Does cancer immunotherapy work differently in men vs. women?

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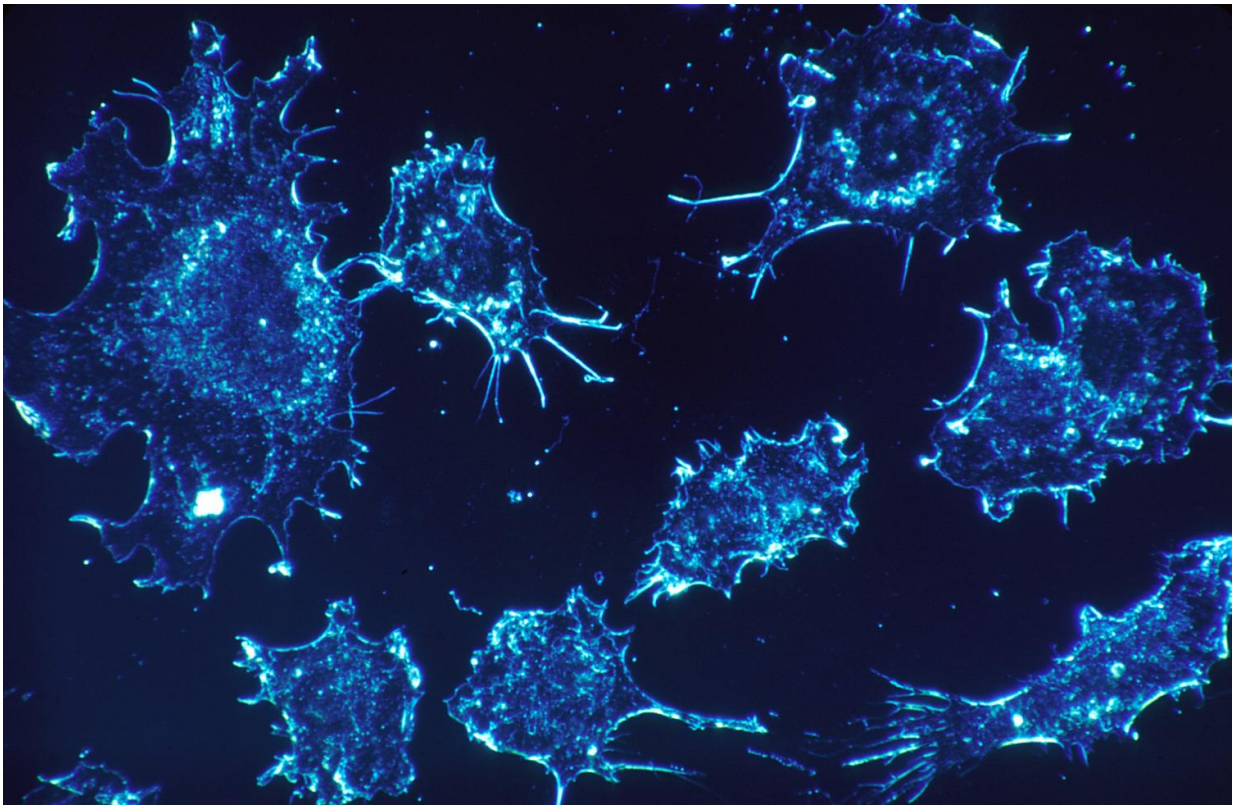

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A class of cancer immunotherapy called checkpoint inhibitors has revolutionized cancer treatment. It's a new way to attack the disease by unleashing the immune system. However, not every patient benefits from the treatment, and it can cause severe, sometimes life-threatening,

side effects in some. New research shows that one group of patients may be at greater risk. The results, published in *JAMA Network Open* December 2nd, show that women with advanced melanoma are twice as likely as men to die when treated with the same combination of checkpoint inhibitors.

"This is the first large population-based study that demonstrates a significant difference in outcomes for women treated with two checkpoint inhibitors at the same time," says senior author on the study, Grace Lu-Yao, Ph.D., MPH associate director for Population Science at the Sidney Kimmel Cancer Center—Jefferson Health, and vice chair and professor in the Department of Medical Oncology at Thomas Jefferson University.

"Are women more likely to die because the therapy isn't working, or because of side effects? We don't know yet, but this is a powerful signal in real-world data that we need to investigate further," says Dr. Lu-Yao.

Women and men have slightly different immune systems. For example, women are at greater risk of auto-immune diseases, but also tend to have stronger immune responses against infection than men. Despite these known differences, men are still over-represented in clinical trials. The results of these trials, assumed to be applicable to women, may not be.

Dr. Lu-Yao's team decided to investigate whether women and men who had undergone checkpoint inhibitor treatment for melanoma indeed had the same outcomes. The researchers examined health records from a national database of cancer patients—SEER (the Surveillance, Epidemiology, and End Results) linked with Medicare files. They included data from 1,369 patients with advanced melanoma diagnosed between 1991 and 2015. The patients were treated with one or several checkpoint inhibitors, such as pembrolizumab, nivolumab or ipilimumab.

They didn't see any differences in survival between men and women treated with a single checkpoint inhibitor. However, Dr. Lu-Yao and her team did find that the risk of death was 2.06 times higher for women than it was for men given a combination of the checkpoint inhibitors nivolumab plus ipilimumab.

The baseline rate of death for both men and women taking PD-1 inhibitors was 40%. For those on combination anti-PD1 and anti-CTLA-4 therapy, that rate continued to be 40% for men, but jumped to 65% for women.

Despite the accumulating evidence of the potential role played by sex in influencing drug effectiveness, differences between men and women is rarely examined by sex. This lack of attention on the effect association of sex with the effectiveness of ICI-based immunotherapy efficacy may have significant negative consequences, especially since these treatments are associated with high toxicity and high treatment cost.

"This data is a wake-up call based on the experience of hundreds of patients on these drugs," says Dr. Lu-Yao. "This real-world data demonstrates that the results derived from men might not be applicable to women and it is critical to design studies with sufficient power to evaluate treatment effectiveness by sex."

Using more current datasets, Dr. Lu-Yao and her colleagues plan to examine whether the risk exists for women with other cancer types. They also plan to collaborate on research to understand the ways in which the immune system in women differs from that of men.

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More information: Se Ryeong Jang, Nikita Nikita, Joshua Banks,

Krupa Gandhi, Scott W Keith, Jennifer M Johnson, Melissa Wilson, Grace Lu-Yao, "Sex and Immune Checkpoint Inhibitor Outcomes in Patients with Melanoma," *JAMA Network Open*, 2021.