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Obesity That Makes Kidney Cancer More Likely but Helps Fight It More Strongly

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Kidney tumors, including renal cell carcinoma, are among the top three most common genitourinary cancers and are ranked as the seventh and ninth most malignant disease in men and women, respectively (1). In the United States each year some 65 000 people are diagnosed with a kidney cancer, and 13 000 annual deaths are attributed to this malignancy (2). Over the past two decades the incidence rate of kidney tumors has risen substantially (3). Whereas more frequent abdominal imaging in recent years may have played an important role for the higher diagnostic ascertainment of renal masses, there appears to be a true rise stemming from higher prevalence of the risk factors of kidney malignancies among Americans, in particular the higher rate of obesity. According to observational studies, almost half of all kidney tumors are linked to obesity (ie, body mass index [BMI] >30 kg/m^2), and renal cancer risk is 20% to 35% higher for every 5 kg/m^2 of higher BMI (4). This association is no surprise given the role of obesity as the chief culprit in a diverse array of portentous and fatal conditions from malignancies to cardiovascular and renal diseases, with the prevailing commonality of a high death risk among these conditions.

Despite the presumably true role of obesity in the development of many chronic disease states, such as cancer, and acute devastating illnesses, such as coronary events, once these conditions have emerged, being obese appear to counterintuitively provide protective advantages and even survival benefits (5). Notwithstanding the disparaging impact of obesity on health and disease, emerging data suggest the existence of an obesity paradox, in that higher BMI may protect against worse outcomes in many acute and chronic disease states. The seemingly counterintuitive association between higher BMI and greater survival was first observed in patents with end-stage kidney disease undergoing maintenance hemodialysis treatment (6). Recent observational studies have also suggested a consistent obesity paradox in patients with heart failure (7) and those with malignancies (8), as well as among geriatric populations (9). These provocative observations have also been referred to as "reverse epidemiology" of cardiovascular risk factors when also considering data on lipid paradox and hypertension paradox (ie, survival advantages of higher lipid concentrations or higher blood pressure values among dialysis or heart failure patients) (7). Similarly, in a recent study among more than half a million patients with incident acute myocardial infarction without prior cardiovascular disease, in-hospital mortality was inversely associated with the number of coronary heart disease risk factors, including hypertension, smoking, dyslipidemia, diabetes, and family history of coronary heart disease (10). Although the biologic plausibility of the obesity paradox has remained unclear, the consistency of the data is remarkable, leaving little doubt that these observational data are beyond statistical confounding.

In this issue of the Journal, Hakimi et al. (11) examined a contemporary cohort of 2119 patients with clear cell renal cell carcinoma who underwent partial or total nephrectomy over 17 years (ie, from 1995 to 2012). Interestingly there were three seemingly counterintuitive findings consistent with the obesity paradox: First, compared with normal-weight patients, overweight (BMI 25 to <30 kg/m^2) and obese (BMI >30 kg/m^2) patients had 39% and 35%

lower likelihood of presenting with more advanced kidney cancer stage, respectively. Second, in those with a kidney malignancy, higher BMI was inversely associated with lower kidney cancer stage and milder grade. Third, among deaths due to this malignancy, higher BMI was inversely associated with lower mortality risk in unadjusted models, and in multivariable-adjusted models higher BMI still showed no association with increased mortality as would have been expected. Genome-wide examination across BMI categories showed a potential explanation for the obesity paradox by discovering meaningful differences in gene expression of metabolic and fatty acid genes, including fatty acid synthase, which was downregulated in obese patients but upregulated in normal-weight patients with renal cell carcinoma. This pattern provides a first-hand reasonable explanation and offers a novel mechanistic model as the putative pathophysiology of the obesity paradox, given that this genotype may be associated with growth advantage to cells under inadequate nutrition milieu. Indeed in this study the overweight and obese patients with higher serum albumin levels exhibited the lowest incidence of cancer-specific death (11). Hence, this study adds an important dimension to evidence supporting the obesity paradox in oncology in general and in kidney cancer in particular, as it is the first to examine the role of BMI and nutritional status in the severity of renal cell carcinoma and cancer survival while shedding some light into the biologic plausibility of the obesity paradox.

Whereas BMI is not a perfect surrogate for obesity or fat mass at individual level, there is little doubt that at population level higher BMI is associated with larger adipose tissue mass and higher risk of metabolic syndrome along with poor cardiovascular outcomes. Nevertheless, the study should be qualified for lack of a more reliable indicator of visceral fat such as waist circumference or elaborate imaging techniques to assess different types of adipose tissue. Moreover, the association of change in weight or body composition over time and cancer-free survival or other pertinent outcomes remains unclear. Notwithstanding these limitations, the study is one of the first to provide a step closer to a true biologic plausibility for the obesity paradox, at least among renal cell carcinoma patients, and provides convincing evidence about a more indolent nature of the kidney cancer in obesogenic milieu, the very same condition that has predisposed to the development of the very cancer. This and other similar studies underscore an important question pertaining to the role of obesity in disease and health. Nevertheless, the unfavorable role of obesity in increasing the risk of de novo renal cell carcinoma should not be forgotten (4), no matter what favorable impact it may have once the cancer has developed.

Is obesity like a bad friend that puts you in trouble but stands by you to protect you during the hardship he has caused you in the first place? Undoubtedly the impact of obesity in disease and health is not a simple black-and-white story. Such provocative findings as those in the study by Hakimi et al. (11) should not be considered as an attempt to undermine the legitimacy of an antiobesity campaign that is in the best interest of public health. After all, the then highly provocative discovery of favorable outcomes of moderate alcohol intake in the 1970s and 1980s has not legitimized alcoholism. The history of science encourages us to be bold and inconsiderate; in regard to the discovery of the true nature of obesity and all of its bad and good aspects, "we are obliged to say what the real truth is" (12).

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