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Biomarker-Based Early Cancer Detection: Is It Achievable?

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Abstract

A new mathematical model evaluates the power of blood-based biomarkers for early cancer detection

For cancer patients, time is a matter of life and death: Those whose tumors are detected at an early stage generally fare better than do those with advanced cancers, who often succumb to death from metastatic disease. This grave realization has generated major advances in the area of molecular diagnostics and in our ability to screen tissue or blood samples for tumor-specific genomic, proteomic, and epigenetic signatures, which in turn has fueled the search for biomarkers that can detect the presence of tumors early in their development. General adoption of these tests for population screening requires that the assays are accurate, relatively inexpensive, noninvasive, and provide sufficient lead-time—that is, the test detects the tumor well before symptoms develop to allow for effective intervention, thus improving disease outcome and survival. Naturally, considerations of expense and noninvasiveness have focused attention on biomarkers in blood, urine, or other bodily fluids. However, despite recent strides the question remains: Can tumor by-products that are diluted in blood or other bodily fluids really provide the diagnostic accuracy and lead-time required for clinically meaningful early cancer detection? In this week's issue of *Science Translational Medicine*, Hori and Gambhir describe a new model that addresses this crucial question (1).

The hope among patients, clinicians, and scientists alike is that widespread use of biomarkers for early tumor detection will lead to significant reductions in cancer mortality. Unfortunately, this aspiration has been slow to materialize. A number of blood-based biomarkers are already in clinical use for prognosis, response to therapy, and to assess cancer progression, but few blood-based biomarkers or biomarker combinations display high enough sensitivity (ability to detect cancer) and specificity (ability to avoid false positives) to be useful as population screens for early detection of cancer. Thus, few candidate biomarkers have been validated clinically or tested in the context of population-based screening.

To be effective for early cancer detection, biomarkers must provide authentic clinical benefits after accounting for overdiagnosis—the diagnosis of a disease that in fact would not give rise to symptoms or cause death—and lead-time bias—which may occur when a new test provides an earlier diagnosis than was previously possible but does not lead to a prolonging of a patient's life. The prostate-specific antigen (PSA) screening test is a case in point. Although widely used in the United States and Europe for prostate cancer screening, the United States Preventative Services Task Force (USPSTF) recently published draft

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recommendations against the test's use, suggesting that the test offers no benefit or that the harms outweigh the benefits (2). This apparent lack of progress begs the question: Why have scientists not identified biomarkers capable of detecting cancers at an early stage with adequate sensitivity and specificity? Where is the bottleneck?

To explore the basis of the current limitations, Hori and Gambhir used mathematical modeling to identify important mechanistic determinants of blood-based biomarker detection. Modeling in this context allows the systematic exploration of the consequences of specific assumptions about biomarker secretion (both by the tumor and normal tissues), transport into the vasculature, degradation, excretion/clearance, and ultimate detection by the assay. This model can therefore be considered a tool for assessing the dynamic plasma-biomarker kinetics in relation to the genesis of cancer, beginning with a single parental tumor cell, through its clonal expansion, to the tumor's earliest possible detection with a biomarker assay—a best-case scenario. Furthermore, sensitivity analyses of the model, which the authors carry out for the ovarian tumor marker protein cancer antigen 125 (CA125), allow the identification of biomarker-associated parameters that significantly affect the probability for early detection and how such parameters would need to be optimized in order to improve cancer detection.

As a simple benchmark, the authors considered “the minimum period of time a growing tumor cell population would need to proliferate before being detectable by blood-based assays.” This minimum time was also expressed in terms of tumor diameter or approximate tumor volume (caliper size³). For most solid cancers, diagnosis occurs at a diameter of several centimeters or more (Fig. 1).

Although tumor size in itself is not a perfect predictor of clinical outcome, there is evidence that small tumors may sojourn several years before they give rise to subclones with metastatic potential (3). Remarkably, for the case of ovarian cancer and CA125 Hori and Gambhir (1) estimated minimum tumor sojourn times (that is, the time it takes for a tumor to reach the detection size threshold) of 8.8 to 10.6 years. In their best-case scenario, in which normal tissue does not release, or shed, the selected biomarker into the blood, the model predicted that a tumor will grow to a diameter of 0.85 cm before a blood biomarker would be detectable. The 0.85-cm value constitutes a fivefold improvement compared with the mean diameter of 4.2 cm for clinical diagnosis of ovarian cancer by using pelvic ultrasound. However, this improvement is inadequate if the goal is to detect a tumor at the sub-millimeter level, as Hori and Gambhir suggest.

