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Body Size and Breast Cancer Prognosis: A Statistical Explanation of the Discrepancies[1]

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ABSTRACT

A historical cohort of 68 female breast cancer patients from one institution who were enrolled in a multicenter randomized controlled trial between 1971 and 1973 were followed up to the beginning of 1986. Weight and height at the time of mastectomy were transformed into two indices of body size, namely the Quetelet Index and a weight to "ideal weight" ratio. These two indices were analyzed for their relation with overall and disease-free survival, while controlling for the effect of several potential confounding variables. While neither index was linearly related to the hazard of death or recurrence, a significant quadratic (curvilinear) relation was found for both indices and both hazards. In all cases the hazard function was concave up, indicating that not only overweight but also underweight status is predictive of an unfavorable prognosis of breast cancer. This finding offers a possible explanation for the discrepancies among previous studies on this topic.

INTRODUCTION

The effect of obesity producing an increased risk of breast cancer has been suggested by several studies (1–3) and, although other investigators have not reproduced this result (4, 5), the association is now widely accepted. Similarly, a relation between obesity and an unfavorable prognosis of breast cancer has been supported by some studies (6–12) but contradicted by others (13–15). The studies of the prognostic importance of obesity were often based on heterogeneous samples in terms of age, extent of disease, mode of selection of subjects, and treatment. Moreover, different measures of obesity and different statistical techniques were used. For example, two studies (9, 11) which found significant differences in disease-free and overall survival rates when body weight was used as the basis for measuring obesity found no significant differences when the measurement of obesity was based on a function of weight and height, namely the Quetelet Index.

The purpose of the present study is to explain the contradictions regarding the relationship between body size and the prognosis of breast cancer, using a clearly defined complete sample from a population of patients enrolled in a randomized clinical trial. Since all patients meet predetermined eligibility requirements and were treated by three specific surgical or radiation therapy regimens (with equivalent therapeutic outcomes), they constitute a reasonable base on which to evaluate the effects of body size on prognosis.

MATERIALS AND METHODS

A retrospective cohort of 73 patients was formed using all patients of one institution (Sir Mortimer B. Davis Jewish General Hospital) enrolled in a multicenter randomized controlled trial (National Surgical Adjuvant Breast Project protocol B-04) between 1971 and 1973. The patients had been randomized to receive radical mastectomy, total mastectomy with irradiation, or total mastectomy with no further treatment. No patients received adjuvant chemotherapy or hormone therapy. Only stage I and II breast cancer cases were eligible, and patients with grave signs (fixation, extensive peau d'orange, ulceration) were excluded. A review of the patients' records identified the following information at time of mastectomy: age, menopausal status, clinical stage, treatment, height, and weight. The follow-up information included the survival time and time to first recurrence. If a patient was disease free at the date of last visit (every 6 months), this censoring time was used for disease-free survival. The censoring date for overall survival was taken to be January 1, 1986, the last date of follow-up data abstraction.

Two measures of body size were used. The first one is the Quetelet index, given by: 0.01 times the weight in pounds divided by the height squared in inches, herein denoted by QUET[3] = 0.01 W/H^2. The second measure is, in fact, a relative measure: the percentage ratio of actual weight to "ideal weight," given as a function of height in the United States Air Force Table of Standard Weights for females (10), herein denoted by WIR = 100 W/IW, where W and IW are the weight and ideal weight of the subject, respectively.

Statistical analysis consisted of standard methods for censored data (16). The Kaplan-Meier product limit method was used to estimate survival probabilities. Cox's proportional hazards regression approach was used to relate QUET and WIR to the instantaneous risk (hazard) of death and recurrence, while controlling for the effect of the potentially confounding variables available in this study, namely age, stage, menopausal status, and treatment. This approach was used after confirming the fact that none of these covariables are, in this study, effect modifiers, *i.e.*, that the measure of association between body size and survival is equal for all values of the covariables, a verification performed by testing interaction terms in the model. In addition, the proportional hazards assumption was tested using the method of defined covariates (16), which indicated that this model was adequate. Finally, predicted survival probabilities were obtained from the hazard regression functions by the method described in Ref. 16. Only the results of overall survival are presented, as the disease-free survival results are similar.

RESULTS

One patient, lost to follow-up and disease free in August 1978, was censored at that date. Missing data on height, treatment, and stage reduced the sample by 5 subjects. The analysis was therefore based on 68 subjects. The average age was 52.7, ranging from 29 to 72 years; 31% were stage II, 38% were premenopausal, and 41 and 37% received treatments 1 and 2, respectively. Finally, QUET ranged from 2.4 to 5.0, with a mean of 3.4, and WIR ranged from 78 to 157, with a mean of 111.

