



OBESITY

The fat advantage

Obese people have a higher incidence of kidney cancer, but are also more likely to survive the disease. Is the ‘obesity paradox’ real or an artefact of how studies are conducted?

BY SUJATA GUPTA

Attendees at the 2015 Genitourinary Cancers Symposium in Orlando, Florida, were presented with a head scratcher. At a poster session on renal cancer, a team at the Dana-Farber Cancer Institute in Boston, Massachusetts, led by Laurence Albiges, now at Gustave Roussy near Paris, presented its findings from a study of 4,657 individuals with metastatic kidney

cancer. Almost two-thirds were classified as overweight or obese on the basis of their body mass index (BMI)¹. That breakdown made sense — it is well established that obesity puts people at greater risk of developing kidney cancer. But the researchers found something striking: the higher the patient’s BMI, the longer their survival time.

That counter-intuitive finding added to a growing body of evidence for an obesity paradox in kidney cancer. Similar results are found

in obese people with other disorders, including heart disease, diabetes and even hip fractures. Kidney specialist Kamyar Kalantar-Zadeh at the University of California, Irvine, was one of the first to report these confounding results. He compares the situation to having the wrong sort of friend. It’s like “that guy who led you to prison, becomes your friend in prison”, he says.

This idea is controversial, however. Indeed, attendees at same session at the Orlando symposium could also find a poster purporting

TOMMY PARKER



to discredit the obesity paradox. Researchers led by Kathryn Wilson from Brigham and Women's Hospital and the Harvard T. H. Chan School of Public Health, both in Boston, had combed through data from two longitudinal studies to identify 575 individuals who had gone on to develop kidney cancer. The people had been followed for three decades or more as part of two long-term epidemiological studies. When the researchers zoomed in on these patients' medical histories and looked at their BMI trajectories they found that obese participants were more likely not only to develop kidney cancer, but also to die from it.

"The real question is whether the obesity paradox is a true biological phenomenon," says Martin Lajous, an epidemiologist at Harvard T. H. Chan School of Public Health, who was not involved in the study. It is more likely, he contends, that the perplexing results are merely "the result of a poor analytic strategy".

Determining whether the obesity paradox

is valid in kidney cancer matters for clinicians who treat and manage the disease. Do fat and thin people develop different types of kidney cancer, for instance? Should treatments take body weight into consideration? And should clinicians be advising overweight people who develop kidney cancer to refrain from dieting?

"Since obesity is reaching these epidemic proportions," says Helena Furberg, an epidemiologist at the Memorial Sloan Kettering Cancer Center in New York City, "we've got to figure out what's going on with this paradox."

ROOTS OF A PARADOX

In the early 1980s, a team in France found that dialysis patients with advanced kidney disease had fewer cardiovascular complications and longer survival times if they were overweight. Research over the next few decades confirmed that finding. In 2012, researchers in South Korea found evidence that the paradox also applied to kidney cancer.

The most common type of kidney cancer is renal-cell carcinoma. And the biggest risk factor for this disease is obesity, which accounts for 40% of all cases in the United States and 30% in Europe. Moreover, the rate of kidney cancer worldwide has been growing — there was a 2.6% annual increase between 1997 and 2007 in the United States. In South Korea, it grew by 6% a year between 1999 and 2007. To further investigate the role of obesity in kidney cancer, South Korean researchers identified 1,543 patients who had undergone surgery to remove a kidney tumour between 1994 and 2008. The team found that obese people with kidney cancer had a 53% lower risk of dying from renal-cell carcinoma than patients who were normal weight².

To see if their findings matched those of other labs around the world, the team scoured the literature and turned up 15 studies of cancer-specific survival from Europe, Asia and the United States. The researchers found that the 5-year survival rate of patients in the lowest BMI category was around 76% compared with almost 93% for those in the highest BMI category.

But the study was purely observational. "We do not know the exact mechanism," says co-author Jung Eun Lee, an epidemiologist at Sookmyung Women's University in Seoul.

FINDING THE MECHANISM

On the other side of the world, Furberg and kidney specialist Ari Hakimi, also at the Memorial Sloan Kettering Cancer Center, came across the obesity paradox in their research. But their team realized that it could take the analysis up a notch.

