

Is Early Detection of Cancer with Circulating Biomarkers Feasible?

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Early cancer detection before metastasis in asymptomatic patients is one of the primary objectives of cancer research initiatives. Early detection generally means more opportunities for intervention that ultimately lead to improvement in patient outcomes. Many studies have concluded that early detection of breast cancer in women older than 50 years with mammogram screening programs improves survival by 20%–25% (1). Patients with stage I ovarian cancer detected by transvaginal ultrasound (approximately 42-mm mean tumor diameter) have a 5-year survival rate of 93%, compared with 30% for patients with stage III to stage IV disease at diagnosis (2).

Many blood-based biomarker tests are routinely used in clinical practice for cancer surveillance, therapy monitoring, prognosis, and risk stratification. Most experts, however, would agree that there are no blood-based biomarkers suitable for population screening or early diagnosis of cancer, despite the considerable intellectual and financial efforts worldwide. The majority of potential biomarkers fail the initial phases of the biomarker evaluation process and never make it to the clinic (3).

The list of requirements for a circulating-biomarker test for early cancer detection is lengthy (4). The test must have adequate diagnostic sensitivity and specificity. In addition, the test must be inexpensive and safe if it is to be applied to mass populations. Other important criteria include analytic reproducibility and sufficient lead time. Lead time is defined as the time between asymptomatic cancer still localized to the organ of origin and clinical diagnosis. Aggressive cancers have shorter lead times than indolent cancers.

Ultimately, the utility of a circulating-biomarker test for early cancer detection depends on the evidence that its benefits, such as patient survival, outweigh its

harms, such as overdiagnosis and lead time bias. Overdiagnosis is often followed by overtreatments that themselves can have serious consequences with respect to patients' health. Lead time bias indicates that early diagnosis does not necessarily affect survival. Prostate-specific antigen is an example of a biomarker whose screening utility in prostate cancer is still hotly debated for those reasons.

Hori and Gambhir used mathematical modeling in a recently published study to address the crucial question of the feasibility of using circulating biomarkers for early detection of cancer (5).

Their first objective was to use mathematical modeling to quantify the smallest tumor diameter that could be detected by currently available biomarker tests. The second and more important objective was to identify biomarker-related parameters that affect early cancer detection and to quantify through simulations how much each parameter has to be adjusted (increased or decreased) to improve it. The authors chose a solid tumor diameter of 1 mm as the goal for early detection. Tumor biomarker-related parameters that were tested in the model were: rate of tumor biomarker secretion/shedding into the vasculature, its transport into the vasculature, clearance and excretion, percentage of the tumor volume consisting of tumor cells, and analytical sensitivity of clinically available biomarker tests.

The model was designed to predict changes in the blood biomarker as a function of time and to relate them to the corresponding tumor diameter or volume. The concentration of a blood biomarker with respect to time is a function of the difference between the rate of biomarker entry into the circulation and the rate of its elimination from the circulation. The rate of biomarker entry into the circulation is determined by (a) the fraction of the total biomarker that is secreted by the tumor and enters the circulation, (b) the rate of biomarker shedding, and (c) the number of biomarker-secreting tumor cells.

Two growth models were used in the study. The first was represented by a monoexponential growth equation that assumed strictly increasing tumor growth starting from tumor genesis at time zero. The second model was represented by a Gompertzian equation that assumed monoexponential growth as well as tumor decay. For each growth model, the authors

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tested 2 scenarios. In one scenario a biomarker was 100% tumor specific; in the other, a biomarker was secreted by both tumor and normal cells.

Ovarian cancer growth-related and cancer antigen 125 (CA-125)-related parameters from the published literature were used to “prime the model,” thereby establishing the “baseline parameters” for the earliest detection time or the smallest tumor diameter or volume that could be detected by current CA-125 ELISA assays. This exercise was designed to assess the performance of current clinical biomarker assays and, more importantly, to provide realistic baseline values for subsequent model simulations.

