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Chronic inflammation and breast cancer recurrence

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On page #### of this issue, Pierce and colleagues [1] present some of the most persuasive evidence yet that chronic inflammation might increase the risk of breast cancer recurrence. In a multi-site study of 734 women treated successfully for early stage breast cancer, high levels of circulating acute phase proteins (APPs) ~3 years after treatment were associated with a 2-fold elevation in the risk of subsequent disease recurrence and mortality. Risk ratios were similar across primary tumor types (stage, ER/PR 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 new a strategy for assessing the risk of breast cancer recurrence in apparently 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 suggests that the prognostic value of APPs stems from their role as stable markers of cumulative exposure to pro-inflammatory cytokines, principally IL-6 [9, 10]. The “cytokine reporter” interpretation of APP levels is consistent with a 2006 *Journal of Clinical Oncology* report linking total C-reactive protein (CRP) levels to breast cancer incidence, but finding no relationship to “non-cytokine” variation in CRP levels driven by polymorphisms in the *CRP* gene [11] (similar to Mendelian randomization analyses of CRP’s role 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*, up-regulating 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. 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 NSAID use and reduced breast cancer incidence [16, 17] both suggest that the association observed in the present study could stem at least in part from a causal

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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 host characteristics that causally influence disease recurrence as opposed to consequences of sub-clinical tumor development.

A growing body of laboratory research has shown that pro-inflammatory 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 so uncommon as to warrant their own diagnostic category [23, 24]. However, the biological processes that drive metastasis or maintain residual disease during therapy may be very 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 re-growth of the primary tumor, development of its micrometastases, or the 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 extend over long periods of time. Long-term NSAID use has been linked to reduced risk of primary breast cancer [16, 17], but its effectiveness as an adjuvant therapy following successful therapy 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 COX2 inhibitors are 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 and colleagues continued to find that residual variation in APP levels predicted breast cancer recurrence. That 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 socio-economic status [9, 12, 29–31] might also influence the risk of breast cancer recurrence. Mitigating such effects through lifestyle change is a daunting challenge for both patients and clinicians, but one that many breast cancer survivors might undertake if they appreciate its potential for preventing breast cancer recurrence and the development of other cancers and cardiovascular disease [32]. Pierce et al.'s observation that disease recurrence was significantly elevated only in the upper tertile of the APP distribution

implies that resource-intensive lifestyle interventions could potentially be targeted to a subset of patients based on inflammatory biomarkers of disease risk.

Regardless of the specific remedial approach, the present findings underscore the need to address the broader environment of a patient's global health and behavior as an influence on localized neoplastic disease and the resurgence of clinically latent breast cancer. By taking a systemic approach to the control of minimal residual disease, there may yet be new opportunities to reduce the risk of relapse following successful treatment for early-stage breast cancer.

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