In the mid-2000s, the US National Cancer Institute and the National Human Genome Research Institute began profiling the genomes of different cancers for the Cancer Genome Atlas. Cancer institutes around the United States and Canada began collecting

genomic information on tumours — Memorial Sloan Kettering was one of them. When The Cancer Genome Atlas Research Network reported its genomic profiling of clear-cell kidney tumours, about one-quarter of participants (126 patients) had been operated on at Memorial Sloan Kettering³.

Furberg, Hakimi and their colleagues pulled up the medical data from these 126 people and calculated each patient's BMI just before surgery⁴. They wanted to see if a person's BMI

"The real question is whether the obesity paradox is a true phenomenon."

had any bearing on the tumours' gene expression. It did. They found lower expression of the gene *FASN* in people who were obese.

FASN encodes the enzyme fatty acid synthase, which is responsible for making fatty acids — an essential source of energy. The altered gene expression may have led to slower-growing kidney tumours.

Albige's team followed up on Furberg and Hakimi's work by comparing survival rates of normal weight and obese individuals with kidney cancer that had metastasized. Not only did obese patients have better survival outcomes, but they also had lower expression of fatty acid synthase. By explaining a potential genetic mechanism, says Kalantar-Zadeh, the Memorial Sloan Kettering team has "brought this paradox to a higher level of understanding".

THE LAYOUT OF BODY FAT

Obesity-paradox sceptics such as Lajous criticize the use of BMI as a proxy for fatness. Because muscle weighs more than fat, a bodybuilder could have the same BMI as someone who is obese. Smokers, who are typically thinner, are often included in analyses. And BMI does not account for conditions that cause muscle wasting, potentially giving an obese sick person a normal BMI measurement. People with cancer and sarcopenia are known to have poor outcomes.

To understand the obesity paradox in kidney cancer, some researchers are now homing in on the fat that surrounds the kidneys. Besides providing protection, the fat around the body's organs may also serve a metabolic purpose.

"If you stripped away all of that fat, more than likely the kidney wouldn't function optimally," says Steven Heymsfield, a metabolism researcher at Pennington Biomedical Research Center in Baton Rouge, Louisiana.

Molecular oncologist Ricardo Ribeiro at the University of Lisbon has been studying the fat around various organs by looking at its molecular characteristics and measuring its thickness using tools such as CT scanners. "We are looking at the relevance of specific fat depots," says Ribeiro.

Although Ribeiro's research into kidney fat is too new to have borne results, his earlier work

on prostate cancer could hold some clues about the kidney-cancer obesity paradox. Fat in the body, including around the organs, is known to come in different colours, from brown to white. Babies are born with predominantly brown fat; as humans get older, more and more of the brown fat is replaced by white fat. Exercise, however, seems to transform white fat into beige fat — a middle ground between white and brown.

Ribeiro has shown that the colour of fat around the prostate influences prostate-cancer aggressiveness⁵. Molecular analysis and microscopic observations revealed that the fat around the cancerous prostate is mostly white. When Ribeiro studied the interaction between different-hued fat cells and prostate-tumour cells in the lab, he found that the tumours were more aggressive in the presence of white fat. This would suggest that fat offers no survival advantage — and that the obesity paradox does not exist in prostate cancer.

The fat around kidneys seems to remain more brown-like regardless of weight. Ribeiro's team is now investigating the molecular composition of the fat around the kidneys, particularly tissue in close contact with tumours. It is also using CT scans from more than 200 patients with kidney cancer to see if the thickness and density of those renal fat deposits are a better measure of obesity than BMI.

It's still too early to know exactly what's going on, Ribeiro says. But he thinks that both the colour of the fat around the kidneys and its thickness might provide some insight into why obesity seems to suppress kidney tumours.

A PROBLEM OF METHODOLOGY

But even if researchers such as Ribeiro find more precise ways to measure fatness, critics of the obesity paradox contend that there is a more pervasive bias in how patients are selected for such studies.

Take the Memorial Sloan Kettering study. When Hakimi, Furberg and colleagues started researching the obesity paradox in kidney cancer, they looked into all the ways that their approach might skew the results. "Our first question was: 'Is this a phenomenon that could be explained away by other potential confounding factors?'" Hakimi says.

