Obesity and breast cancer prognosis: an expanding body of evidence

In recent years, interest has grown in the relationship between obesity and cancer. Increasingly, obesity has been identified as a significant risk factor for many cancers and, after tobacco use, may be the single greatest modifiable cancer risk factor [1–3]. Obesity also may affect prognosis after cancer through numerous pathways, including associated adverse disease features, hormonal influences, comorbidities that can interfere with treatment and other as yet unknown mechanisms. As earlier detection and more successful treatments continue to improve the long-term survival of cancer patients, obesity may become an even more important facet of cancer management.

For breast cancer, a clear association between obesity and disease risk seems to have been established (particularly in post-menopausal women [4]), and new studies confirming this observation and investigating explanatory hypotheses for the relationship continue to appear regularly [5, 6]. With respect to prognosis after disease diagnosis, however, the evidence is much less clear. Since the often cited review by Goodwin and Boyd in 1990 [7], numerous studies have been conducted in a variety of settings, many of which were summarized in a recent updated overview by Chlebowski and colleagues [8]. While this review, like the earlier one, concluded that obesity is indeed prognostic, many of the studies summarized indicate a very modest (or in some cases absent) influence of obesity on outcomes.

The present study by Berclaz and colleagues of the International Breast Cancer Study Group (IBCSG) [9] lends a new view to the situation, and while the authors similarly conclude that obesity is prognostic, both their opening paragraph, highlighting the aforementioned uncertainty regarding the prognostic importance of obesity, and the effect estimates they obtain, are perhaps more at odds with rather than supportive of the consensus opinion. Specifically, their findings would seem to depart from the general notion that obesity is a major prognostic factor, in that the effects they obtain are small [hazard ratios in the range of 1.10–1.20 for obese compared with normal weight women, according to World Health Organization definitions based on body mass index (BMI)], at least for breast cancer-specific outcomes. These estimates contrast much of the published work, where hazard ratios in the range of 1.3 to well over 2.0 are reported [8]. One finding not greatly emphasized in the IBCSG report was that disease-free survival (DFS) comparisons with non-breast cancer deaths treated as censored observations suggested an even more modest prognostic effect that did not achieve conventional statistical significance in this large patient cohort. In fact, the effect of BMI on overall survival was in general larger than the effect on DFS, suggesting that non-cancer causes of death contribute to the less favorable outcomes noted for obese patients. These findings are largely congruent with our recent report from analysis of women who participated in a randomized trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP B-14) [10]. In that study, we analyzed a cohort of >3500 women with negative lymph nodes and estrogen receptor (ER)-positive tumors in order to determine whether obesity might be particularly deleterious for women with early, hormone-sensitive disease, and, furthermore, whether obesity might modify the effect of tamoxifen, since it has been hypothesized that the enhanced estrogen availability mediated by excess body fat may be the principal mechanism by which obesity is prognostic. Interestingly, while obesity was not associated with greater recurrence risk and did not alter tamoxifen efficacy, it was associated with elevated risk of second primary breast tumors as well other second cancers (and, consequently, an effect of obesity on DFS). Overall mortality, and in particular those deaths likely to be non-breast cancer-related, were greater for obese women compared with those of normal weight. Another recent observational cohort study of women with ER-positive tumors has reported similar findings with respect to both the prognostic influence of obesity and its potential to modify tamoxifen response [11].

A unique and powerful aspect of the IBCSG study is the data source. Unlike those summarized in the aforementioned review [8], the present study uses data from randomized clinical trials, which offer a number of advantages over other sources. Patients from clinical trials are homogeneous with respect to disease stage at diagnosis and other protocol-specific entry criteria, and have minimal concurrent serious morbidity at study entry. Treatment delivery is uniform and quality controlled, and detailed clinical and pathologic disease features are available. The large number of participants and long follow-up duration provides high statistical power to test the effect of obesity on multiple end points, and, to a lesser extent, to examine its differential prognostic influence in certain patient subsets. Indeed, the inclusion of >6000 patients in this study results in statistical significance for the small relative hazards that were seen, which indicate a 10–20% excess DFS and survival hazard for obese compared with normal weight women. It is not clear why this and other [10, 12] studies of obesity specifically in randomized trial cohorts obtain more modest effect estimates, but we can speculate on possible reasons. The thorough staging work-up necessary to establish patient eligibility may result in more accurate staging and consequently a greater separation of obesity from its relationship to more advanced disease at diagnosis [13]. Also, protocol mandated treatment, including monitoring of dosing, may assure in general that obese patients are not inadequately dosed, which the IBCSG authors and others [12, 14] have pointed out as a potential secondary deleterious effect of...
obesity on breast cancer prognosis. Outside of clinical trials, it is entirely possible that obese women more often fail to receive adequate systemic therapy due to comorbid conditions or concerns about appropriate dosing.

Whether related to breast cancer or not, the excess risks for obese women found in these studies are not inconsequential, particularly if these risks were modifiable. Current and future research should focus on the elucidation of mechanisms and the determination of whether prospective interventions might alter risk. For example, is any prognostic effect of obesity due to enhanced post-disease estrogen exposure mediated by the increased aromatization activity in fat cells, or is obesity at diagnosis merely a marker for estrogen exposure incurred over a lifetime, or a host of other factors associated with both obesity and prognosis? Will the introduction of newer hormonal agents (such as aromatase inhibitors) have a modifying effect on the association between obesity and outcomes? In addition, the widely observed phenomenon of weight gain during breast cancer treatment may, as some studies have suggested, impart additional risk beyond that attributable to obesity at diagnosis [15]. Other clinical ramifications of obesity, such as correct dosing of chemotherapeutic agents that may also inadvertently affect prognosis, deserve further study [12, 14]. There is also a myriad of non-clinical factors that must be considered when attempting to relate obesity to outcomes after cancer, including race/ethnicity, socioeconomic status, health behaviors, and energy balance/nutrition, among others. For these factors, the current clinical trial database may be inadequate, since in the interest of simplifying the clinical trial process, much of this information is not collected.

So while interest regarding the link between obesity and cancer has been stirred, many questions remain. This interest naturally encompasses not just cancer risk but also the potential consequences of obesity for the cancer patient and for the growing population of cancer survivors. We particularly encourage large-scale studies in well defined populations as performed by Berclaz and colleagues, particularly when putatively explanatory factors such as menopausal and tumor hormone receptor status can be incorporated into the analyses. In order to determine not just whether, but also how, obesity may be related to prognosis, such focused investigations are critical. These studies provide credible information about the potential mechanisms by which obesity influences outcomes, and thus can hopefully serve as a bridge to prospective interventions aimed at both disease prevention and improving the short- and long-term welfare of individuals with cancer.

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