Cancer Prognosis: Role of BMI and Fat Tissue

By Anna Azvolinsky

Data are emerging that individuals with advanced cancers—and other acute or chronic diseases—may have advantage against poorer outcomes if they have a higher body mass index (BMI). That obesity increases risk of acute and chronic disease diagnosis but protects individuals against worse outcomes once diagnosed is the so-called obesity paradox. But how best to explain this observation is far from clear.

Many prospective clinical trials have linked excess body weight—typically represented as a BMI of 25 kg/m² of body surface area or greater—with a higher risk of development of cancers, including postmenopausal breast cancer in women and esophageal, colon, pancreatic, endometrial, and kidney cancers in both sexes. The number of obese Americans will increase by an estimated 65 million by 2030, increasing cancer diagnoses by 500,000 (*Lancet* 2011;378:815–25).

Fat and Muscle Reserves

A recent meta-analysis of 97 studies suggests that overweight and class 1 obese individuals (BMI of 25–35) had a 6% lower risk (hazard ratio, 0.94; 95% confidence interval, 0.91–0.96) and 5% lower risk (hazard ratio, 0.95; 95% confidence interval, 0.88–1.01) of mortality, respectively, than those of healthy weight (*JAMA* 2013;309:71–82). Still, very obese individuals were not protected: Those with a BMI of 35 or higher had a 29% higher risk of mortality than those of healthy weight.

For adults in general, the least overall mortality risk has long been thought to be a BMI of 18.5–25.

"If you are either underweight or overweight or obese, then the risk of mortality goes up," said Vickie E. Baracos, Ph.D., professor of oncology at the University of Alberta. But higher mortality is not linked to obesity when a disease, such as advanced cancer, involves weight loss and wasting.

Baracos recently showed that, of 1,473 patients with advanced solid tumors, those with the highest BMI had the longest survival (*J. Clin. Oncol.* 2013;31:1539–47). Research has found similar results in symptomatic heart failure and renal failure patients undergoing hemodialysis (*Circulation* 2007;116:627–36, *J. Epidemiol.* 2012;175:793–803, and *J. Am. Coll. Cardiol.* 2004;43:1439–44).

Baracos's study showed that ongoing loss of weight and severe muscle depletion were independent indicators of poor prognosis, even for obese individuals. Both a muscle and a fat reserve may be important for advanced cancer patients, but exactly how protective and in what contexts is not yet clear. She also points out that further work is required to understand the amounts and types of resources a cancer patient needs for optimal outcome.

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Higher BMI, Better Prognosis?

A recent study of 2,119 clear-cell renal cell carcinoma (RCC) patients found that overweight and obese patients were 39% and 35% less likely, respectively, to present with advanced disease than their healthy-weight counterparts (*J. Natl. Cancer Inst.* 2013;105:1862–70). A higher BMI was also associated with a reduced cancer-specific mortality even when data were adjusted for comorbidities. The results are somewhat surprising since risk of RCC increases with higher BMI (*Lancet* 2008;371:569–78). The study underscores the complexity of cancer initiation and prognosis, as well as the paucity of mechanistic explanations.

"The link between obesity after a cancer diagnosis has been studied for some cancers, such as breast and colorectal cancer, but for less common cancers, the research is just getting going," said Susan Gapstur, Ph.D., M.P.H., vice president of epidemiology at the American Cancer Society.

Genome expression analysis in the RCC study showed that obese patients had lower expression levels of metabolism and fatty acid genes than healthy-weight patients. Some of these genes were previously found to be overexpressed in tumors, conferring a growth advantage. At least for clear-cell RCC, the study suggests that a lower risk of mortality among obese patients could be due to their propensity to develop a more slow-growing form of tumor than healthy-weight individuals. The study offers among the first potential mechanisms of how fatty tissue influences tumor pathophysiology—and supports the obesity paradox.

Susan Gapstur, Ph.D., M.P.H.

Higher BMI, Worse Prognosis?

Higher BMI may be advantageous for patients diagnosed with late-stage cancers, such as lung or esophageal tumors, which are treated relatively aggressively because patients generally survive for 5 years or less. But for slower-growing cancers, higher BMI may not confer any advantage and may worsen prognosis. For example, obese people generally have a worse prognosis when diagnosed with either earlier-stage prostate or breast cancer and have a higher risk of recurrence.

"But for metastatic disease, the scenario can flip and the patient is drawing on their energy reserves through aggressive disease and treatments," Baracos said.

Body composition—the ratio of fat to muscle—and how it changes during the

cancer patient's disease probably plays a role in prognosis. For patients who have high BMI–linked chronic diseases such as type II diabetes or heart disease, not enough evidence is yet available of how these comorbidities may affect cancer progression and risk of recurrence.

