Title: Exploring a possible relationship of germline CDKN2A mutations with breast cancer in a multi-gene panel cohort

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Background

Germline mutations in CDKN2A have been known to increase the risk of melanoma and pancreatic cancer compared to the general population. With the advent of multi-gene panels, individuals who may not have melanoma or pancreatic cancer are undergoing CDKN2A analysis. Previous studies in homogenous populations have suggested that breast cancer risks may also be increased in CDKN2A. This study aims to further evaluate a possible relationship of CDKN2A mutations with breast cancer through a series of case-control comparisons.

Methods

Clinical histories and molecular results were retrospectively reviewed for patients undergoing CDKN2A analysis as part of two diagnostic pan-cancer panels at a single laboratory to ascertain CDKN2A mutation carriers (n=104) and patients negative for all genes analyzed (n=20,280). Patients with a personal and/or family history (1st and 2nd degree relatives) of pancreatic cancer and/or melanoma were excluded from case-control analysis.

Results

The majority of CDKN2A mutation carriers (82.6%, n=86/104) had a personal history of cancer documented on the test requisition form. The most common cancers were breast (n=38, 52.8%), melanoma (n=37, 43.0%) and pancreatic (n=6, 7.1%). The average age of breast cancer diagnosis in this cohort was 49.3 years (range 25-84). Family history of breast, melanoma, and/or pancreatic cancer was reported for 54.9%, 46.1%, and 34.3% of CDKN2A mutation carriers, respectively. Females with breast cancer were not more likely to test positive for a CDKN2A mutation than females with cancer other than breast (OR=0.84, p=0.79) or unaffected females (OR=1.02, p=1).

Conclusions

Although CDKN2A mutations were not significantly associated with breast cancer in this cohort, these findings do not necessarily rule out an association of CDKN2A mutations with breast cancer, particularly if risks are moderate or if genotype-phenotype correlations exist. Additional studies involving breast cancer cases unselected for age and family history and/or longitudinal studies of CDKN2A carriers are needed to better understand the relationship between CDKN2A and breast cancer risk.