Minimal Residual Disease in Breast Cancer: In Blood Veritas

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In this issue of Clinical Cancer Research, Beaver and colleagues studied plasma tumor DNA (ptDNA) to detect PIK3CA mutations in early-stage breast cancer patients’ circulation (1). Fragmented DNA is found in the circulation within the cell-free component of whole blood. In the field of oncology, studies of cell-free DNA derived from tumors, usually termed circulating tumor DNA (ctDNA) or ptDNA, have flourished in the recent years (2). Notably, however, clinically relevant applications for ptDNA have yet to emerge. This is because most reports have been descriptive, based on retrospective analyses, and often did not tackle questions of immediate clinical applicability.

The study by Beaver and colleagues (1) represents a significant step forward. The authors performed a ptDNA prospective analysis to begin addressing a clinically relevant issue: whether plasma-derived tumor DNA can be used to monitor residual disease after surgery in patients with early-stage breast cancer. The question is significant as reliable methods for detecting residual disease after surgery are presently not available for solid tumors such as breast or colorectal cancers. As a result, oncologists typically prescribe adjuvant therapy to the majority of patients even though the disease is confined to the breast and/or extend locally into the axillary lymph nodes. Unfortunately, nearly 30% of women are diagnosed at an early stage, when neoplastic cells are thought to be confined to the breast and/or extend locally into the axillary lymph nodes. Unfortunately, nearly 30% of women with localized disease and 75% of women with nodal...
involvement eventually relapse, most likely due to undetectable micro-metastases (10). Accordingly, additional treatments are administered after surgery to eradicate the undetectable residual cancer cells. Subsequent adjuvant treatments typically involve radiotherapy and/or chemotherapy that can be associated with localized or systemic toxicity (11).

As stated above, a large proportion of women with early-stage breast cancer will never relapse and do not need adjuvant treatment and its consequent side effects. Distinguishing those patients who can be spared from chemotherapy is, therefore, central. To tackle this, hundreds of randomized clinical trials have been performed (3, 12). Despite these efforts, reliable methods to detect microscopic residual disease after surgery remain undefined. Accordingly, oncologists will typically recommend adjuvant therapy to the vast majority of women to benefit relatively few. In this regard, if confirmed in large prospective studies, the approach described in this issue of *Clinical Cancer Research* could transform clinical practice.

Although data from Beaver and colleagues are clearly inspiring, the present report remains, in essence, a “feasibility” study limited by the low number of cases and the relatively short follow-up period. Considering the conceivable clinical impact of the approach, there is no question this work will lead to follow-up analyses in large cohorts of patients. In some instances, such as women with estrogen receptor/progesterone receptor (ER/PR)–positive breast cancer, which typically relapses many years after surgery, studies assessing whether liquid biopsies predict recurrence will require decades to complete. In addition, *PIK3CA* mutations are found in less than 40% of patients with breast cancer. To perform far-reaching longitudinal studies, blood-based markers capable of capturing the entire patient population must be developed. This issue should be fairly easy to address, for example, by tracking *TP53* mutations.
that are prevalent in this tumor type. HER2 amplification could also prove valuable in 10% patients and ddPCR technique has already shown some promising results (13). Alternatively, one can envision the identification of patient-specific genetic markers such as translocation events, which are known to occur in nearly every solid tumor (6).

Even with these limitations, the present study is noteworthy as it sets the stage for the use of ptDNA detection for minimal residual disease in solid cancers. It may well be possible that in 5 to 10 years oncologists will recommend liquid biopsies as a routine test for patients with solid cancers such as those of breast, colorectal, prostate, or lung origin. The results could be used to individualize decisions about adjuvant systemic therapies and to recommend surveillance of patients at high risk for recurrence.

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No potential conflicts of interest were disclosed.

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Conception and design: A. Bardelli
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References
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