ACE inhibitors may increase risk of recurrence in breast cancer survivors

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ACE inhibitors, commonly used to control high blood pressure and heart failure in women, may be associated with an increased risk of recurrence in women who have had breast cancer, according to a study by researchers at UCLA's Jonsson Comprehensive Cancer Center.

Beta blockers, used to control high blood pressure and cardiac arrhythmias, appear to have a protective effect, helping to prevent recurrence. When used together, beta blockers appear to help ameliorate the negative affect of ACE inhibitors, said Dr. Patricia Ganz, director of cancer prevention and control research at UCLA's Jonsson Cancer Center and first author of the study.

Ganz characterized the results of the retrospective analysis done using data from the Life After Cancer Epidemiology (LACE) study, which includes 1,779 Kaiser patients diagnosed with early stage breast cancer, as "hypothesis-generating only." She underscored that the results need further corroboration in other, larger clinical data bases.

However, the surprising negative effect of the ACE inhibitors on chances for recurrence is, at the least, cause for caution.

"The message from this is we have to be aware of other chronic health problems and medications that patients take after their diagnosis of breast cancer," said Ganz, an international expert in the fields of quality of life after cancer and cancer survivorship. "We are learning that some medications, while they may be very helpful for treating cardiovascular

disease and hypertension, may have an adverse effect on breast cancer survivors."

In the study, just published online in the journal *Breast Cancer Research and Treatment*, Ganz speculated that ACE inhibitors and beta blockers may work differently in the breast cancer microenvironment, affecting different pathways of inflammation, and that may be the key to their disparate impact on breast cancer recurrence.

It's long been thought that inflammation fuels cancer growth in humans. A September 2010 Jonsson Cancer Center study showed that chronic stress acts as a sort of fertilizer that feeds breast cancer progression through inflammatory signaling, significantly accelerating the spread of disease in mouse models.

The researchers discovered that stress was biologically reprogramming the immune cells trying to fight the cancer, transforming them from soldiers protecting the body against disease into aiders and abettors. The study found a 30-fold increase in cancer spread throughout the bodies of stressed mice compared to those that were not stressed.

The animal study provided a model that not only demonstrated that stress can speed up cancer progression, but also detailed the pathway used to change the biology of immune cells that inadvertently promote the spread of cancer to distant organs, where it is much harder to treat.

In addition to documenting the effects of stress on the spread of cancer, the researchers also were able to block those effects by treating stressed mice with beta blockers, which halted the nervous system's reprogramming of the metastasis-promoting immune cells, called macrophages. The findings from the animal model experiments formed the basis of Ganz's efforts to find a breast cancer patient sample in which to test whether exposure to beta blockers could reduce the risk of

breast cancer recurrence.

Working with investigators at Kaiser Permanente Northern California, Ganz examined the influence of beta blockers and ACE inhibitors on the risk for breast cancer recurrence in a large cohort of early stage breast cancer patients followed for an average of eight years, and for whom pharmacy data on the use of various medications was available. Information about cancer stage, treatments and other chronic conditions also was available.

Of the 1,779 women in the LACE study, 292 experienced a breast cancer recurrence. Ganz said 23 percent of the women in the study were exposed to either a beta blocker or an ACE inhibitor. The women taking these drugs were generally older, post-menopausal and had other health issues, such as being overweight and having hypertension or diabetes.

In analyses that controlled for these differences in health issues, Ganz found that women exposed to ACE inhibitors had a significantly increased risk for recurrence, while those on beta blockers alone had a lower risk of recurrence. Exposure to both beta blockers and ACE inhibitors had an intermediate risk for recurrence, suggesting that the beta blockers might modify the increased risk associated with ACE inhibitor therapy.

"The ACE inhibitor findings were not expected. These observations need to be confirmed and suggest that greater attention should be focused on the potential effect of these commonly used medications on recurrence and breast cancer survival," Ganz said.

In addition, along with Jonsson Cancer Center researchers Steve Cole and Erica Sloan, Ganz is examining the effects of ACE inhibitors in the mouse model system to develop a better understanding of what is happening at the tissue level.

Ganz said that understanding the biology of stress and inflammation at the cellular level is critical, as healthy lifestyle behaviors such as exercise and stress reduction techniques also may influence the same biological pathways in the tumor microenvironment. Those strategies might also be employed to help prevent recurrence.

"There is an increasing interest in the relationship between host lifestyle factors and the outcomes of cancer treatment," the study states. "Behavioral factors, comorbid conditions and non-cancer-related pharmaceutical exposures may affect breast cancer outcomes."

Ganz currently is working with researchers in Denmark and Canada to examine these same medications and their relationship to recurrence in much larger samples of breast cancer patients. She hopes to confirm the findings in this study within the next year to have a clearer picture of the effects of beta blockers and ACE inhibitors on the risk for recurrence. If beta blockers do prove to be protective in these additional studies, it may lead to prevention trials in women at high risk for recurrence, such as those treated for triple negative breast cancer, for which few effective therapies exist beyond chemotherapy.

"If giving beta blockers could help reduce risk of recurrence, that would increase the tools we have to fight this deadly form of breast cancer," Ganz said. "There is only so much that treating the cancer cells can do. Up until recently, there's been a lot of focus on the cancer cell, but we need to understand that these malignant cells live in a microenvironment of growth signals and fat cells, insulin and inflammation, and these things may affect the way they behave."

Ganz also is launching a Phase II randomized trial in younger women with breast cancer focusing on stress reduction with mindfulness meditation to evaluate its effects on stress, healthful behaviors and the immune system.

"Instead of focusing on the cancer cell, what I'm doing is looking at the host lifestyle factors and how amenable those are to modification in an effort to prevent recurrence," Ganz said. "These cancer cells are not living in isolation."

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