Editorial

Fat but fit for the improved survival in lung cancer surgery

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"*Anger as soon as fed is dead, Tis starving makes it fat.*"

Emily Dickinson, *Poems*, Second Series, 1891.

Introduction

Obesity is associated with higher gastrointestinal, prostate, and breast cancer mortality rates. Nevertheless, obese individuals die lesser of diffuse large B-cell lymphoma, renal and lung cancer. In lung cancer patients, the improved survival in patients with a body mass index (BMI) >30 kg/m^2 remains unexplained, since obesity showed a favourable effect on both in-hospital outcomes and long-term survival.

A recent well-written study of Sepesi *et al.* from the MD Anderson Cancer Centre of Houston (USA) evaluated the influence of BMI on overall survival of 1,935 patients underwent surgical resection for lung cancer. Authors found that the BMI is an independent predictor of survival after lung cancer surgery, and a BMI >30 kg/m^2 was associated with improved OS (1).

Nonetheless, the study is retrospective with a selection bias (not well studied metabolic profiles) and the few information on adjuvant chemotherapy could also limit the survival analysis (1). Also, since anthropometric variables are subject to within-person variability over time, measurements at baseline could dilute the associations among the predictors and the outcome (regression dilution bias) (2). In effect, a retrospective study does not eliminate the possibility of a residual confounder, and only future controlled clinical trials should eliminate this possibility (3). Few meta-analyses investigate this association. Even with significant heterogeneity, the pooled results suggested that a high BMI increased the survival from lung cancer. Nevertheless, not all of the studies were adjusted for gender, age and smoking and self-assessed BMI was employed in the vast majority of the studies (4-8).

The relation between the BMI and lung cancer

Methodological questions arose when examining the correlation between BMI and lung cancer risk. The definition of obesity according to the WHO classification is defined as a BMI of ≥30 kg/m^2. Nevertheless, the distribution according to BMI differs worldwide. The obesity ratio is normally lower in Asia than in Western countries (9). Initially, smoking is a well-known risk factor associated with the weight and may be a confounder. Smokers are disposed to be thinner than non-smokers; heavy smokers are disposed to have higher weight than mild smokers and is related to an insalubrious regime. If limiting the analysis to never smokers, the correlation between BMI and lung cancer vanished. Furthermore, preclinical properties of lung neoplasm and weight loss may misrepresent the association between lung cancer and BMI. Limited studies have tried to challenge the methodological problems using Mendelian randomisation approach (10). The low prognostic nutritional index may rise the disease-specific mortality risk with a meagre prognosis. It is significantly related to large tumour size and showed a non-

significant correlation with high tumour marker levels. A low prognostic nutritional index may be associated with tumour aggressiveness (11).

Cancer cachexia is a hypercatabolic condition with a multifactorial aetiology and is a complex metabolic syndrome with low BMI related to muscle injury and loss of fat mass. Cachexia is a related problem in lung cancer patients and should be addressed explicitly for ideal patient management. Since the BMI not discriminate between fat and body mass, a healthy BMI may also reproduce low muscle obesity with an amplified fat mass but lessened body mass. Certainly, sarcopenic obesity has been described as independent risk factor for reduced survival highlighting the rank of evaluating the cachexia in the target palliative management of lung cancer patients (12). The levels of serum albumin are frequently used as nutritional status indicator, and high pre-treatment levels were related with improved survival between not small cell lung cancers. Since lymphocytes have an essential role in the cell-mediated immunity, a low count may predict reduced survivals in resectable not small cell lung cancers (11).

The obesity paradox

Based on the above estimates, an obesity paradox might exist in lung cancer surgery. The possible mechanisms underlying the obesity paradox remain under debate. The following perspectives are generally considered when trying to explain this unexpected phenomenon. First, with the popularity of fatty fast food and the reduction of physical exercise, an increasing number of people are becoming obese at a young age. Stronger physiological functions and better recovery capabilities in young patients may provide improved tolerance to surgical attacks and help maintain the postoperative internal environment. These factors may be the primary reasons for lower in-hospital morbidity and mortality rates among obese patients. Second, because obese patients are considered at higher risk of cardiovascular disorders, they are generally treated at an early age with medicines to control blood pressure and prevent hyperglycemia. Also, physicians advise these patients to do regular exercise to arrange fit dietary customs. Few patients with normal BMI obtain focussed care and health guidelines, so they disregard the healthiness until they have severe diseases. This situation may be another important reason for the obesity paradox. Third, obese patients can better stock nutrients to counterattack the surgical damages compared to normal or underfed patients. The protecting properties of peripheral adipose tissues have been proved in previous investigations, and they also contribute to the better prognosis for surgical patients. Lastly, another reasonable lookout suggest obesity not as a protector but the underweight as a possible poorer outcome. Nutritional depletion is commonly recognised as a predictor of the poor prognosis of surgical patients, and significant weight loss is a critical component. Underweight patients tend to be affected more by adverse events, such as cancers, smoking, chronic obstructive pulmonary disease and diabetes. Almost all of the current evidence indicates that low BMI and being underweight are independent risk factors for poor surgical outcomes. These findings can quickly create an illusion that obesity has a paradoxical benefit in surgical populations (6). The current guidelines for dropping the lung cancer risk among the general population recommend a BMI between 18.5 and 30 kg/m^2, and, in the meantime, avoiding the obesity is also essential seeing that obesity growths the risk of cancers and cardiovascular disorders (8).

The biological mechanisms beneath the obesity paradox

Some biological mechanisms sustain the reasonableness for the association between BMI and lung cancer risk. Inverse associations between BMI and benzo-α-pyrene DNA adduct levels amongst smokers were described in the literature, signifying that augmented body fat influences the levels of adduct, affecting the spreading of the carcinogens (10). On the other hand, a potential protecting role of BMI on DNA damage from smoking or occupational exposures have been detected. The elements focused on tissue-specific mechanisms rather than systemic physiological explanation (13). The differential metabolism of smoking-associated carcinogens in obese individuals and a dilution of these molecules in adipose tissue should also explain this mechanism. Alleles of the obesity genes have been linked to BMI and lung cancer risk, offering a molecular link (7). Excess body fat is linked to the high production of insulin, increasing insulin-like growth factor I and secretion of sex steroids, which subsequently promotes cell proliferation and suppresses apoptosis, and thus improve immune function and inhibit carcinogenesis. Moreover, the reduction of the risks of lung cancer associated with the use of menopausal hormones contributed to the hypothesis that oestrogens may exert beneficial effects against lung cancer, and adipose tissue is the primary site for oestrogen synthesis. The biological mechanisms behind such harmful obesity and

the lung cancer links remains uncertain, and consequently, better designed studies on molecular and epidemiologic aspects and in exploring the underlying carcinogenic mechanism are necessary (8).

Conclusions

Exploring the relationship between BMI and lung cancer published in the literature, being overweight appears to be more favourable than being fat, healthy weight, and underweight for the survival after surgical resection for lung cancer. Among either non-smokers or smokers, overweight patients had significantly longer survival than thin, healthy weight, and obese patients. Nevertheless, the mechanism of how the BMI affects lung cancer survival remains to be elucidated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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