Age-Specific Breast and Ovarian Cancer Risks Associated with Germline BRCA1 or BRCA2 Pathogenic Variants – An Asian Study of 572 Families

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INTRODUCTION

Female carriers of *BRCA1* or *BRCA2* pathogenic variants (PV) have increased risks of both breast and ovarian cancer, necessitating enhanced surveillance or risk-reducing strategies.[1-5] Large-scale studies on European-ancestry carriers estimate cumulative breast cancer risks by age 70 at 66% for *BRCA1* and 61% for *BRCA2*, with corresponding ovarian cancer risks at 41% and 15% respectively.[6] However, data on Asian carriers remain limited.[7-10] These studies are constrained by small sample sizes, varying methodologies, and assumptions of constant risk across ages, limiting their clinical utility.

This study analyses data from Malaysian and Singaporean families with *BRCA1* and *BRCA2* PVs to provide age-specific, ethnicity-specific, and mutation-specific breast and ovarian cancer risk estimates, addressing the gap in Asian-specific risk data to inform clinical management guidelines.

METHODOLOGY

Study Population

Data was collected from 572 Malaysian and Singaporean families with *BRCA1* or *BRCA2* PV.[11-14] Two recruitment schemes were used:

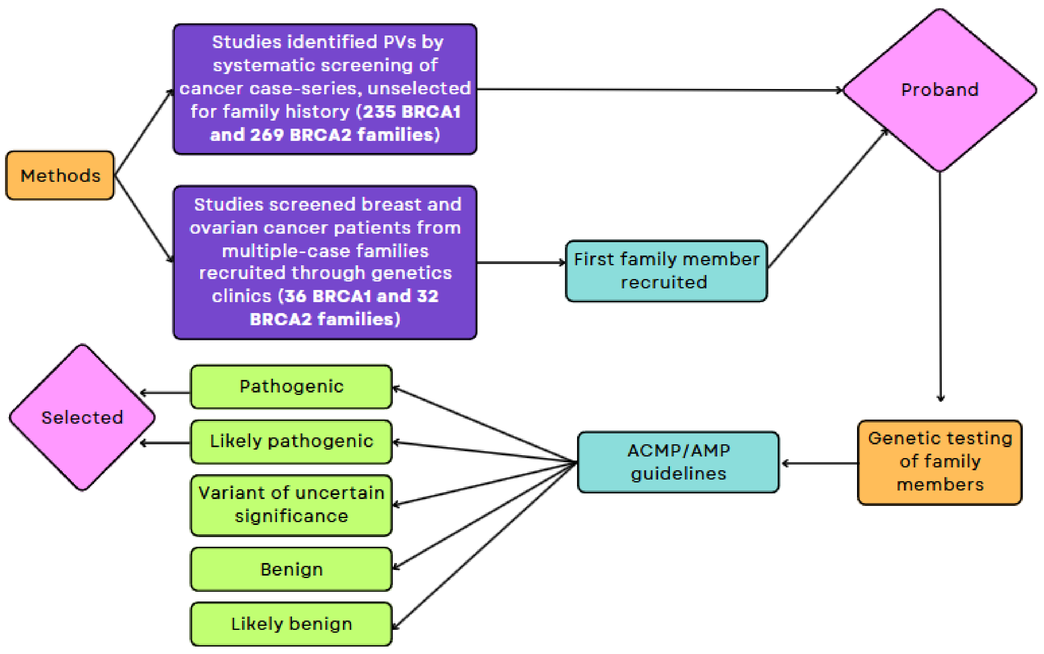


Fig 1. Flowchart illustrating recruitment scheme used for selection of families

Statistical Analysis

Breast and ovarian cancer relative risks (RR) for *BRCA1* and *BRCA2* were estimated using modified segregation analysis[16], adjusted for ascertainment bias (ascertainment assumption-free method).[1,4,17] Family members were censored at age of cancer diagnosis, death, last follow-up, or 80 years.

Models assumed:
1. Constant RR across ages.
2. Constant RR within 10-year age intervals (20–29, 30–39, etc.).

The above models were also stratified according to country, birth cohort, ethnicity, and PV location.

