was no significant difference in survival from the start of endocrine therapy (P=0.95), nor the time to progression of disease (P=0.29) between patients above and below the median weight of 64 kg. Among the patients with operable disease, there was no difference in overall survival (P=0.42), relapse free survival (P=0.69), and survival from the start of endocrine therapy (P=0.85) according to body weight.

Most epidemiological evidence suggests that high body weight and obesity are correlated with the incidence of breast cancer, particularly in postmenopausal women (Dewaard, 1982). Furthermore, these factors are generally associated with a worse prognosis (Papatestas et al., 1986; Abe et al., 1976; Eberlein et al., 1985; Greenberg et al., 1985; Donegan et al., 1978; Tartter et al., 1981; Newman et al., 1986; Boyd et al., 1981), although one small study did not confirm this effect (Sohrabi et al., 1980). Similarly in mice, obesity and a fat enriched diet increase the incidence and speed of onset of mammary tumours (Waxler et al., 1979).

High body weight was correlated with advanced tumour stage (P=0.002) and progesterone receptor (PR) positivity (P=0.01), but not with the presence of oestrogen receptor (ER P=0.21). The association between high body weight and PR positivity was particularly noticeable among ER positive tumours. There was no significant relationship between the nature of the response to therapy and weight (P=0.57). There was no significant difference in survival from the start of endocrine therapy (P=0.95), nor the time to progression of disease (P=0.29) between patients above and below the median weight of 64 kg. Among the patients with operable disease, there was no difference in overall survival (P=0.42), relapse free survival (P=0.69), and survival from the start of endocrine therapy (P=0.85) according to body weight.

Patients and methods

Patients

Between November 1975 and December 1983, 670 patients with advanced cancer of the breast were treated at this centre. Four hundred and twenty-nine of these received endocrine therapy as first systemic treatment after relapse. This was either by ovarian ablation or with tamoxifen in 393. Of this group 115 cases were excluded because they were not assessable for response, 15 because they had had adjuvant endocrine therapy and 36 because details of their weight were not available. This left 227 patients for study and their details are given in Table I. One hundred and thirty-three of 227 (59%) presented with operable disease and 94/227 (41%) with locally advanced disease. Twenty-seven (12%) were treated by ovarian irradiation or oophorectomy and 200 (88%) by tamoxifen. The details of the patients at the start of endocrine treatment are given in Table II.

All were assessable for response by UICC criteria (Hayward et al., 1977). Tumour oestrogen and progesterone receptors were analysed as previously described (Harland et al., 1983; Barnes et al., 1977).

Statistical methods

Survival curves were calculated by the Kaplan–Meier method and compared by the log-rank test (Peto et al., 1977). Body weight as a continuous variable and other factors of potential prognostic importance (recorded in Tables I and II) were included in a multivariate analysis using the Cox proportional hazards model (Cox, 1972). The distribution of body weight in relation to several patient and tumour variables and response to treatment was investigated by one-way analysis of variance. Pairwise comparisons were made when a significant difference was found using Scheffe’s Test. Body weight at the start of endocrine therapy was related to response, time to progression and survival from the start of therapy. Body weight at presentation was used for the other analyses.

Results

The median weight of the patients was 64 kg. There was no significant difference in the survival of the whole group from the start of endocrine therapy, between patients who were above or below the median weight (P=0.95, Figure 1a). There was also no difference in the time to progression of
disease between the two groups \( (P=0.29, \text{Figure} \, 1b) \). Amongst those patients who presented with operable disease \( (n=133) \), there were no significant differences in overall survival \( (P=0.42) \), relapse-free survival \( (P=0.69, \text{Figure} \, 1c) \), or survival from the start of endocrine therapy \( (P=0.85) \), between those patients who were above or below the median weight. Menopausal status did not affect these results.

There was also no relationship between the time to progression and survival between the two groups when individual response categories (i.e., complete and partial response, no change and progressive disease) or individual receptor categories (i.e., ER+, ER-, PR+, PR-) were considered.