These results give reason to pause and reevaluate the targets for early cancer detection. A fivefold decrease in tumor diameter represents a 125-fold decrease in volume, which eliminates almost seven tumor doublings. This provides a 2.3-year lead-time advantage, assuming a mean tumor doubling time of 120 days (4). Although a lead-time increase of 2.3 years may be considered too little, ovarian tumors that are less than 1 cm in diameter are most likely early-stage tumors and thus should be highly treatable, if not curable (5). Indeed, a small percentage of ovarian cancers are found at an early stage when they are small and still confined to the ovaries, and cure rates approach 90% (5). Unfortunately, for ovarian cancer most deaths arise from serous carcinomas in stage III and IV, which are rarely detected at an early stage and may represent a refractory target for early detection. Still, the goal of Hori and Gambhir to push detection to the sub-millimeter range may be setting the bar too high. However, assuming the goal for early cancer detection is to catch tumors in the sub-millimeter range, Hori and Gambhir calculate that a 10,000-fold increase in CA125 shedding would be required to achieve this goal. Even if the uncertainty in model structure and its parameters were to bias the predictions toward diminished sensitivity, the gap

between the predicted threshold values of current protein-based assays (represented by CA125) and what the authors aim for (sub-millimeter tumor sizes) remains huge.

Whether one sets a higher or lower bar for the minimum size for early tumor detection, there appears to be a gap between current biomarker detection scores and desirable lead-times for early cancer detection. This gap may be closed by a variety of biological effects that Hori and Gambhir allude to but do not consider explicitly in their model. For example, tumor growth is both stochastic and highly heterogeneous, reflecting differences in the evolution of distinct tumors (Fig. 1). Stochastic cancer growth may include extensive cell turnover through nearly compensatory cell division and death (apoptosis), which may lead to much higher effective biomarker shedding than assumed by a deterministic cancer model that does not explicitly consider the tumor cell kinetics, including cell death. Moreover, an immune response to the tumor may result in detectable host-associated biomarkers that are amplified by an adaptive immune response. Although these considerations are somewhat hypothetical, recent research involving tumor-specific microRNAs and mitochondrial DNA signatures is showing promising results. Both are likely shed in greater numbers into the blood stream than are protein-based markers (6). It would be interesting to see extensions of the Hori-Gambhir model that encompass these nonproteomic markers and a comparison of alternative approaches for early cancer detection.

Despite its limitations, the model by Hori and Gambhir is consistent with recent studies of several ovarian cancer biomarkers, including CA125, that show only modest lead-time gains (~1 year) for ovarian cancers (7). Although CA125 and other candidates tested cannot be praised as early detection markers—they lack sensitivity in screening asymptomatic patients—CA125 is widely used to monitor ovarian cancer recurrence.

With an increasing number of tumor-specific biomarkers in the pipeline for clinical validation and improvements in molecular diagnostics, steady progress can be expected. For example, a recent report by Taguchi *et al.* (8) demonstrates specific lung-cancer signatures in plasma that discriminate between non-small-cell lung carcinoma (NSCLC) and SCLC on the basis of proteome profiling in various genetic mouse models that develop lung tumors. Although these signatures have been validated only in retrospective human studies, their test performance characteristics are impressive, and their utility for early detection is promising.

Full validation and evaluation of a biomarker (or biomarker panel) requires a sequence of difficult and time-consuming steps or phases. Five phases have been defined by Pepe *et al.* (9): (i) biomarker discovery, (ii) development of assays that are reproducible within and between laboratories, (iii) detection of preclinical disease by using markers collected longitudinally from research patient cohorts, (iv) prospective screening in large populations, and (v) large-scale population studies. The U.S. National Cancer Institute (NCI) supports this phased approach and in the year 2000 created the Early Detection Research Network (EDRN), a collaborative group focused on the discovery and development of early-detection biomarkers and markers for cancer risk. The most recent (2008) report from EDRN describes over 120 biomarkers in development, alone and in combination, with 27 in phase-2 and 5 in phase-3 development (10). Recently, the Cancer Surveillance and Information Network (CISNET) (11), a group of cancer-control modelers funded by NCI, has begun a collaborative effort with EDRN to incorporate biomarkers into CISNET cancer models. In this context, the model by Hori and Gambhir is a laudable early step, which promises to stimulate the development of predictive models that facilitate the evaluation and cost-benefit analysis of biomarker-based early detection and curative interventions and their impact on reducing cancer mortality.

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Fig. 1. Good and bad timing

The lead-time for early detection of cancer using a blood biomarker depends on the growth trajectory of the cancer. An aggressive cancer (light blue dotted and solid lines) may have a short lead-time for biomarker detection, whereas a slower progressing cancer (dark blue dotted and solid lines) may have a much longer lead-time. In either case, the biomarker lead-time expands (see yellow arrows) if the threshold for biomarker diagnosis is decreased (purple arrow).