RESULTS

Relative Risks (RR) Findings

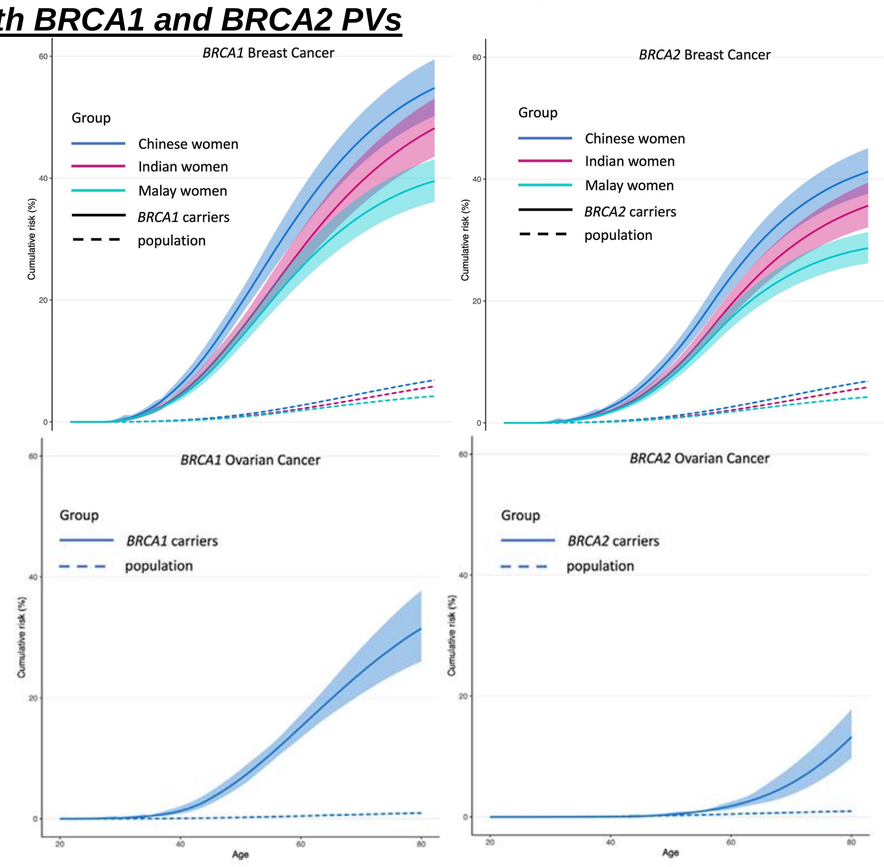
- Age-specific RR for *BRCA1* and *BRCA2* PV carriers were similar across ethnic groups and countries
- RR for both breast and ovarian cancer vary significantly with age for both *BRCA1* and *BRCA2* carriers

Breast cancer: RR patterns for breast cancer were largely similar to those reported in women of European ancestry, except for those aged 40–49 in *BRCA1* PV carriers where the breast cancer RR were lower

Ovarian cancer: RR for ovarian cancer increased with age for both *BRCA1* and *BRCA2* as compared to that in European populations, where RR peaked between aged 40-49 for *BRCA1* and 50-59 for *BRCA2*

