Anxiety increases cancer severity in mice, research finds

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Worrywarts, fidgety folk and the naturally nervy may have a real cause for concern: accelerated cancer. In a new study led by researchers at the Stanford University School of Medicine, anxiety-prone mice developed more severe cancer then their calm counterparts.

The study, to be published online April 25 in PLoS ONE, found that after hairless mice were dosed with ultraviolet rays, the nervous ones — with a penchant for reticence and risk aversion — developed more tumors and invasive cancer. Consistent anxiety also came with sensitivity to chronic stress and a dampened immune system. Though other researchers have already linked chronic stress to higher risks for cancer and other maladies, the study is the first to biologically connect the personality trait of high anxiety to greater cancer threats.

"Anxiety may be defined as increased sensitivity to physically existent, or non-existent but perceived or anticipated, stressors," said stress expert and immunologist Firdaus Dhabhar, PhD, first author of the study.

Dhabhar's previous work has investigated the balance of "good" and "bad" stress. Short-lived stressors — like being chased by a lion, or giving a weighty presentation to your boss — can actually boost your immune system by preparing your body for battle. But constant stress, such as caring for a disabled loved one, breaks down the body's ability to fight off disease over time, he said.

The question is: How much stress is too much? Because stress responses

vary between individuals, Dhabhar turned to understanding the link between base-level anxiety and actual stress.

For mice, stress comes from striking a balance between exploring to find food and mates, and protecting themselves from danger. Highly anxious mice, Dhabhar hypothesized, would err on the side of avoiding danger. He and his research team placed hairless mice on a raised, cross-shaped track, which had one walkway enclosed by walls and the other open. Then they measured how often each mouse ventured to the open arms. Likewise, he placed them in a large box, half lit and half dark, and noted those that spent the most time in the dark side.

"It's similar to the idea that if someone is very anxious they may be more worried about, and less likely to, walk down a dark alley," said Dhabar, an associate professor of psychiatry and behavioral sciences and a member of the Stanford Cancer Institute and the Stanford Institute for Immunity, Transplantation and Infection.

With their evaluation of anxiety complete, the researchers exposed all the hairless mice to UV rays for 10-minute bouts, three times a week, for 10 weeks — exposure similar to that of humans who spend too much time in the sun. Tumors cropped up a few months afterward. "This skin cancer model is really valuable," Dhabhar said, "because it closely mimics human skin cancer."

Additionally, these types of tumors are vulnerable to an immune system attack. In some cases, the immune system could destroy them, he said.

Though all the mice eventually developed skin cancer, the anxious mice had more tumors and were the only ones to develop invasive forms of cancer.

When he and his team compared the immune responses of the low- and

high-anxiety mice, they found that nervous mice had higher levels of immune-suppressing cells called regulatory T cells, which normally thwart overzealous responses. The high-strung mice were also making fewer of the chemical signals that fire up an immune attack on the tumors.

Lastly, the researchers looked at the hormone corticosterone. In mice and other animals, the adrenal system — the "fight or flight" controller of the body — secretes corticosterone in response to disease and stress. The levels of this hormone were cranked up in anxious mice, suggesting that they have more sensitive stress sensors and, perhaps, a lower threshold for feeling under the gun.

"Identifying a psychological trait right at the beginning — before any experimental manipulation — and seeing that it can be associated with increased tumors months later, and with biology that can begin to explain mechanisms, was a rewarding surprise," Dhabhar said.

This hasn't been tested in humans yet, and that needs to be done, Dhabhar said.

"It's bad enough that cancer diagnosis and treatment generates stress and anxiety, but this study shows that anxiety and stress can accelerate cancer progression, thus perpetuating a vicious cycle," Dhabhar said. "The goal is to ameliorate or eliminate the effects of anxiety and chronic stress, at least at the time of cancer diagnosis and during treatment."

The team's next step will be examining whether knocking down the negative effects of anxiety and stress can increase the benefits of cancer treatment. A shot of anxiety medication, such as Valium, for limited periods of time may be helpful, Dhabhar said. There may also be combinations of drugs and behavioral changes that could be most effective in the long run. "Ultimately," he said, "we really want to

harness the patient's mind and body while doing everything that medicine can from the outside to maximize treatment success."

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