But higher fat stores in the body and higher BMI are linked to higher risk of metabolic syndrome, which increases risk of heart disease, diabetes, stroke, and potentially cancer.

"A critical question our group is focusing on is whether obesity itself increases risk of cancer or whether obesity is a proxy for high levels of other factors such as insulin," said Lorelei Mucci, Sc.D., associate professor of epidemiology at the Harvard School of Public Health.

A longitudinal study of more than 15,000 patients with prostate, breast, and colorectal cancer linked insulin resistance and hyperglycemia with overall cancer mortality (*Cancer Causes Control* 2010;21:631–42). Other studies focused on colorectal and breast cancer found higher risk of mortality for patients with insulin resistance.

Researchers are beginning to focus on the underlying mechanism of how obesity may influence cancer progression. Mucci and colleagues had previously shown that among men diagnosed with prostate cancer, those with a higher BMI and high plasma concentrations of C-protein (a by-product of insulin) 10–15 years before diagnosis had a fourfold-higher risk of dying of their disease than men who had a BMI of less than 25 and low C-protein levels (hazard ratio, 4.12; $p = 0.001$) (*Lancet Oncol*. 2008;9:1039–47). They also found that men with prostate cancer whose tumors harbor a common gene fusion event, TMPRSS2:ERG, are more susceptible to the effects of obesity on prognosis, possibly through insulin signaling (*J. Natl. Cancer Inst*. 2013;105:1881–90).

A recent study of two large prospective cohorts comprising 902 patients with pancreatic cancer also shows that a high BMI before diagnosis is linked to statistically significantly decreased survival (*J. Clin. Oncol*. 2013;31:4229–34). Even after controlling for diabetes, researchers found that high BMI still indicated a worse prognosis. Previous studies linked high BMI with increased risk of pancreatic cancer, but this study is among the first to suggest that obesity is also linked to a poorer pancreatic cancer prognosis. Pancreatic cancer causes weight loss around time of diagnosis, and so the key to the study was to gather data on BMI as many as 20 years earlier, said senior author Brian Wolpin, M.D., M.P.H., medical oncologist at the Dana–Farber Cancer Institute in Boston. In follow-up studies, Wolpin is exploring whether higher BMI results in a different mutation profile of pancreatic tumors, similar to how smoking results in a distinct lung cancer mutational profile.

"Chronic obesity may lead to a different set of mutations in the tumor that may translate into different tumor biology," Wolpin said.

Mucci has investigated the role of adiponectin, a cytokine produced solely by fat tissue and that inhibits inflammation. Overweight men have lower levels than healthy-weight men. Men with higher levels of the cytokine before prostate cancer diagnosis had a lower risk of developing high-grade prostate cancer and a lower risk of dying (*Clin. Chem*. 2010;56:34–43).

"The lower risk was substantial and appears to at least partly explain the association with BMI," Mucci said. Still, not enough of an understanding has emerged about which metabolic components are important and whether different components play a role in different individuals.

"The theme emerging is that obesity doesn't translate to the same outcomes for everyone. For some, being overweight is linked to higher insulin levels, and for others, other inflammatory markers may influence cancer progression," Mucci said.

Moreover, metabolic syndrome can also occur in people who are lean but have energy and insulin imbalances due to physical inactivity and high caloric intake.

Mucci is taking part in the National Cancer Institute's Specialized Programs of Research Excellence (SPORE) project, examining pathways that influence prostate cancer prognosis and that can influence secondary prevention, including adiponectin levels.

"The effects of obesity may be local or systemic, and there are many pathways implicated, including the PI3K pathway—and not just in prostate cancer but also breast cancer," Mucci said.

It's Complicated

"We don't have definitive answers of how obesity influences the biology of cancer," Baracos said.

And answers may not be imminent: Investigating these links takes long-term patient follow-up and detailed histories of weight status. The major gaps include the ways obesity, and fat tissue in particular, influences hormones, metabolism, and tumor growth. NCI has pooled more than 20 patient cohorts as part of its BMI and All-Cause Mortality Pooling Project and is examining the role of weight loss and waist circumference on both incidence of cancer and mortality—particularly in less common cancers such as multiple myeloma and head-and-neck cancer.

The broader implications of understanding the biology of obesity during cancer go beyond prognosis.

"If obesity really does lead to a different kind of tumor or promotes the growth of preexisting tumors, then knowing the biology of how that happens is likely to be very important in identifying lifestyle interventions and new treatments," Wolpin said.