Editorial

Is obesity a disease?—the evolving concepts, cancer paradox and association with improved cancer immunotherapy efficacy

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Obesity represents a growing health problem in the United States and worldwide, with a prevalence that has doubled since 1980 (1). In the United States, 70% of adults and 37% of adolescents are overweight or obese. The chronic health implications of obesity make it a public health issue with significant economic ramifications. By promoting an altered whole-body physiology, obesity increases the risk for chronic diseases including diabetes, cardiovascular disease, and cancer (2).

To address the accelerating rate of obesity in the United States, the American Medical Association (AMA) House of Delegates took the stance of defining obesity as a disease state in 2013 (3,4). Recognizing obesity as a disease has the potential to improve access to treatment and stimulate the advancement of novel therapies. However, providing a disease label has other important consequences. Medicalizing obesity gives the status of "disease" to tens of millions of adults and children in the United States. It runs the risk of relying on costly medical treatment while neglecting preventive public policy measures to address the underlying societal determinants of obesity (5). Moreover, historically our classifications of health, disease, and obesity have been riddled with ambiguities.

Our perception of disease is shaped by sociocultural contexts and evolving health expectations, diagnostic capabilities, and socioeconomic driving forces. Osteoporosis, for example, had been previously considered an inevitable part of normal aging but was recognized as a disease by WHO in 1994 (6). By contrast, in the early 20th century, homosexuality was considered to be an endocrine disorder and later on an organic mental disorder before finally in 1974 becoming de-pathologized and removed from the Diagnostic and Statistical Manual IV. Obesity, on the other hand, is regarded as the product of an "obesogenic" environment consisting of commercially driven high caloric diets and reduced physical activity in the context of low health literacy and food deserts. The World Obesity Federation further defines obesity as a "chronic, relapsing, progressive, disease process" that requires intervention (3).

The lack of accurate metrics to classify obesity calls into question the utility of defining obesity as a disease in order to improve health outcomes. Efforts to define obesity are complicated by the imperfect measures available to classify the condition. The most widely accepted and established measure of obesity is the body mass index (BMI) scale, which was developed by Adolphe Quetelet in the late 1800s (7).The BMI scale, however, suffers from important limitations including failure to account for variations in body composition; measurements tend to overestimate adiposity in athletes who have higher lean body mass and underestimate in the elderly who have diminished lean mass (8). Other less universal methods to measure body composition include waist circumference, waist to hip or height ratio, skin fold thickness, and dual energy X-ray absorptiometry.

The challenges of classifying obesity using BMI are further illustrated by its nuanced role in cancer therapeutics and survival outcomes. Although obesity appears to promote tumorigenesis particularly in hormone receptor-positive breast cancer in post-menopausal women, high BMI also

has a protective role in other cancers—a phenomenon known as the "obesity paradox" (9-11). Such findings may be partly related to the deleterious effects of cachexia, but also suggest the need for tools beyond BMI to characterize the body habitus. In oncology, body composition analysis is a more accurate method of quantifying muscle mass and adiposity. Martin and colleagues found that BMI greater than 25 kg/m^2 is associated with a survival advantage in GI and respiratory tract tumors, but this protective effect of obesity was eliminated in the presence of a low fat-free mass index, or sarcopenia (12). Sarcopenia visualized on CT imaging is significantly correlated with diminished overall survival across tumors of all stages due to greater rates of surgical complications, treatment toxicity, and markers of systemic inflammation (13). The nuanced role of obesity in oncology underscores the importance of accurately defining the body habitus to help guide tailored intervention in the era of precision medicine.

In a recent issue of *Nature Medicine*, Wang *et al.* [2019] demonstrated that checkpoint blockade with PD-1/PD-L1 inhibitors harnesses the paradoxical effect of obesity in order to enhance tumor response to immunotherapy (14). While obesity promotes a meta-inflammatory state in which leptin is associated with increased PD-1 expression and T cell dysfunction, these features can be successfully targeted by PD-(L)1 checkpoint inhibition and therefore serve as a paradoxically positive prognostic factor. These findings are supported by other reports that link obesity with improved overall survival and progression-free survival in patients with metastatic melanoma, bladder cancer, colorectal cancer, lung cancer, and renal cell carcinoma treated with targeted or immunotherapy (15-21). Importantly, immune checkpoint blockade has achieved augmented survival outcomes for only a subset of patients, creating a critical need to identify predictive biomarkers to guide patient selection for treatment. New studies further indicate that the gut microbiome may also modulate cancer response to immune checkpoint inhibitor therapy and is an area of active research (22-26).

Obesity also impacts health in indirect ways. In radiology, for example, image quality and acquisition are compromised by the body habitus of an obese patient. The increased soft tissue mass in obesity diminishes the signal-to-noise ratio and complicates the radionuclide dosimetry calculations used in PET imaging (27). Since radionuclide dosimetry is dependent on weight (mCi/kg), obese patients who exceed the maximum allowed dose may require tailored scans using the highest field gamma cameras and imaging for longer durations in order to maximize counts.

The AMA decision to declare obesity as a disease is a well-intentioned effort to legitimize the condition and shift public discourse from blame and stigmatism to medical therapy. However, disease implies the need for costly treatment in the form of drugs, medical technologies, and bariatric surgery. To call obesity a disease is to furthermore ignore the limitations of obesity measurement tools that tremendously impact management and prognosis (5). Obesity may be better characterized as a multidimensional risk factor that requires social and policy reform as well as continued efforts to elucidate the components of the body habitus in order to inform preventive and therapeutic efforts, including those that harness the paradoxical effect of obesity to enhance immunotherapy response.

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Footnote

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