Genomic analysis of primary tumors does not address the prevalence of metastatic cells in the population

Ramaswamy *et al.*[1] compared gene expression profiles of adenocarcinoma metastases to unmatched primary adenocarcinomas. They found an expression pattern that distinguished primary tumors from metastases but also reported that a subset of primary tumors had the expression pattern of metastases. This finding led them to challenge "the notion that metastases arise from rare cells within the primary tumor"[1]. In fact, their finding provides no evidence to contradict this notion.

To produce a metastasis, a tumor cell must complete a series of sequential steps, including detachment, invasion, survival in the circulation, attachment, extravasation, proliferation, induction of neovasculature and evasion of host defenses[2]. Because metastases are largely clonal in origin[3–5], the successful metastatic cell must have a set of characteristics that enable it to complete each step in the sequence. Lack of any single characteristic derails the process and prevents the cell from developing into a metastasis. Thus, the successful metastatic cell has been likened to a decathlon champion, who must be proficient in all ten events, not just a few, to be successful[2]. A primary tumor may contain many different cells, each of which can complete some of the steps in the metastatic process but not all. In aggregate, all of the steps may be represented among cells of the primary tumor, but it may still be the rare cell that can complete all the steps and thus give rise to a metastasis. The study by Ramaswamy *et al.*[1] looked at primary tumors in aggregate and, therefore, cannot rule out this possibility. The authors seem to have overlooked the large body of evidence indicating that primary tumors are heterogeneous with respect to many characteristics, including those associated with metastasis[2,6,7]. One example came from our work in which we found, by cloning, that unselected tumor cell lines with low metastatic potential contained a small number of cells with high metastatic potential, as well as many non-metastatic cells[3]. More recently, *in situ* hybridization was used to detect the expression of genes associated with the metastatic phenotype, specifically, those encoding MMP-2, MMP-9 and E-cadherin[8–10]. This approach allows not only the detection of gene expression but also its visualization in the tumor. These studies showed that expression of these three genes varied independently between the peripheral and central zones of the tumor and among other regions in a single section of the tumor. It stands to reason that the more cells express such genes, the higher the likelihood will be that the tumor will eventually give rise to metastases, a correlation substantiated in retrospective studies[9,10]. The findings of Ramaswamy *et al.*[1] using a genomics approach are consistent with those using *in situ* hybridization but have the added advantage of being able to identify previously unknown genes involved in the metastatic process.

Much evidence supports the view that progression from a benign to a malignant tumor is associated with acquisition of a set of genetic and epigenetic alterations that provide the phenotypic characteristics of malignancy[11–13]. These changes accumulate at different rates in different tumors and are reflected, albeit imperfectly, in the pathologist's classification of tumor stages. The stage I and II lung adenocarcinomas and early breast cancers studied by Ramaswamy *et al.*[1] generally expressed the non-metastatic pattern of genes, and only a few expressed the metastatic pattern. This probably reflects the fact that some of these primary tumors have indeed generated unique cells with full metastatic capabilities, as indicated by the patient survival data. The true significance of the study of Ramaswamy *et al.*[1] is not that it runs contrary to popular dogma, which, in our opinion, it does not, but that it may enable the identification of the small subset of tumors designated as early stage by pathologic criteria that nonetheless have already released a few metastatic cells. Thus, the study constitutes an important step in the quest to predict the behavior of tumors detected at an early stage, even though it does not address the prevalence of fully metastatic cells in primary tumors.

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Genetic background is an important determinant of metastatic potential

Recently there has been some debate about the etiology of cancer metastatic potential. Using microarray gene expression patterns of breast carcinomas, van't Veer *et al.*[1] reported that a set of 117 genes predicted metastatic potential. More recently, a small set of 17 genes was reported to predict metastatic potential for a variety of solid tumors[2]. These findings suggest that most primary tumor cells express a 'metastasis signature', in contrast to the classic model, which predicts that only a rare subpopulation of primary tumor cells have accumulated the numerous alterations required for metastasis. Based on this evidence, Bernards and Weinberg[3] recently posited that combinations of early oncogenic alterations, not specific events that promote metastasis, determine metastatic potential. This hypothesis might explain why metastasis occurs in some individuals with small, localized tumors (that is, tumors whose