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.