Breast Cancer Cell-free DNA (cfDNA) Profiles Reflect Underlying Tumor Biology: The Circulating Cell-free Genome Atlas (CCGA) Study

**BACKGROUND**

- Breast cancer is the leading cause of death among women in the United States.
- Approximately 250,000 women were diagnosed with breast cancer in 2018.
- New breast screening approaches are needed to detect breast cancer early, when the prognosis is better.
- Mammography is the main screening paradigm/standard-of-care.
- Mammography is problematic in women with dense breasts, has a high rate of false positives, and can result in overdiagnosis.
- Approximately 40,000 women die each year from breast cancer in the U.S.

**METHODS**

- The Circulating Cell-free DNA Atlas (CCGA) Study is a cohort of 12,292 women.
- Controls were recruited from 10 institutions.
- Participants were included based on age, family history of breast cancer, and medical status.
- Blood samples were collected from all participants.
- Clinical N staging was utilized.

**RESULTS**

- The majority (82%) of samples from participants with cancer were stage I/II.
- Participants with breast cancer and control participants were comparable in terms of race and ethnicity and age at diagnosis.
- Assay data was available for 845 cancers (878 participants with stage information).
- The majority of participants (60%) had clinically diagnosed breast cancers.
- Sensitivity was estimated at 98% specificity after accounting for clonal hematopoiesis.
- Sensitivity was also higher in breast cancers detected via clinical presentation vs detected via screening.

**CONCLUSIONS**

- Breast cancers with detectable cfDNA signals at time of diagnosis included clinically aggressive subtypes (e.g., triple-negative breast cancer [TNBC], HR−/HER2+ breast cancer). Specificity was lower for TNBC vs HR−/HER2+ vs HR+/HER2+ vs HR+/HER2− breast cancer.
- Sensitivity at 98% specificity was higher in breast cancers detected via clinical presentation vs detected via screening.
- Sensitivity was also higher in breast cancers detected via clinical presentation vs detected via screening.
- Advances in sequencing technology have demonstrated the promise of using cfDNA-based assays to develop early cancer detection tests.

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