Germline pathogenic variants (GPVs) – including class 4 likely pathogenic and class 5 pathogenic variants in PALB2 – are associated with an increased risk of female (FBC) and male breast cancer (MBC), tubo-ovarian cancer (TOC) and pancreatic cancer, following an autosomal dominant inheritance pattern. The risk of a second primary breast cancer has not been accurately quantified.

The risk estimates are for truncating variants only. Missense GPVs are rare.

Risk of breast and ovarian cancer varies with family cancer history

Triple negative (ER, PR and HER2 negative) breast cancers are somewhat enriched for PALB2 GPVs, but most PALB2 carriers will develop ER+ disease.

The largest study of PALB2-associated cancer risks has shown no evidence of association with prostate, colorectal or other cancers.

GPV in PALB2, when associated with a somatic inactivating PV, confer a deficiency in the homologous recombination repair pathway (HRD). This may have implications for response to chemotherapy (more vulnerable to platinum-based agents) and targeted therapies (such as PARP-inhibitors).

Population cancer risk to age 80

- Breast (female)*: 7.18 (5.82-8.85) – approximately 10%
- Breast (male): 7.34 (1.28-42.18) – rare
- Tubo-ovarian **: 2.19 (1.40-6.04) – 5% (2-10)
- Pancreatic (female): 2.37 (1.24-4.50) – 2% (1-4)
- Pancreatic (male): 2.37 (1.24-4.50) – 3% (2-5)

* Lifetime risk of breast cancer for a female with two affected first-degree relatives increases to 76% (95% CI 69-83)

** Lifetime risk of tubo-ovarian cancer increases to 16% (95% CI 8-28) when two first degree relatives are affected. The cumulative risk up to age 50 is under 1% without a family history, and 2% with 2 affected first degree relatives

Management recommendations

Surveillance

FBC: Refer to "Very High-Risk" breast screening programme (annual MRI breast from 30 years, annual mammography from 40 years).
Earlier commencement of annual MRI breast from age 25 may be considered for women with an individualised 10-year breast cancer risk of ≥8%.
For women with previous breast cancer, as above if residual breast tissue.
TOC: Not currently recommended as no evidence-based screening programme. Screening should only be offered in the context of a research study.
Pancreatic: Not currently recommended outside of research. Consider EUROPAC study if family history on same side of family as PALB2 GPV.

Risk reducing surgery

FBC: Discuss risk reducing mastectomy with consideration of personalised risk assessment and shared decision making with individual. Age-specific risks (e.g. within next 10 years) should be discussed to allow individuals to make an informed decision.
TOC: For PALB2 carriers with ≥5% lifetime risk.
RRSO should be considered at 50 years. Studies have estimated risk up to age 50 to be under 1%. RRSO can be considered in carriers younger than 50 following individualised risk assessment including assessment of menopausal symptoms and shared decision making.

Lifestyle advice

- Provide information about regular self-breast examination
- Provide information on ovarian cancer symptom awareness
- Provide information on the benefits of smoking cessation, minimising alcohol intake and maintaining a healthy weight to lower the chance of getting cancer.
- Contraception: Use of oral contraceptive pill (OCP) is not contraindicated. No specific studies of OCP use in PALB2 carriers have been undertaken. Population studies suggest OCP use may reduce the risk of developing ovarian cancer. There have been conflicting studies on breast cancer risk with OCP but recent studies suggest that OCP use does not significantly increase risk in women at increased familial risk.

Family matters

- Refer to Clinical Genetics to facilitate genetic testing in at-risk family members.
- Refer to Clinical Genetics for discussions on reproductive options.

References


Population cancer risk figures to age 80 years based on CRUK data (personal communication with CRUK Cancer Intelligence team) and reflect the risk of cancer for people born in 1961 (Further information is available in the FAQ document v2 for BRCA1 and BRCA2)

Individualised breast, contralateral breast and ovarian cancer risk estimates which incorporate germline PV carrier status, personal risk factors and where relevant breast cancer receptor status, polygenic risk score and breast density, are available at https://canrisk.org/ (Lee et al., 2021)

Patient resources

- breastcancernow.org “Someone like me” https://breastcancernow.org/information-support/support-you/someone-me-telephone-support
- Coppafeel https://coppafeel.org/
- Information for PALB2 carriers and their families https://www.palb2.org/resources-palb2-partner-localizer-brca2