For the cohort as a whole, product limit estimates (±1 SE) of the probability of overall survival are 96 ± 2% at 1 year, 73 ± 5% at 5 years, and 54 ± 6% at 10 years (Fig. 1).

A strictly linear relationship between QUET and overall survival was not significant (P = 0.47). However, a quadratic

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[3] The abbreviations used are: QUET, Quetelet index, WIR, weight to ideal weight ratio.

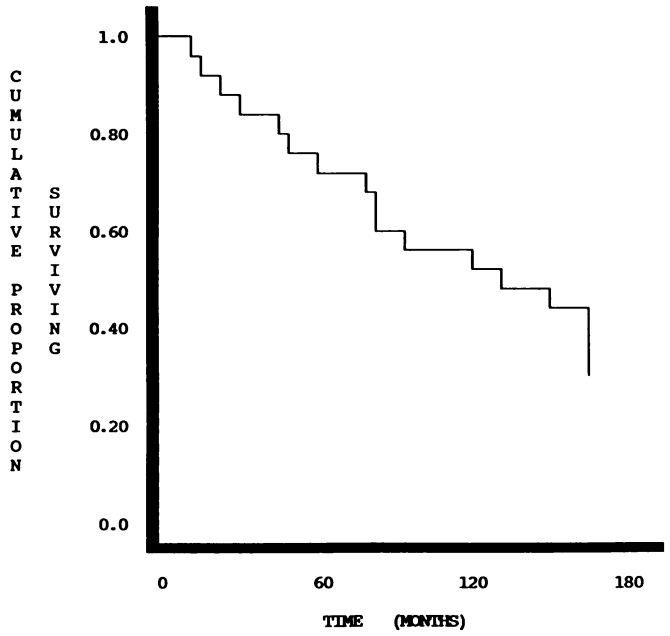

Fig. 1. Overall survival function estimated by the Kaplan-Meier product limit method.

Table 1 *Estimated coefficients of proportional hazards model of overall survival with QUET or WIR*

Variable	QUET			WIR		
	Estimate	SE	P^a	Estimate	SE	P^a
Age (yr)	0.066	0.025	0.009	0.067	0.025	0.007
Stage (II *versus* I)	0.404	0.398	0.309	0.389	0.388	0.317
Menopausal status (yes *versus* no)	−0.948	0.482	0.049	−0.999	0.487	0.040
Treatment						
2 *versus* 1	0.661	0.387	0.087	0.683	0.389	0.079
3 *versus* 1	−0.444	0.541	0.412	−0.447	0.539	0.407
QUET	−8.172	2.823	0.004			
$QUET^2$	1.210	0.398	0.002			
WIR ($\times 10^{-1}$)				−2.871	0.992	0.004
WIR^2 ($\times 10^{-2}$)				0.133	0.044	0.003

[a] *P* is two-sided.

relationship in QUET was found to be significant after controlling for the effect of age, stage, menopausal status, and treatment. This quadratic relationship was tested using two distinct hypotheses that address the questions of whether the quadratic model is an improvement over a model which excludes QUET totally and a strictly linear model in QUET. The quadratic fit was significant on both counts ($P = 0.016$ and 0.002, respectively). Similarly, a quadratic relationship in WIR was also found to be significant for both hypotheses ($P = 0.015$ and 0.003, respectively), while the strictly linear relationship with WIR was not significant ($P = 0.48$). Moreover, the hazard function was concave in QUET and WIR, indicating that, in each case, a unique minimal value could be found for the hazard of death (Table 1).

Using the coefficients given in Table 1, it may be shown that the estimated hazard function is minimized when QUET = 3.4 (see Appendix). Using the δ method (17), an approximate SE can be estimated (see "Appendix") for this value of QUET which minimizes the hazard function and can be used to compute its confidence interval. The 95% confidence interval for QUET*, the value of QUET which minimizes the hazard of death, is 3.1 to 3.6. Similarly, the estimated hazard function is minimized when WIR = 108. The 95% confidence interval for WIR*, the value of WIR which minimizes the hazard, is 100 to 116.

Using the hazard regression equation and fixing the covariates at their mean value, the predicted overall survival function (16) was calculated for three values of QUET (2.4, 3.4, and 5.0) and of WIR (80, 108, 150), which represent, respectively, three extreme types of subjects: underweight, "normal" weight, and overweight. Predicted survival was used instead of actual survival because of the small sample size; dividing 68 subjects into 3 subgroups would produce unstable estimates of actual survival probability by the Kaplan-Meier product limit method. The predicted survival functions, plotted in Figs. 2 and 3, clearly reflect the significant quadratic relationship found between overall survival and each of these body size measures. In addition, to illustrate this quadratic relationship differently, the predicted overall survival function at 5 years was plotted as a function of QUET, at the covariate means, in terms of the

