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EDITORIAL

Chronic Inflammation and Breast Cancer Recurrence

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In this issue of *Journal of Clinical Oncology*, Pierce et al[1] present some of the most persuasive evidence yet that chronic inflammation might increase the risk of breast cancer recurrence. In a multisite study of 734 women treated successfully for early stage breast cancer, high levels of circulating acute phase proteins (APPs) approximately 3 years after treatment were associated with a two-fold elevation in the risk of subsequent disease recurrence and mortality. Risk ratios were similar across primary tumor types (including stage and estrogen-receptor and progesterone-receptor status) and independent of potential confounders such as age, estrogen level, and adiposity. These results are consistent with previous studies linking circulating inflammatory markers to progression of metastatic breast cancer.[2-8] However, the findings of Pierce et al are novel in suggesting that serum inflammatory markers might provide early information about disease recurrence risk in patients with no history of metastatic disease and no current evidence of cancer. If the present findings are replicated in larger cohorts with more recurrent cases, post-treatment APP monitoring could provide a new strategy for assessing the risk of breast cancer recurrence in seemingly cured patients.

As the evidence linking chronic inflammation to breast cancer progression grows, it becomes increasingly important to understand why this risk exists and what can be done to ameliorate it. Much research has suggested that the prognostic value of APPs stems from their role as stable markers of cumulative exposure to proinflammatory cytokines, principally interleukin-6 (IL-6).[9,10] The cytokine reporter interpretation of APP levels is consistent with a 2006 report[11] in *JCO* that linked total C-reactive protein (CRP) levels to breast cancer incidence, but found no relationship to noncytokine variation in CRP levels driven by polymorphisms in the *CRP* gene (similar to Mendelian randomization analyses of the role of CRP in cardiovascular disease[12]). The cytokine reporter interpretation is also consistent with several studies showing that high serum and tumor levels of IL-6 confer poor prognosis in breast cancer.[2,5-7,13] In contrast to *CRP*, upregulating polymorphisms in the *IL6* promoter have been linked to increased risk of breast cancer progression.[14,15] If the high APP levels observed by Pierce et al[1] emerged solely as a consequence of undetected tumor growth, they might still provide a useful indicator of sub-clinical disease recurrence. However, the existence of cytokine genetic influences on breast cancer progression and links between long-term nonsteroidal anti-inflammatory drug use and reduced breast cancer incidence[16,17] both suggest that the association observed in the study by Pierce et al could have stemmed at least in part from a causal influence of inflammation on breast cancer recurrence. Longitudinal analyses of APP levels in breast cancer survivors would provide additional information regarding the extent to which elevated plasma inflammatory markers reflect stable patient characteristics that causally influence disease recurrence as opposed to consequences of subclinical tumor development.

A growing body of laboratory research has shown that proinflammatory cytokines can facilitate tumor growth and metastasis by altering tumor cell biology and activating stromal cells in the tumor microenvironment, such as vascular endothelial cells, tumor-associated macrophages, and fibroblasts.[18-21] Systemic inflammation may also condition the vasculature in ways that enhance the extravasation, engraftment, and growth of micrometastases[18,21] or reactivate dormant tumors at distant sites.[22] The emerging role of inflammation in breast cancer progression is remarkable in light of the fact that primary breast tumors rarely in themselves involve significant inflammation. Markedly inflamed breast tumors are uncommon enough to warrant their own diagnostic category.[23,24] However, the biologic processes that drive metastasis or maintain residual disease during therapy may be quite different from those driving primary oncogenesis.[25] Under Paget's analogy,[25] chronic inflammation may fertilize the soil of systemic tissue in ways that promote dissemination and growth of metastatic seeds. Analyses comparing the location and molecular characteristics of primary and recurrent tumors could shed considerable light on the extent to which inflammation fosters disease recurrence by supporting regrowth of the primary tumor, development of its micrometastases, or emergence of entirely new malignancies.

What are the prospects for mitigating effects of systemic inflammation on breast cancer recurrence? Effects of cytokine gene polymorphisms on breast cancer progression[14,15] suggest that even partial reductions in inflammatory signaling could be protective if they were extended over long periods of time. Long-term nonsteroidal anti-inflammatory drug use has been linked to reduced risk of primary breast cancer,[16,17] but its effectiveness as an adjuvant therapy after successful treatment of early stage disease remains largely untested. It is clear that tamoxifen reduces APP levels,[26-28] raising the possibility that some protective effects of endocrine therapy might stem from their anti-inflammatory actions. Long-term use of other anti-inflammatory agents such as glucocorticoids, cytokine antagonists, and cyclooxygenase-2 inhibitors is associated with adverse effects that would likely limit their role in adjuvant prevention. Perhaps the most salutary approach would target the upstream factors that drive chronic inflammation, including adiposity and physical inactivity.[9,29] In analyses controlling for age, adiposity, and self-reported physical activity, Pierce et al[1] continued to find that residual variation

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in APP levels predicted breast cancer recurrence. This does not imply that adiposity and physical activity are unimportant, but it does suggest that other influences on chronic inflammation such as sub-clinical infections, smoking, heavy alcohol consumption, major depression, and low socioeconomic status[9,12,29-31] might also affect the risk of breast cancer recurrence. Mitigating such effects through lifestyle change is a daunting challenge for both patients and clinicians, but it is one that many breast cancer survivors might undertake if they appreciated its potential for preventing breast cancer recurrence and the development of other cancers and cardiovascular disease.[32] The observation of Pierce et al[1] that disease recurrence was significantly elevated only in the upper tertile of APP distribution implies that a subset of patients could potentially be targeted with resource-intensive lifestyle interventions on the basis of inflammatory biomarkers of disease risk.

Regardless of the specific remedial approach, the present findings of Pierce et al[1] underscore the need to address the broader environment of a patient's global health and behavior as influences on localized neoplastic disease and the resurgence of clinically latent breast cancer. In taking a systemic approach to the control of minimal residual disease, there may yet be new opportunities to reduce the risk of relapse after successful treatment for early stage breast cancer.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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