

Title

Circulating Ensembles of Tumor Associated Cells are Ubiquitous in Breast, Ovarian and Cervical Cancers and Atypical in Asymptomatic Individuals.

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Abstract*Background*

Screening modalities for breast, ovarian and cervical cancers include mammography, CA125 and PAP smears, respectively, which are not confirmatory and necessitate a follow up invasive biopsy for confirmation of malignancy. Additionally, mammography is associated with false positives, CA125 tends to be elevated in non-malignant conditions and PAP smears are associated with risks of false negatives. A non-invasive blood-based test with high specificity and sensitivity is an unmet medical need. Considering that unprovoked thromboembolism is a significant risk in multiple cancers, we hypothesized that circulating thrombotic emboli in peripheral blood could comprise cancer cells and would serve as a reliable biomarker for detection of cancers.

Methods

We obtained 15 ml of blood from 8672 females, out of whom 1344 had a confirmed diagnosis of Ca Breast, 285 had a confirmed diagnosis of Ca Ovary, 316 had a confirmed diagnosis of Ca Cervix and 6727 were asymptomatic individuals with age related elevated risk who underwent bilateral mammography, PAP smear and evaluation of serum CA125. Peripheral blood mononuclear cells (PBMC) were isolated by centrifugation and treated with commercially available stabilizing agents in a proprietary process that enriched apoptosis resistant clusters of tumor associated cells which were immunostained for EpCAM, PanCK and CD45. C-ETACs (Circulating Ensembles of Tumor Associated Cells) were defined as clusters of 3 or more cells which were positive for EpCAM and CK, irrespective of CD45 status.

Results

C-ETACs were detected in 89.1% of breast cancers, 90.5% of ovarian cancers and 89.9 % of cervical cancers respectively. Among the asymptomatic females, C-ETACs were detected in 3 (10.3%) out of 29 who had suspicious findings on PAP smear, 3 (5.56%) out of 54 who had elevated CA125 and 22 (7.5%) out of 292 who had abnormal findings on mammography (BIRADS $\geq$ 2). C-ETACs were detected in ~3.5% of the asymptomatic individuals who had no abnormal findings in any of the screening investigations.

Conclusions

C-ETACs were ubiquitously detected in cancers of Breast, Ovary and Cervix and pose significant latent risk of thromboembolism and metastasis/recurrence. The relative undetectability of C-ETACs in the asymptomatic cohort indicates causative connection with malignancies.