Population-based cancer risk estimates for pathogenic variants in breast cancer high-risk genes

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Background

Germline pathogenic variants in breast cancer high-risk genes including *BRCA1*, *BRCA2*, and *PALB2* are also associated with elevated risks for other cancers, such as ovarian, prostate, and pancreatic caners. However, most of the risk estimates are from 'high-risk' families or participants. These estimates might not be applicable to general population, for which genetic screening is becoming a reality. We aimed to estimate the 'population-based' cancer risks associated with the pathogenic or likely pathogenic (P/LP) variants using the UK Biobank.

Methods

This study analyzed the prospective data from 457,580 UK Biobank participants, including 409 *BRCA1*, 1,300 *BRCA2*, and 708 *PALB2* carriers with P/LP variants classified in the ClinVar through whole-exome sequencing data. Twenty-five types of incident cancer during a median of 12 years follow-up were identified via cancer and death registry linkage. Cox regression models were used to estimate hazard ratios (HRs) for P/LP variants across all 25 cancers, with additional analyses evaluating the interaction between P/LP variants and polygenic score (PGS) for each carrier-associated cancer.

Results

For female breast cancer, the population-based risks for *BRCA1* (HR=6.08), *BRCA2* (HR=4.9), and *PALB2* (HR=3.69) P/LP variants carriers in our study were lower than estimates derived from multiple-case family studies (e.g., Antoniou et al., Am J Hum Genet, 2003: *BRCA1* HR=11, *BRCA2* HR=9.2, Antoniou et al., N Engl J Med, 2014: *PALB2* HR=9.07). For ovarian cancer, estimates for *BRCA1* (HR=27.84) and *BRCA2* (HR=18.61) carriers were also reduced compared with family-based estimates (Antoniou et al., Am J Hum Genet, 2003: *BRCA1* HR=48, *BRCA2* HR=7.3). These findings highlight that population-based relative risks are generally lower than those derived from high-risk families and individuals. Furthermore, *BRCA2* P/LP variants were associated with male breast (HR=13.15), prostate (HR=2.5), pancreatic (HR=3.87), and gallbladder (HR=4.86) cancers. *PALB2* P/LP variants were associated with pancreatic (HR=4.13) cancer. No evidence of increased risk was found for other cancers. Significant negative interactions between P/LP variants and PGSs were observed for *BRCA1* in breast cancer (HR=0.62), *BRCA2* in breast (HR=0.71) and ovarian (HR=0.7) cancers, and *PALB2* in breast (HR=0.62) and ovarian (HR=0.38) cancers, indicating that the effect of PGS on cancer risk was weaker in carriers than noncarriers. No such interactions were detected for other cancers.

Conclusions

This prospective study confirms elevated risks of multiple cancers, with reduced risk estimates, for population-ascertained carriers of *BRCA1*, *BRCA2*, and *PALB2* P/LP variants. Cancer-specific PGS can modify the effect of these P/LP variants on breast and ovarian cancer risks, highlighting the role of PGS in improving cancer risk assessment among carriers.