

Researchers identify biological markers that may indicate poor breast cancer prognosis

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A team of researchers has found an association between breast cancer survival and two proteins that, when present in the blood in high levels, are indicators of inflammation. Using data from the Health, Eating, Activity and Lifestyle (HEAL) study sponsored by the National Cancer Institute, part of the National Institutes of Health, the researchers found that breast cancer patients with elevated levels of C-reactive protein (CRP) and serum amyloid A (SAA) were approximately two to three times more likely to die sooner or have their cancer return than those patients who had lower levels of these proteins, regardless of the patient's age, tumor stage, race, body mass index, or history of previous cardiovascular issues. The results of this study were published online, May 26, 2009, in the *Journal of Clinical Oncology*.

Inflammation is an immune response. It is part of the body's natural defense against harmful elements, such as pathogens, damaged cells, or other irritants, and helps facilitate the healing process. Inflammation can be classified as either acute or chronic. Acute inflammation is the short-term, beneficial response to harmful stimuli. [Chronic inflammation](#) is a disease in which the inflammatory state persists and may result in tissue damage.

CRP and SAA accumulate in the blood in response to inflammation. CRP is produced by the liver, as well as by [fat cells](#), and has several immune-related functions. SAA, which is also secreted by the liver, is involved in both the transport of cholesterol from the liver to the bile, and the recruitment of immune cells to sites of inflammation. Both

proteins are found in higher concentrations in the blood of people with low-grade chronic inflammation. Chronic inflammation is believed to contribute to the development and spread of breast cancer, and breast cancer survivors with chronic inflammation may be at a higher risk of recurrence. Elevated CRP is also linked to increased risk of [heart disease](#).

"This HEAL study of inflammation and breast cancer survival contributes uniquely to this emerging research in that it is the largest study to date to examine this association," said Rachel Ballard-Barbash, M.D., M.P.H., a co-author of the study and principal investigator of the HEAL study at NCI, in the Division of Cancer Control and Population Sciences. "Because of the detailed data on diet, physical activity and weight in the HEAL study, we were able to examine the extent to which these health behaviors altered this association."

This study joins an increasing body of research identifying CRP and SAA as indicators of reduced survival from cancer. Previous studies have shown an association between elevated levels of CRP and poor survival outcomes in metastatic prostate cancer, as well as gastroesophageal, colorectal, inoperable non-small-cell lung, and pancreatic cancers. In other studies, a similar association was shown for SAA and gastric cancer and renal cell carcinoma. Although research has indicated that inflammation may play a role in the progression of cancer, the exact mechanism by which this happens has been unclear.

This is one of many papers to come out of NCI's HEAL study, an initiative designed to investigate the effects that physical activity, eating habits, weight patterns, diet, hormones, and other factors have on breast cancer prognosis. For this study, 1,183 women with early-stage breast cancer were recruited from three cancer centers, including the Fred Hutchinson Cancer Research Center in Seattle, the University of New Mexico, Albuquerque, and the University of Southern California, Los

Angeles. Participants completed a lifestyle questionnaire when they joined the study and the researchers collected blood samples (which were analyzed for CRP and SAA levels) and height and weight measurements at a subsequent visit two years later (approximately 2.5 years after their initial diagnosis). The women will be followed for a total of 10 years.

This is the first large, population-based study to look at the relationship between breast cancer survivorship and biomarkers of inflammation that were measured after treatment. Because the biomarkers were measured approximately 31 months after diagnosis, enough time had passed so that the researchers could accurately assess the effect of chronic inflammation, as opposed to acute inflammation that may have been a result of the breast cancer treatments each patient received.

The researchers examined the relationships between the inflammation biomarkers and both overall survival and disease-free survival. Overall survival was defined as the amount of time from the follow-up appointment until the patient died (from any cause) or the study period ended. Disease-free survival was defined as the amount of time from the follow-up appointment until the patient's breast cancer returned, another, new cancer was diagnosed, the patient died, or the study period ended. The researchers found that elevated levels of both SAA and CRP were associated (statistically significant) with reduced overall survival. Women with high levels of SAA were three times as likely to die sooner, and women with high levels of CRP were two times as likely to die sooner. They found similar, but weaker, associations with disease-free survival, in that women with high levels of SAA were two times as likely to die or have their cancer return, and women with high levels of CRP were more than 1.5 times as likely to die or have their cancer return. This suggests that SAA and CRP may be more closely related to overall survival than disease-free survival. More research is needed to get a better understanding of these associations and other potential mediating

factors, in order to create more precise risk estimates.

"Inflammation has been associated with several modifiable risk factors, such as obesity, low physical activity, and cardiovascular disease, all of which can affect a cancer survivor's prognosis," said Robert Croyle, Ph.D., director of NCI's Division of Cancer Control and Population Sciences. "Investigating the effect that reductions in these markers, through medications or lifestyle changes, can have on breast cancer recurrence and survival will be an important next step."

More information: Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, Baumgartner KB, Gilliland FD, Sorensen BE, McTieran A, Ulrich CM. Elevated Biomarkers of [Inflammation](#) Are Associated With Reduced Survival Among [Breast Cancer](#) Patients. Online May 26, 2009, *J Clin Oncol* 27.

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