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Breast Cancer Patients' Persistent Fatigue Is Real, May Actually Speed Up Aging

The persistent fatigue that plagues one out of every three breast cancer survivors may be caused by one part of the autonomic nervous system running in overdrive, while the other part fails to slow it down.

That imbalance of a natural system in the body appears linked to the tiredness and exhaustion that can burden cancer patients as much as a decade after their successful treatment.

The effect is so great, researchers say, that it may be a sign of accelerated aging in fatigued patients, causing them to seem as much as 20 years older compared with patients who aren't fatigued.

Those new research findings, just reported in the journal *Psychoneuroendocrinology*, are the latest from a three-decade-long study of the impact that stress can have on the human body.

Christopher Fagundes, a postdoctoral fellow at Ohio State University's Institute of Behavioral Medicine Research (IBMR), and Janice Kiecolt-Glaser, a professor of psychiatry and psychology and a member of the IBMR, drew early data from a larger ongoing study testing whether yoga can combat continuing fatigue in breast cancer patients.

They were looking for a new biomarker, a signal that could point to the initial cause of this fatigue. Their target was the autonomic nervous system, that part of the body that controls unconscious activities like breathing, heartbeat, digestion and such, which earlier research had indicated might play a role.

The autonomic nervous system has two main parts -- the sympathetic and the parasympathetic. The former is responsible for what has become known as the fight-or-flight response, a triggering of short-term, energized activity. The latter deals with opposite situations. It is the resting phase, best recognized by the sleepiness that may follow eating a big meal.

While the sympathetic system is an energy hog, the parasympathetic conserves energy, and the two should remain in balance in healthy individuals. The researchers were looking for differences between fatigued and non-fatigued cancer survivors.

"We started looking for biomarkers for cancer-related fatigue," Fagundes said. "Other research has indicated that a systemic inflammation through the body might be a reliable biomarker for this.

"Sick people with inflammation become tired and lethargic, which makes sense since their bodies are using energy to fight off infections. You can imagine that a long-term, systemic inflammation, year-in and year-out, might produce this fatigue."

For the study, 109 women participated and were placed in one of two groups -- those who reported long-term fatigue and those who didn't. The women varied from being two months to two years after being treated for their disease.

Fatigue is a normal response to breast cancer treatments like chemotherapy and radiation therapy, but one-third or more of breast cancer survivors report continued debilitating fatigue long after treatment has ended.

After a short relaxation period, each woman had blood drawn to establish a baseline level for norepinephrine, a stress hormone that served as an indicator of activity by the sympathetic nervous system. Each participant had to give a five-minute speech before a two-person panel and then do a series of verbal arithmetic problems aimed at increasing stress levels. Additional blood samples were taken immediately after the stressor and then a half-hour later.

The norepinephrine levels rose as expected from the baseline in both groups after the stressful episode but the researchers were surprised to see something different. Regardless of the stressor, women who had persistent fatigue showed higher levels of norepinephrine than those who weren't fatigued.

"They had higher sympathetic activity and lower parasympathetic activity," Fagundes said, an indication that other researchers have suggested is a signal for inflammation.

The researchers also gauged another measure in the study, the natural variability in heart rate which decreases as a person ages. A lessened heart rate variability (HRV) is also an indicator of activity in the parasympathetic, or "resting," system.

"People who were fatigued had weaker parasympathetic activity than those who weren't," he said. "One of the things we know best is that exercise can enhance a person's HRV," Kiecolt-Glaser said. "Exercise is also the best documented treatment for fatigue, so this all begins to make sense.

"Fatigue isn't a symptom that should be ignored. It's a

marker for other things that might be going on," she said. Higher norepinephrine levels and lower HRV have been linked to high blood pressure, myocardial infarctions, strokes and diabetes.

"When a cancer patient reports persistent fatigue following treatment, it is something that deserves attention. It may be a symptom of other things that matter."

Working with Fagundes and Kiecolt-Glaser on the work were William Malarkey, Charles Shapiro, David Murray, Beom Seuk Hwang, Jean Philippe Gouin and Julian Thayer, all from Ohio State; and John Sollers from the University of Auckland.

The work was supported in part by the National Institutes of Health and the American Cancer Society.

Journal Reference: 1.Christopher P. Fagundes, David M. Murray, Beom Seuk Hwang, Jean-Philippe Gouin, Julian F. Thayer, John J. Sollers III, Charles L. Shapiro, William B. Malarkey, Janice K. Kiecolt-Glaser. Sympathetic and parasympathetic activity in cancer-related fatigue: More evidence for a physiological substrate in cancer survivors. *Psychoneuroendocrinology*, 2011; DOI: 10.1016/j.psyneuen.2011.02.005