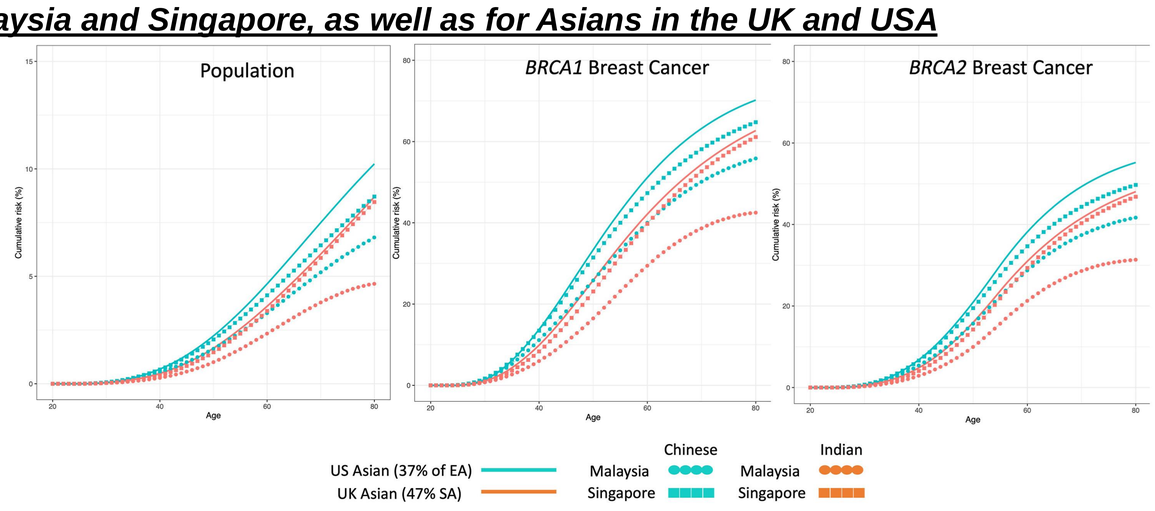
RESULTS

Fig 2. Estimated cumulative risk of developing breast and ovarian cancer for women with BRCA1 and BRCA2 PVs



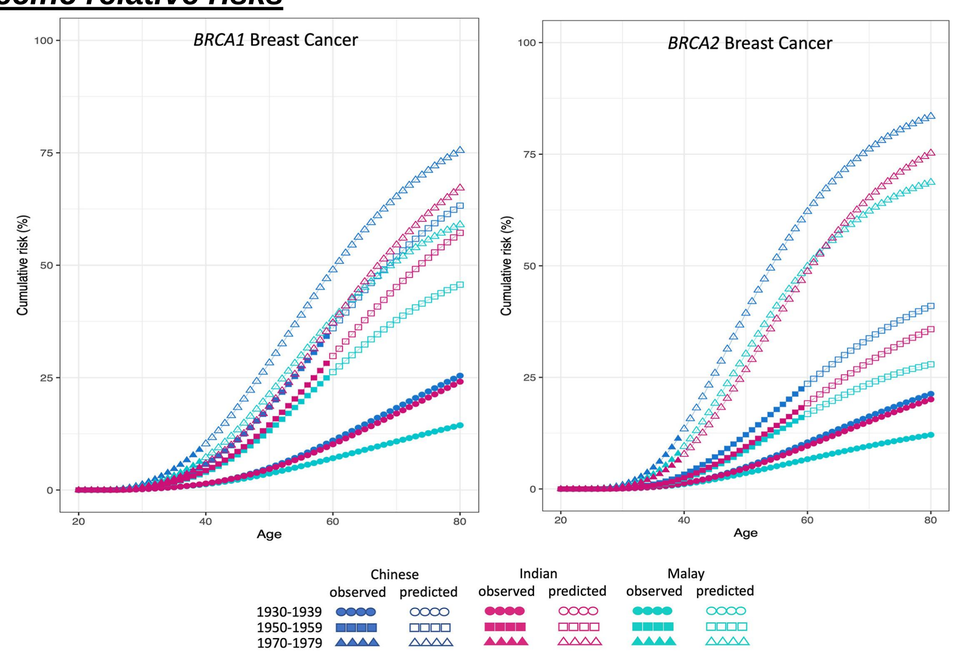
- Cumulative risk of breast cancer by age 80 was highest for Chinese women, followed by Indian and then Malay women for both *BRCA1* and *BRCA2* carriers

Fig 3. Estimated cumulative risk of breast cancer for Chinese and Indian women in Malaysia and Singapore, as well as for Asians in the UK and USA



- Cumulative risk can vary within the same ethnic groups across different countries
- Cumulative risks of Chinese women in Singapore were similar to Asians in the US, and higher compared to Chinese women in Malaysia
- Cumulative risks of Indian women in Singapore were similar to Asians in the UK, and higher compared to Indian women in Malaysia

Fig 4. Estimated cumulative risk of developing breast cancer for women with germline BRCA1 and BRCA2 pathogenic variants, using a model that allows for cohort-specific relative risks



- Cumulative risk by age 80 was predicted to be higher in PV carriers born in 1970–79 compared to PV carriers born in 1930–39, across all three ethnicities

CONCLUSION

This study shows that the absolute age-specific cancer risks of Asian carriers vary depending on the underlying population-specific cancer incidences and hence should be customised to allow for accurate tailoring of cancer prevention strategies. Future research should focus on expanding the dataset and exploring gene-environment interactions to further optimize risk prediction models for Asian populations.

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