All the above analyses were repeated after dividing patients into three groups by weight (<60 kg, 60–70 kg and >70 kg) and similar results were found.

**Table I** Characteristics of patients at presentation \( (n=227) \)

|               | \( n \) | \%  |
|---------------|--------|-----|
| Age           |        |     |
| <50           | 53     | (23) |
| 50+           | 174    | (77) |
| T-stage       |        |     |
| T0            | 3      | (1)  |
| T1            | 15     | (7)  |
| T2            | 98     | (43) |
| T3            | 32     | (14) |
| T4            | 74     | (33) |
| unknown       | 5      | (2)  |
| N-stage       |        |     |
| N0            | 107    | (47) |
| N1            | 80     | (35) |
| N2            | 22     | (10) |
| N3            | 16     | (7)  |
| unknown       | 2      | (1)  |
| Operable      |        |     |
|               | 133    | (59) |
| ER            |        |     |
| +             | 115    | (51) |
| unknown       | 53     | (23) |
| PR            |        |     |
| +             | 84     | (37) |
| –             | 82     | (36) |
| unknown       | 61     | (27) |

There was no relationship between the time to progression and survival between the two groups when individual response categories (i.e., complete and partial response, no change and progressive disease) or individual receptor categories (i.e., ER+, ER-, PR+, PR-) were considered.

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**Table II** Characteristics of patients at start of endocrine treatment

|                  | \( n \) | \%  |
|------------------|--------|-----|
| Previous adjuvant chemotherapy |        |     |
| No               | 194    | (85) |
| Yes              | 33     | (15) |
| Number of relapses |        |     |
| 1                | 174    | (77) |
| 2                | 44     | (19) |
| 3+               | 9      | (4)  |
| Age              |        |     |
| <50              | 41     | (18) |
| 50+              | 186    | (82) |
| Menopausal status |        |     |
| PRE              | 34     | (15) |
| PERI             | 9      | (4)  |
| POST             | 168    | (74) |
| Unknown          | 16     | (7)  |
| Karnofsky performance status |        |     |
| <50              | 5      | (2)  |
| 60               | 7      | (3)  |
| 70               | 35     | (15) |
| 80               | 55     | (24) |
| 90               | 108    | (48) |
| Unknown          | 17     | (8)  |
| Dominant site of disease |        |     |
| Soft tissue      | 68     | (30) |
| Bone             | 72     | (32) |
| Lung             | 50     | (22) |
| Liver            | 15     | (6)  |
| Other            | 22     | (10) |
| Number of major sites |        |     |
| 1                | 100    | (44) |
| 2                | 74     | (33) |
| 3+               | 53     | (23) |
| Type of treatment |        |     |
| Ovarian ablation | 27     | (12) |
| Tamoxifen        | 200    | (88) |

The distribution of body weight was unrelated to the age of the patient, menopausal status, histology of the tumour, axillary node status and the nature of the response to endocrine therapy (Table III). There was however, a significant association between body weight and the stage of the tumour at presentation \( (P=0.002, \text{Table} \, III) \).

There was no significant relationship between body weight and the ER status of the primary tumour and this held true when the first time of measurement was considered, i.e., either on presentation, or first relapse, or at the start of endocrine treatment (Table IV). However, an association was noted between high body weight and PR positivity which
Table III  Response to endocrine treatment and T-stage in relation to body weight

| Progressive disease | Mean body weight at endocrine treatment (kg) |
|---------------------|--------------------------------------------|
| No change           | n = 51, 64.8, P = 0.64                      |
| Partial response    | n = 52, 64.9                                |
| Complete response   | n = 18, 68.6                                |

Weight at presentation was unknown in 20 patients, but was recorded in all patients at the start of endocrine treatment.

