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Obesity: The heavyweight of cancer

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Obesity rivals tobacco as the leading preventable risk factor leading to cancer and is associated with reduced patient survival. While most people are aware of the connection between smoking and cancer, the connection with obesity is currently underappreciated. In fact, it is estimated that obesity is responsible for up to 20% of cancer-related deaths in adults.

Cancer patients can die from "metastasis" - this is when the cancer spreads to organs that are important for survival, and impairs the ability of those organs to function properly. For breast cancer patients, metastases to the lung will develop on average 2 years earlier if they are obese. The purpose of our study was to find out why.

To answer this question, we fed laboratory mice a high-fat diet until they became obese, and then looked at the health of their lung tissue. Compared to lean mice (which are healthy and normal weight), obese mice had a lot of inflammation - this means that cells of the immune system were abnormally high. One particular immune cell type, the neutrophil, stood out. The normal function of neutrophils in our bodies is to fight infection. However, neutrophils are also known to promote lung metastasis, in response to signals supplied by cancer cells, and their numbers were 2-3 times higher in lungs from obese mice.

We found that in obese mice, breast cancer metastasis to the lung was significantly higher compared to lean mice. Interestingly, when we experimentally reduced the numbers of neutrophils in obese mice, we no longer saw this difference. This meant that the neutrophils were playing an important role during breast cancer metastasis in obese mice. It also suggests that unresolved lung inflammation in obese patients may increase their risk of cancer metastasis.

The challenge, though, is that neutrophils are an important part of the immune system - you cannot simply deplete neutrophils in patients. Low levels of neutrophils are a clinical condition called "neutropenia", and this can be lethal if the patient gets an infection and develops a fever. This is one of the common risks of chemotherapy treatment, and a reason why cancer patients have to frequently measure their temperature. To get around this challenge, we instead decided to figure out how neutrophils were getting into the lungs of obese mice, and then try to develop a way to stop them.

During an infection, neutrophils mature in the bone marrow, and are then released into the blood to patrol the body. We decided to first look at what was different in the bone marrow and blood of obese individuals. We found that there were certain "obesity factors" that were abnormally high in the blood of obese mice and humans. When we eliminated the different obesity factors from mice (taking advantage of special antibodies), neutrophil numbers decreased in the lungs of obese mice, and breast cancer metastasis was also reduced. This suggests that targeting these obesity factors might be an alternative way to reduce lung metastasis in overweight individuals.

Finally, we wanted to know if these drug interventions were really necessary - perhaps we could achieve the same effect with weight loss. We enrolled our obese mice on a strict diet to lose weight. Using this lifestyle intervention strategy, lung neutrophils were reduced in mice that had lost weight, compared to those who were maintained on the high-fat diet. Strikingly,

this corresponded to a reduction of breast cancer metastasis.

We have evidence that this intervention might work in humans as well. In a clinical weight loss trial, morbidly obese women were placed on a strict diet to lose 10% of their body weight. Blood samples revealed that both the obesity factors and the number of neutrophils in their blood decreased after weight loss. These women did not have cancer; but if they did, our data suggest that a weight loss program might help reduce the risk of lung metastasis and, ultimately, mortality.

If you are thin, you may think this doesn't apply to you - but you could be wrong! About 20% of lean individuals are actually metabolically obese even though they appear thin on the outside. This means that their metabolism and immune system *within* their bodies mimics those of an obese person; therefore, they have similar health risks to obese individuals, including increased cancer risk. So, our findings not only apply to the obese population, but also apply to a subset of lean people as well, together representing a significant overall proportion of the adult population. Research that aims to understand these phenomena is therefore important for us all.

Like smoking, it will be critical for clinicians and scientists to continue to investigate how obesity accelerates cancer mortality, and to raise awareness that simple lifestyle changes could substantially impact survival outcomes for patients.