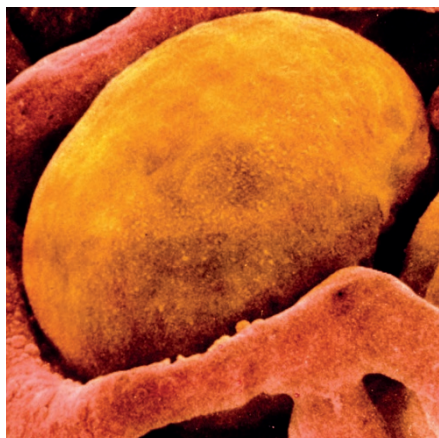
To find out, the researchers ran through several variables. They measured tumour size and found that people with normal weight and excess weight presented with similar-sized masses. They also measured albumin, a proxy for nutritional status, and found no differences between groups. (Low albumin can indicate that a person has begun to waste away from disease.)

"Is this a phenomenon that could be explained away by other confounding factors?"

Whenever possible, they asked patients if they had lost weight before surgery. But that too did not change the results.

"The findings persisted regardless of different adjustments," Furberg says.

The one piece of information that the study lacked was patients' weight trajectory over many years — the study included only a single weight measurement taken just a few weeks before surgery. But critics of the obesity paradox see that single BMI measurement as problematic, especially when it comes to can-



A brown fat cell — deposits of these cells are found around the kidneys.

cer. Unlike other diseases that have an obesity paradox, such as diabetes and cardiovascular disease, cancer can trigger unexpected weight loss well before the disease's clinical symptoms appear, says Hailey Banack, an epidemiologist who recently completed her doctorate at McGill University in Montreal, Canada. So measuring a person's BMI just before surgery, and even asking about recent weight loss, might lump formerly obese people in with people who have had a normal BMI for many years. What's more, protracted weight loss can be a harbinger of more aggressive forms of cancer. This could explain the poor outcomes for normal weight individuals with kidney cancer.

This line of reasoning is what made the findings presented by Wilson's group so striking. In that study, researchers had access to the medical histories of participants enrolled in the Nurses' Health Study, which began in 1976 to assess the health of US women, and the corresponding men-only Health Professionals Follow-up Study, which began in 1986. Participants had their BMI measured every two years. When viewed across many years, the benefits of obesity for people with kidney cancer disappeared.

MEDICAL ADVICE

As researchers try to make sense of what is going on, doctors must work out how to advise people with a kidney-cancer diagnosis. "It comes right down to the bedside,"

Heymfield says. "Should you be telling someone, 'No, this isn't the right time to go on a diet?'"

Most people studying the obesity paradox in kidney cancer think that changing medical guidelines to endorse obesity or weight gain rather than weight reduction is misguided. Being fat does not suddenly become beneficial after diagnosis.

Instead, Banack and Furberg both think that a plausible explanation for the difference between fat and thin people is that they develop different subtypes of kidney cancer. Although excess weight probably contributed to kidney cancer in an obese (or formerly obese) person, something else, such as environmental factors or genetic predisposition, is likely to have been the culprit for the cancer in a normal-weight person. Somehow, that 'thin-person' cancer is more aggressive.

"Obesity appears to be protective," Banack says, but that's an illusion. More likely, she says, is that the disease variants that come from other causes are so much worse.

Furberg hopes that it will one day be possible to use an individual's BMI — or some other, more suitable, proxy for obesity — to develop treatments that are specific to a person's cancer subtype, as well as to provide better prognoses. "My colleagues and I are doing research to see whether we can better understand the types of kidney cancer that different body sizes impart," Furberg says.

DREAM TEAM

Rather than ratchet up the competition, the various players investigating the obesity paradox in kidney cancer did something unusual in the cutthroat world of scientific research: they decided to collaborate.

"It just makes more sense for us to work together on this," says Mark Preston, a urologist at Brigham and Women's Hospital.

The plan is for the Memorial Sloan Kettering team to evaluate the genetic profiles of tumours excised from patients in the two longitudinal cohorts used by Wilson, Preston and their colleagues. The various groups will also address shortcomings in the weight measurements by assessing both BMI and waist circumference, a better proxy for obesity (bodybuilders rarely sport a bulging belly).

"Right now we seem to be getting these two diametrically opposed answers," says Preston. "I think there's probably truth in both." ■

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1. Albiges, L. J. *Clin. Oncol.* **33** suppl, abstr. 405 (2015)
2. Choi, Y. et al. *Int. J. Cancer* **132**, 625–634 (2013).
3. The Cancer Genome Atlas Research Network *Nature* **499**, 43–49 (2013).
4. Hakimi, A. A. et al. *J. Natl Cancer Inst.* **105**, 1862–1870 (2013).
5. Ribeiro, R. et al. *BMC Med.* **10**, 108 (2012).