Table IV  Receptor status in relation to body weight at presentation

| Number of patients | Mean weight (kg) | P value |
|--------------------|------------------|---------|
| Primary tumour     |                  |         |
| ER+                | 95               | 66.0    | 0.47   |
| ER-                | 39               | 64.4    |        |
| PR+                | 68               | 67.9    | 0.07   |
| PR-                | 65               | 64.1    |        |
| First recorded     |                  |         |
| ER+                | 112              | 66.4    | 0.21   |
| ER-                | 50               | 63.9    |        |
| PR+                | 82               | 68.1    | 0.010  |
| PR-                | 79               | 63.4    |        |
| Primary tumour     |                  |         |
| ER - PR-           | 34               | 65.7    |        |
| ER + PR-           | 30               | 61.4    | 0.028  |
| ER + PR+           | 64               | 68.2    |        |
| First recorded     |                  |         |
| ER - PR-           | 43               | 64.7    |        |
| ER + PR-           | 36               | 61.8    | 0.010  |
| ER + PR+           | 75               | 68.6    |        |

Discussion

We were surprised to find that body weight was unrelated to survival and response to endocrine therapy in this group of patients who either developed or presented with advanced breast cancer.

Several studies have reported an association between high body weight and axillary lymph node involvement (Abe et al., 1976; Eberlein et al., 1985; Greenberg et al., 1985; De Waard et al., 1977). In some of these there was also an association between high body weight and reduced disease free and overall survival (Abe et al., 1976; Eberlein et al., 1985; Greenberg et al., 1985). Patients above the median weight are more likely to be obese and to have large breasts where small tumours are more difficult to detect than in small breasts and it is well described that the larger the tumour the more likely axillary nodes are to be involved. The reported reduced survival of obese patients may be due to relatively late presentation, however, in some studies the adverse effect of obesity persisted after adjustment for tumour size and axillary node status (Greenberg et al., 1985; Tarter et al., 1981; Boyd et al., 1981). There was a significant association between high body weight and tumour stage in this study. However, in patients who will relapse, or who present with locally advanced disease, node status and tumour size are relatively unimportant indicators of prognosis. They are most important for the determination of the probability of the presence of metastatic disease which is not relevant to the series presented here since all patients presented with or developed advanced breast cancer.

In one study of adjuvant endocrine therapy in 749 patients (Boyd et al., 1981), the overall disease-free survival of women who weighed >64 kg was significantly less than that of those who weighed <64 kg. Among the premenopausal women aged >45 years, who weighed >64 kg, there was a significantly longer disease-free survival among those women who received adjuvant endocrine therapy compared to those who received no treatment. This effect was not seen in those who weighed <64 kg which suggests that in this selected group of women, those of above average weight are more likely to respond to endocrine therapy.

However, in the group of patients with advanced disease in our study there was no relationship between body weight and the probability of response to endocrine therapy.

In the multivariate analysis for factors which affect survival from the start of endocrine therapy, response was of overriding importance. There was no association between body weight and the ER content of the tumour which is in agreement with one study (Eberlein et al., 1985) but not another in which a higher incidence of ER−ve tumours in heavier patients was reported (Papatetaxas et al., 1986). For ER positive tumours, PR is significantly more likely to be present among heavier women, which is consistent with the fact that oestrogen may combine with its receptor to induce PR.

There was a significant correlation between high body weight and PR positivity and the ER+PR+ combination, which confer a higher likelihood of response to endocrine therapy (Adami et al., 1984). No relationship was established between weight and response. However, the patients who had a complete response were heavier than those in other categories of response and it is conceivable that with more patients, this difference would have reached significance.

Our original hypothesis was that women of above average weight would have a worse response because their greater production of endogenous hormones might stimulate tumour cell proliferation in receptor-positive tumours and override the inhibitory effects of tamoxifen. Owing to the relatively small numbers of patients in this study, we cannot exclude a small effect of weight on response to therapy, but if an effect is present it is likely to be of theoretical rather than of clinical importance.
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