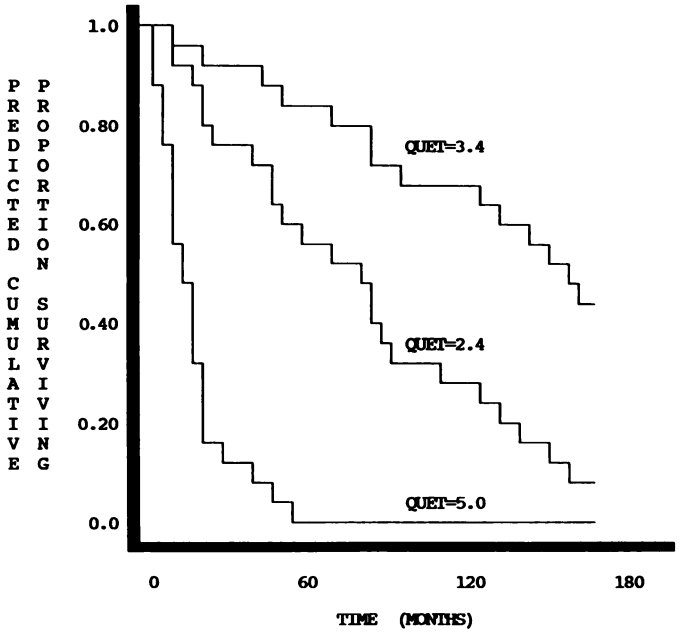

Fig. 2. Predicted overall survival function, as obtained from the Cox regression model, calculated at three extreme values of QUET.

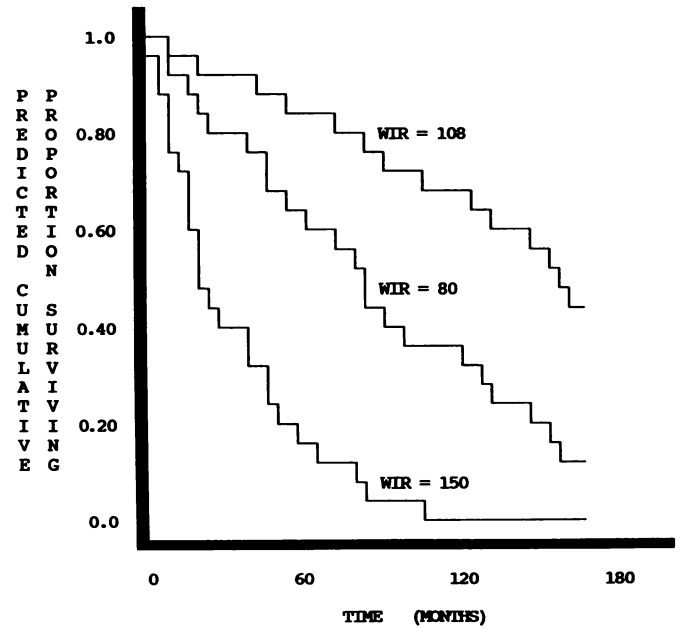

Fig. 3. Predicted overall survival function, as obtained from the Cox regression model, calculated at three extreme values of WIR.

probability of death within the first 5 years after mastectomy (Fig. 4). Although not documented here, similar (but less significant) results were obtained for disease-free survival.

DISCUSSION

The literature concerning the relationship between body size at the time of mastectomy and prognosis of breast cancer is contradictory. Some studies have found this association to be positive, while others have not. Also striking is the fact that, although it seems unjust to base the analysis solely on the crude body weight instead of a height-adjusted body size index (18), some investigators have found a statistically significant association when body weight was measured crudely but no significant association when body weight was measured taking height into account.

In our study of 68 women followed over 13 years, we found that the instantaneous risks (hazards) of recurrence and death were related to two height-adjusted body size indexes (QUET and WIR), after controlling for known potentially confounding factors, namely age, stage, menopausal status, and treatment. However, the relationship was quadratic rather than linear. We found that the hazard of death was concave and lowest when QUET was 3.4 and when WIR was 108, that is, when a woman was 8% above her ideal weight as defined by the United States Air Force Table of Standard Weights for females. It is important to recognize, however, that these significant minima are highly data and model dependent; they should certainly not be exploited until the model is confirmed by larger studies and then would most probably be somewhat different.

The fact that the data come from a randomized controlled trial on a complete and well defined clinical patient population ensures, at least in part, against a selection bias. However, although this relationship is independent of age, clinical stage, treatment, and menopausal status, there could be other variables which were not measured but which could confound this relationship. Finally, the fact that none of the covariables, for example menopausal status (11), are effect modifiers could be due to the size of the sample, which makes it more difficult to detect such interaction effects. In fact, the size of the sample is a limitation of this study and these observations will have to be verified in future investigations that will preferably involve larger groups of patients.

