



A paradox or a challenge?

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Sepesi *et al.* (1) found in a large retrospective series that higher body mass index (BMI) was associated with improved overall survival in patients undergoing surgical resection of non-small cell lung cancer (NSCLC). Is this a paradox? “Paradox” is a rhetorical, not a scientific, term (2). Unfortunately, the term obesity paradox has entered into the medical vocabulary while simultaneously becoming less and less clearly defined. By now, the term is used to refer to almost anything that suggests improved outcomes associated with obesity. The underlying assumption is that any better outcome related to obesity is ipso facto surprising and counterintuitive and thus considered a “paradox”.

The general observation of better outcomes among obese patients with obesity-related diseases or conditions has been around for a long time. The authors of a Swedish study (3) in 1946 were surprised to find unexpectedly lower mortality among the higher weight patients with hypertension. In 1999, Fleischmann *et al.* (4) found that among patients undergoing hemodialysis the 1-year survival rate was significantly higher in the overweight patients. The precise term “obesity paradox,” followed by a question mark, appears to have first been used in PubMed in a 2002 study by Gruberg *et al.* (5). The study by Gruberg *et al.* referred specifically to an observation that among heart failure patients undergoing percutaneous coronary intervention, outcomes were better among patients with obesity than among normal-weight patients. This was described as a “paradox” because obesity was a risk factor for heart failure and it was considered unexpected that a risk factor would show better treatment outcomes.

Should the finding of better survival among higher BMI patients undergoing surgical treatment for NSCLC really be considered surprising? Unlike the situation with hypertension, end-stage renal disease or heart failure, numerous studies have suggested that obesity does not appear to be a risk factor for lung cancer incidence or mortality and in fact may be associated with lower incidence and mortality (6-10). Calle *et al.* (7), despite the limitations of their study, found consistently lower death rates from lung cancer at higher levels of overweight and obesity, relative to normal weight. Smith *et al.* (10) found consistently lower incidence of lung cancer at higher levels of overweight and obesity, relative to normal weight. Whether this is true also among never-smokers has been the source of some discussion (11,12), although a recent meta-analysis found that higher BMI was also associated with lower lung cancer risk in never smokers (13). Given that obesity may be associated with lower risk for incidence and mortality, should it then be considered surprising that survival with specific treatments might be better? This finding is not inconsistent with other studies of the associations of BMI and lung cancer.

The “obesity paradox” formulation invites the idea that the counterintuitive findings may be due to methodological error, such as some form of selection bias (14). This approach has most often been extended to situations in which the condition under study is positively associated with obesity, but not to situations in which the condition appears to be negatively associated with obesity. The idea that obesity is associated with a lower risk of lung cancer also

appears counterintuitive. It has been questioned whether this finding applies for people who have never smoked (11,12,15). Explanations having to do with reverse causality and errors in smoking data have been put forward (16) but have found little evidentiary support to date. BMI is not a precise measure of body composition or of nutritional status. Some data (17,18) suggest that waist circumference provides additional risk information after adjusting for BMI, although multicollinearity due to the extremely high correlations between waist circumference and BMI make interpretation of a contrast between them questionable.

Searching for methodological flaws can obscure the possibility of some underlying biological or treatment effects that deserve further study. Evidence is fairly consistent that there is a difference in survival between higher BMI and lower BMI patients with lung cancer. The reasons for these differences are unknown. Attention is often focused on the reasons why higher BMI patients have better survival, but as pointed out by Li *et al.* (19) and reinforced by Sepesi *et al.* (1), the question that might be more informative is: why do lower BMI patients have poorer survival? A related question might be why is the incidence of lung cancer lower at higher weight levels. Is higher BMI protective? Or is there some aspect of treatment for lower BMI patients that is in some way harmful or inadequate or could be improved? The suggestions put forward include the possibility that higher BMI patients may be younger or have less severe disease, lower BMI patients may have poorer nutritional status than obese patients, or that lower BMI patients may tend to avoid medical care and thus have poorer medical management than obese patients. Other possibilities are lower levels of chromosome damage (20) or higher fatty acid storage (21). As Sepesi *et al.* (1) point out, these and other hypotheses should be addressed in future studies, including metabolic profiles of patients under study and the effects of adjuvant chemotherapy. Such studies might also shed light on the observations of improved outcomes with higher BMI in other conditions as well.

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Footnote

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