Age-Specific Risk of Ovarian Cancer in Families with *PALB2*

Koki Takabatake[1, 2], Stephen B. Gruber[3], Gregory Idos[3], Giovanni Parmigiani[2,4], Danielle Braun[2,4], Nicolas Kubista[2,4]

[1]Boston University Chobanian & Avedisian School of Medicine, Boston, MA
[2]Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA
[3]City of Hope National Medical Center, Duarte, CA
[4]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

Background

- Pathogenic germline variants (PGVs) in *PALB2* have long been associated with increased risk of breast cancer
- However, recent literature has suggested that *PALB2* PGVs may be linked to increased risk to ovarian cancer (OC), but these risks have not been extensively characterized

Objectives

1. Estimate cumulative lifetime risk for OC for *PALB2* PGVs
2. Explore *penetrance* R package's ability to apply a parametric Bayesian approach to quantify age-specific cancer risk based on genetic mutations

Methods

- **Data:** We use family cancer history data collected from the Clinical Cancer Genomics Community Research Network (CCGCRN). CCGCRN is a consortium of 31 active community-based onco-genetic practices across 50 states in U.S. and 4 counties in Latin America. Family data, including cancer occurrence, ages of diagnosis, and genetic test results are collected for the proband and their relatives
- **Analysis:** Employ a parametric Bayesian approach via the *penetrance* R package to calculate age-specific cumulative lifetime risk for OC. These estimations were compared with the penetrance estimations from Surveillance, Epidemiology, and End Results (SEER). SEER is a dataset published by the National Cancer Institute that contains cancer incidence survival data from approximately 28% of the U.S population.
- **Note:** While the SEER dataset includes data from both carriers and non-carriers of various genetic mutations, the rate of *PALB2* PGVs in the general population is negligible, making it an appropriate baseline comparison for OC risk in our cohort

Figure 1. Absolute Risk Curve

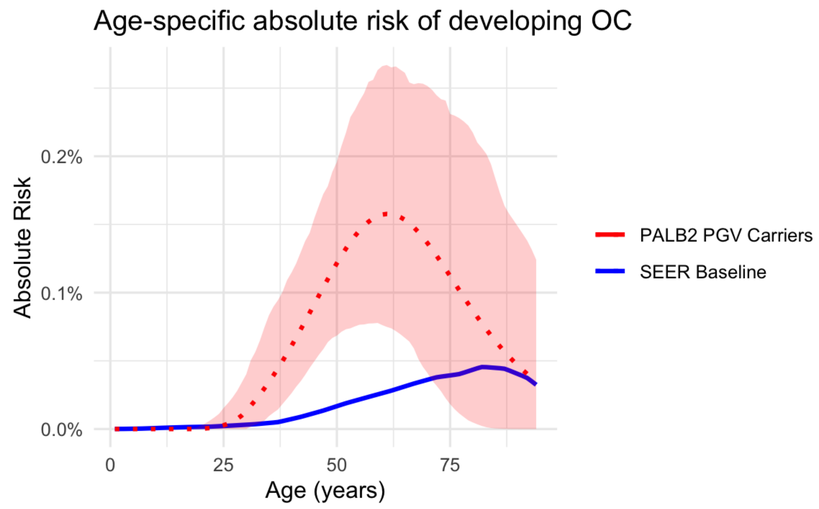
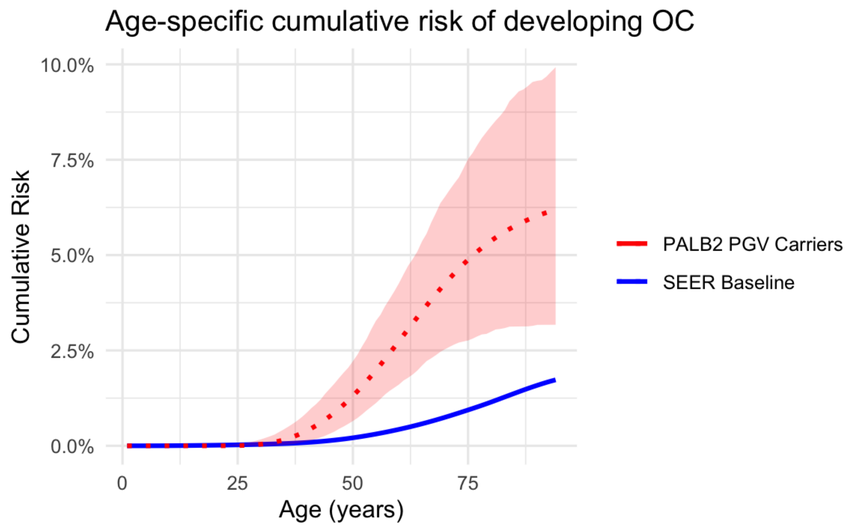


Figure 2. Cumulative Risk Curve



Take-home message

- Our study demonstrates that PALB2 PGVs confer a lifetime risk of 5.4% for OC at age 80 years, slightly higher risk than previous findings in literature
- It also showcases the potential of the *penetrance* package as a tool for Bayesian analysis to quantify age-specific cancer risk based on genetic mutations

Results

- Cumulative SEER baseline risk for OC at 80 years ~1.1%
- Cumulative CCGCRN lifetime risk for OC at 80 years ~5.4% (95% CI [3.0,8.4]). This estimate suggests a modest but significant risk compared to the SEER baseline
- The wide confidence interval reflects uncertainty

Comparison to Literature

- Estimated risk of 5.4% is higher than estimations in other studies
- Song et al. (2021) estimated 3.2% for cumulative risk for OC for *PALB2* PGVs *carriers* after conducting case-control study of 12,500 individuals in Wales and England
- Yang et al. (2020) estimated 4.8% for cumulative lifetime risk of OC at age 80 years after performing a segregation study in 5234 families with *PALB2* PGVs
- These differences highlight the need for future research to refine our understanding of OC risk in *PALB2* PGVs carriers and develop more accurate, individualized risk prediction models

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- Presenter: **Koki Takabatake, MPH**
  - kokitaka@bu.edu