LETTER TO THE EDITOR

Body weight and breast cancer

Sir – In their article, 'The relationship of body weight to response to endocrine therapy, steroid hormone receptors and survival of patients with advanced cancer of the breast', Williams *et al.* (1988) address a topic of clinical importance. In a retrospective analysis they found that body weight influences size and oestrogen receptor status of breast tumours, but not response to endocrine treatment or survival of patients. They conclude, therefore, that body weight does not meaningfully influence the course of breast carcinoma.

I disagree with this conclusion. Williams *et al.* have not consistently taken into account the diversity of hormonal sensitivity of breast tumours. The hormonal responsiveness of breast tumours is heterogeneous from disease outset. Only one-third of tumours are clinically oestrogen-sensitive; two thirds are oestrogen-insensitive. While environmental hormones such as oestrogens derived from gonads, adipose tissue or exogenous sources will not reverse the hormonal insensitivity of tumours, they will influence the degree of hormonal sensitivity of inherently hormone-dependent tumours. Thus, an oestrogen-rich microenvironment will progressively increase the oestrogen sensitivity of hormone-dependent tumours by favouring the growth of oestrogen-responsive subclones, but an oestrogen-rich microenvironment will not reverse the oestrogen insensitivity of tumours composed of receptor-deficient subclones or of subclones with defective receptor-mediated mitogenic pathways.

Since both substrate availability and target responsiveness are necessary for successful interaction, and since clinical experience has shown that only those tumours that develop after menopause are more often than not oestrogen-dependent, it might have been more meaningful for the authors to focus on this particular subgroup of patients. I do not believe that competition between endogenous and exogenous hormones for hormone-sensitive target tissues is only of theoretical interest. Rather, I believe that dose escalation of agonists, both to adjust for large endogenous sources of antagonists and to adjust for tumours that as a consequence contain a high proportion of hormone-sensitive subclones, is as beneficial for patients with hormone-dependent tumours as intensive chemotherapeutic regimens are thought to be for large hormone-independent tumours. Thus, in our own (unpublished) studies we found that body weight does influence length of disease-free survival and response to endocrine treatment in patients with hormone-responsive tumours.

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Reference

WILLIAMS, G., HOWELL, A. & JONES, M. (1988). The relationship of body weight to response to endocrine therapy, steroid hormone receptors and survival of patients with advanced cancer of the breast. *Br. J. Cancer*, **58**, 631.

Reply to the letter from V. Hug

Sir – In response to Dr Hug's letter we would first like to correct the opening remarks. We did not find a significant relationship between body weight and the oestrogen receptor content of breast tumours. We did, however, report a significant correlation between body weight and progesterone receptor (PR) positivity ($P = 0.01$).

Dr Hug proceeds to develop the idea that an oestrogen-rich microenvironment would promote the growth of oestrogen receptor (ER) positive cells within the tumour which would render it progressively more oestrogen sensitive. This hypothesis would predict that a higher proportion of ER positive tumours would be found among heavier women (given the insensitivity of standard assays to low amounts of ER). There is, however, only one small series in the literature to support this contention (de Waard *et al.*, 1984) and our own and one other study (Eberlein *et al.*, 1985) found no evidence of this effect. Furthermore there are reports of a greater incidence of ER negative tumours among heavier subjects, particularly among post-menopausal women (Papatestas *et al.*, 1980, 1986). We do not know of any studies that have related the concentration of ER found in ER positive tumours to body weight, particularly among post-menopausal women which is clearly important to the investigation of this hypothesis. It is not made clear whether or not Dr Hug's (unpublished) studies provide support for the theory of clonal selection. Among ER positive tumours there was a significantly higher incidence of associated PR positivity in heavier patients which, as PR is thought to be induced by the action of oestrogen, provides confirmation that high body weight is associated with increased levels of biologically active oestrogen.

We are accused of not taking consistent account of the diversity of hormonal sensitivity of breast tumours. However, it is clearly stated that the time to progression from the start of endocrine therapy and overall survival were not influenced by body weight in any of the individual receptor categories (i.e. ER +, ER –, PR +, PR –). Furthermore, there was no difference in the time to progression and survival according to body weight in each of the different categories of response (i.e. complete, partial, no change and progressive disease), which is probably a more accurate indicator of 'hormonal sensitivity'.

Any effect of high body weight is more likely to be apparent among post-menopausal women, as in premenopausal subjects the contribution of fat-derived oestrogen to the total body oestrogen production is likely to be insignificant in relation to the ovarian output. In this study 74% of the women were post-menopausal and in the multivariate analysis no differences in clinical behaviour were observed according to menopausal status as we clearly stated. We would agree that post-menopausal women with ER positive tumours are an important group but we found no evidence that their response to tamoxifen and clinical behaviour is influenced by body weight.

This study included 112 women with ER positive tumours, most of whom were post-menopausal, which we believe is a

sufficiently large sample to demonstrate any substantial effect of body weight on response to endocrine therapy. The dose of tamoxifen administered to these patients was the same as that which is known to produce a response in oestrogen sensitive tumours of premenopausal women who have much higher levels of endogenous oestrogen production. We

therefore stand by our original conclusion and await the publication of Dr Hug's results with interest.

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References

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