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BIOMARKERS

Major mathematical hurdles for biomarker-based screening

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A new mathematical model suggests that the successful use of blood-based biomarkers for the early detection of premalignant tumours might require methodological improvements of unanticipated magnitude.

Because the changes in blood-based biomarker concentrations during tumour growth are poorly defined from clinical data, the point during tumour progression at which biomarker screening can become diagnostically useful is unclear. To investigate further, Hori and Gambhir mathematically modelled the combined shedding of biomarkers into the blood from normal and tumour tissues during tumour progression. Their model assumes a constant rate of shedding from normal tissues, with shedding from a tumour increasing as a function of tumour cell number.

Although potentially applicable to any biomarker or tumour type, the authors used their model to investigate CA125 shedding by ovarian tumours. The effectiveness of this biomarker is currently under debate because increased levels of CA125 in the blood do not reliably correlate with the presence of ovarian tumours. The authors used clinically reported parameters, such as the rate of ovarian tumour growth, the rates of CA125 shedding by tumour and normal cells, and the detection sensitivity of a clinical CA125 assay. According to the model, ovarian tumours would need to be ~25 mm in diameter before they could be diagnosed, which corresponds to 10.1–12.6 years of growth from the first transformed cell. These calculations suggest that we are far from being able to detect early, microscopic lesions using this biomarker.

A major application of this model is to predict how extensively the different biological and technological parameters must change to allow a meaningful diagnostic improvement. Shedding of CA125 from putative tumour sites can potentially be enhanced by ultrasound, but the model indicated that even a tenfold increase in the shedding rate would only reduce the diagnostic time point from 10.1 years to 9.0 years of tumour growth.

Finally, when dissecting the parameters that are required to detect a sub-millimetre lesion, a biomarker would need to be secreted exclusively by tumour cells and would require an increase in the shedding rate or assay detection limit to the order of 1,000-fold over current values. However, these challenges might not be insurmountable; for example, the required improvements in assay sensitivities are potentially achievable by emerging nanosensor technologies.

It will be interesting to see whether further data from clinical or animal studies back up the proposed tumour size thresholds for biomarker-based screening, and if the models can be improved by accounting for the heterogeneity and the dynamic behaviour of tumours.

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ORIGINAL RESEARCH PAPER Hori, S. S. & Gambhir, S. S. Mathematical model identifies blood biomarker-based early cancer detection strategies and limitations. *Sci. Transl Med.* **3**, 109ra116 (2011)