In model simulations, the authors asked how much each tumor-associated parameter had to change to improve ovarian cancer detection from the current range of 10.5–40 mm in diameter to a diameter of ≤ 1 mm. The simulation results clearly showed that a 1-mm tumor detection goal is achievable only by substantially increasing the rate of tumor shedding, by finding a biomarker that is almost 100% tumor specific, or by improving the analytical sensitivity of clinical assays. Manipulation of other tumor biomarker-associated parameters—including the fraction of the shed biomarker entering the circulation, the rate of biomarker elimination from the circulation, and the percentage of biomarker-producing cells that make up the tumor volume—improved early detection but was not able to achieve the 1-mm detection goal.

Overall, the findings of this study reinforced what basic scientists and clinicians have known for a while, that identification of an effective circulating biomarker for early cancer detection is not an easy feat. Provided that the current and future versions of the model are freely available to the cancer research community worldwide, such modeling could be used to identify and quantify parameters of cancer biomarkers that are the most likely to improve early cancer detection. This information can help researchers identify criteria for prioritizing biomarkers and can guide investment strategies. Furthermore, mathematical models like this one can be used to perform simulations quickly across a wide range of many biomarker-related parameters. Such simulations would encompass the large between-person biomarker heterogeneity that might exist for the same type of cancer and would make the model generalizable for any solid cancer that secretes a biomarker into the circulation. With the model as currently implemented, only 1- or 2-way sensitivity analyses appear possible, meaning that quantities of only 1 or 2 biomarker-related parameters can be manipulated at a time. Future versions should include simultaneous simulations of multiple parameters. Although the CA-125 biomarker tested in this model is a protein, in prin-

ciple any type of measurable biomarker, such as micro-RNA, epigenetic modifications, or posttranslational modifications, could be used.

The model’s predictive power is limited by the assumptions it uses in the calculations. One assumption is that the biomarker is shed at a constant rate. Furthermore, the rate of CA-125 shedding is obtained from cell culture experiments and therefore may not represent changes in the amount of biomarker shed per tumor cell over time. Future versions of the model may incorporate nonlinear shedding rates. The model also assumes that the fraction of biomarker entering the blood is constant over time. The amount of biomarker entering the blood may change as a function of tumor size, angiogenesis, or necrosis. Nevertheless, one cannot be too critical of the assumptions the model uses. The lack of comprehensive biological and clinical data forces the authors to make these assumptions. The model uses many CA-125-associated parameters from the literature but is forced to make some assumptions to fill in the blanks. New discoveries and improved understanding of solid cancer development and progression will help improve future versions of this model.

The authors’ claim that the model is generalizable to any solid cancer can be challenged at this time. To back up this claim requires that the model be tested on types of solid tumors besides ovarian cancer. That may prove difficult, however, because tumor biomarker-associated parameters used by this model may be known only partially or not known for most other types of solid cancers.

The results of this study indicate that it may not be feasible to use a single circulating tumor biomarker for early cancer detection. According to the model, to detect a tumor with a diameter of ≤ 1 mm requires the biomarker to be almost 100% tumor specific, a shedding rate 10^4 -fold higher than that of any other known protein tumor biomarker, and further improvement in the analytical sensitivity of current clinical assays by 10^4 -fold. It is difficult to imagine how that could be achievable any time soon.

On the other hand, a target of 1 mm for early detection may not be applicable or even necessary for every type of solid cancer. The 1-mm target may be more appropriate for detection of an aggressive tumor with a short doubling time than for an indolent tumor with a long doubling time. Furthermore, a small improvement in early detection will affect the lead time of indolent tumors more appreciably than that of aggressive tumors. It seems that the goals for early cancer detection still need to be debated and that they clearly depend on the type of solid cancer and its aggressiveness.

So, what does the future hold for circulating biomarkers for early cancer detection? We have not been

very successful thus far, but we should not give up yet. We need to keep growing our knowledge of the natural history of cancer development and progression through continued research. This knowledge will allow us to develop powerful mathematical models with accurate predictive capabilities that can help select biomarkers with the characteristics necessary to improve early detection. There is plenty of room to improve the sensitivity of biomarker assays through technological advancements. In addition, there is the possibility of combining panels of circulating biomarkers with new imaging procedures to improve early cancer detection. Even if we succeed in this endeavor, however, we still need to prove for every cancer—without overdiagnosis and overtreatment—that early detection of cancer improves patient outcomes (such as survival).

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