The quadratic relationship found in this study could in part explain the contradiction in the results of some prior studies.

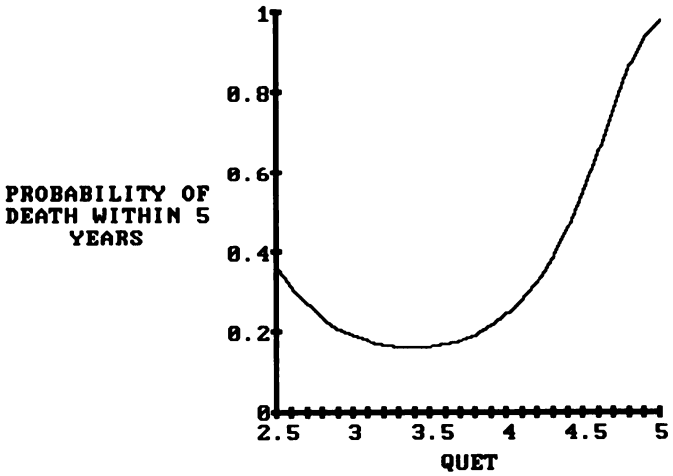

Fig. 4. Predicted probability of death within 5 years of diagnosis, as a function of QUET obtained from the Cox regression model.

Indeed, an analysis aimed at detecting linear trends with body size or at classifying subjects into "obese" or "nonobese" will inevitably result in an attenuated estimate of the measure of the association between body size and survival, assuming of course that the true relationship is as we found it in our data, namely quadratic. The degree of this attenuation would then be a function of the body size distribution in a study, particularly influenced by the proportion of subjects in the lower end of the body size distribution. Because this distribution is never fully described, it is not possible to assess the extent of this bias in other studies. However, a quadratic relationship between body weight and recurrence can be discerned in the study by Donegan *et al.* (6). In this study, the women without positive axillary nodes who weighed 100 pounds or less had a 5-year recurrence rate of 23.5% which decreased to about 10% for women of 100 to 130 pounds and increased to approximately 26% for women who weighed more than 130 pounds.

Certainly, our contention that the relationship between body size and breast cancer prognosis is quadratic stems from a purely statistical argument and, in fact, we eagerly await confirmatory evidence from other studies with larger groups of patients. We do not offer a rationale for the plausibility of such a relationship, nor do we describe the underlying causal process. However, we do report a statistically significant finding using a model not previously investigated in this field, albeit plausible. Such curvilinear models are rarely investigated since, in clinical data analysis, the tendency is to look for linear relationships with continuous prognostic factors and, if these are absent, not to proceed further with the analysis. Some biological relationships, however, are quadratic; the rate of death is high immediately after birth and again at old age; very low and very high hemoglobin levels are poor prognostic markers for overall survival; the classic theory of homeostatis suggests that, for prognostic studies, normal values may be better than values at either extreme. Of course, this notion should not be taken to suggest that such a search for more complex relationships be arbitrarily applied to either higher level polynomials (cubic, quartic, etc.) or other intricate models, an exercise which could produce better (but probably meaningless) fits of the data than the simpler models.

In conclusion, our data offer a potential explanation for the contradictory results on the relationship between body size and prognosis for breast cancer. Furthermore, it reminds investigators that quadratic-type relationships in prognostic studies are real possibilities when dealing with continuous prognostic factors and should be assessed as such. Thus, clinical epidemiological studies of breast cancer therapies could gain by verifying the potentially confounding and/or modifying effects of body size not in linear, but in quadratic terms or at least in three categories; underweight, "normal," and overweight.

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APPENDIX

If β_1 and β_2 are the coefficients of QUET and QUET^2, respectively, in the proportional hazards regression model with several covariates, then the hazard function is a minimum with respect to QUET and, for fixed values of the covariates, when

$$\text{QUET}^* = -\beta_1/(2\beta_2)$$

This parameter is consistently estimated by $-\hat{\beta}_1/(2\hat{\beta}_2)$ and its variance

can be estimated by the δ method (17), which in this case produces the formula

$$\hat{\mathrm{V}}\mathrm{ar}(-\hat{\beta}_1/2\hat{\beta}_2) = [\hat{\sigma}_1^2 - 2\,\hat{\sigma}_{12}(\hat{\beta}_1/\hat{\beta}_2) + \hat{\sigma}_2^2(\hat{\beta}_1/\hat{\beta}_2)^2]/(4\hat{\beta}_2^2)$$

where $\hat{\sigma}_i^2$ is the estimated variance of $\hat{\beta}_i$ ($i = 1, 2$) and $\hat{\sigma}_{12}$ is the estimated covariance between $\hat{\beta}_1$ and $\hat{\beta}_2$.

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