PALB2 – risk management

ID: 1609 v.5 **Endorsed**

Related pages:

- Informing family members about hereditary cancer
- PALB2 genetic testing
- Facts for people and families with a faulty PALB2 gene

Summary

Familial breast cancer predisposition due to a monoallelic germline loss-of-function pathogenic variant in the PALB2 gene is an autosomal dominant condition.

This risk management guideline has been developed for individuals who have **NOT** been diagnosed with a relevant cancer/tumour. The care of **affected** individuals should be individualised based on their clinical situation, and the monitoring they need as part of their treatment and post-treatment follow up.

The risk management of an individual with a pathogenic variant in two or more genes that confer a predisposition to cancer should also be individualised.

Target group

- Unaffected known or obligate carriers of a loss-of-function PALB2 pathogenic variant
- Individuals at 50% risk of being a carrier of a loss-of-function PALB2 pathogenic variant

Exclusion criteria

- Individuals with a missense variant not verified as loss-of-function
- Individuals with a pathogenic variant in another high risk gene
- Women from a high risk breast and/or ovarian cancer family with an uninformative genetic test result or no DNA testing available

Note: biallelic pathogenic variants cause Fanconi anaemia and are NOT covered by this protocol

Lifetime risk of cancer

The risk of breast cancer below varies based on an individual's family history of breast cancer. A validated risk assessment tool (CanRisk) can be used to determine an individual's absolute risk of breast cancer.

Cancer	Risk for PALB2 pathogenic variant carriers by age 80 years	General population risk by age 80 years
Breast (female)	53% (95% CI, 44% to 63%)[1]	11.7%*
Breast (male)	1% (95% CI, 0.2% to 5%)[1]	0.12%*
Ovarian**	5% (95% CI, 2% to 10%)[1]	0.94%*
Pancreatic	2-3% (95% CI, 1% to 4%)[1]	1.18%*

**Source: Australian Institute of Health and Welfare (AIHW) 2018. Australian Cancer Incidence and Mortality (ACIM) books. 2015 data.*
***Ovarian cancer risk is higher if there is a family history of ovarian cancer*

Cancer risk management guidelines

Cancer type	Recommendations***		
Breast (female)	**Surgical**	The appropriateness of RRM should be based on each woman's absolute risk (as per CanRisk) followed by self-surveillance of the breast area	
	Surveillance	• Given the range of risk depending on the family history, surveillance and the modality used should be individualised • In some families later commencement of screening is acceptable	
		Age to begin	**Strategy and frequency**
		30–40 years	Annual MRI, +/- US
		40–50 years	Annual MRI, +/- MMG, +/- US
		Over age 50 years	Annual MMG, +/- US (consider MRI if >50 years with dense breasts)
		Pregnant	No MRI or MMG, consider US
	Risk-reducing medication	Careful assessment of risks and benefits in the individual case by an experienced medical professional is required when considering the use of medication, such as tamoxifen or raloxifene to reduce risk of developing breast cancer in unaffected women. See COSA medication to lower the risk of breast cancer: clinician guide	
Breast (male)	**Surgical**	Not applicable	
	Surveillance	Chest area awareness and pectoral area palpation on a regular basis	
	Risk-reducing medication	No evidence of benefit	
Ovarian/fallopian tube	**Surgical**	• Consider RRSO after age 50 years unless there are early ovarian cancers in the family. The age of RRSO may be individualised based on family history • Peritoneal lavage and close histological examination[#] to exclude occult malignancy	
	Surveillance	Do not offer serum CA125 and/or transvaginal ultrasound (TVU)	
Pancreatic	**Surveillance**	No evidence of benefit from surveillance^	

Abbreviations: *RRM - risk-reducing mastectomy, MRI - magnetic resonance imaging, US - ultrasound, MMG - mammography, RRSO - risk-reducing salpingo-oophorectomy*
****The impact of lifestyle on cancer risk should be discussed e.g. exercise regularly, maintain healthy weight, have a healthy diet, limit alcohol intake, do not smoke and avoid excessive sun exposure.*
[#]Histological examination should be according to the SEE-FIM protocol
^Encourage participation in clinical trials of pancreatic cancer screening in high risk individuals

Evidence for risk management guidelines

At the present time, and while there is no specific evidence related to PALB2 pathogenic variant carriers, these guidelines are inferred from those recommended for management of breast cancer risk in BRCA2 pathogenic variant carriers, and take into account the knowledge that the cancer risk in some PALB2 pathogenic variant families is lower than the usual threshold for recommending risk-reducing surgery or screening from age 30 years.

Breast (female)

The majority of PALB2-associated breast cancers are ER$^+$.[2] There may be poorer breast cancer survival in women with PALB2 pathogenic variants compared to women with sporadic cancers (based on 116 Polish patients with one of 2 founder PALB2 pathogenic variants[2] and 29 Finnish women with PALB2 pathogenic variants[3]).

Surgical

Bilateral risk-reducing mastectomy reduces cancer risk by at least 90% (depending on the operation performed) in BRCA1 or BRCA2 pathogenic variant carriers.[4, 5]

Surveillance

MRI is the preferred screening technique due to its high sensitivity compared with mammogram (MMG) or ultrasound (US). The addition of MMG is limited, and does not lead to a significant increase in sensitivity compared with MRI alone.[6] There is no added value of ultrasound in women undergoing MRI for screening. MRI detects tumours which are smaller and more likely to be node-negative than MMG. MRI has a recall rate (requiring further investigation and/or biopsy) of 15% for initial screening, which decreases with subsequent rounds of screening to <10%.

There is no evidence to date that early detection of breast cancer is associated with a better prognosis and survival in BRCA1, BRCA2 or PALB2 pathogenic variant carriers. However, for women who do not choose risk-reducing surgery, surveillance is strongly recommended.

Risk-reducing medication

Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer in high risk women. To date studies have not included enough BRCA1 or BRCA2 (or PALB2) pathogenic variant carriers to determine if it is effective for primary prevention in this population. Tamoxifen use is associated with a reduction in contralateral breast cancer risk in BRCA1 and BRCA2 pathogenic variant carriers with breast cancer; such benefit is stronger if ovaries are still intact.[7] Similar benefit might be expected in PALB2 pathogenic variant carriers. In view of the potential side effects associated with tamoxifen/raloxifene, risk-reducing medications should be discussed with an experienced medical professional to determine the relevant risks and benefits in an individual pathogenic variant carrier. See COSA medication to lower the risk of breast cancer: clinician guide.

Breast cancer (male)

No trials have evaluated whether manual palpation is effective but mammography not useful. Other factors such as obesity, chest wall radiation and gynaecomastia can increase the risk of male breast cancer.[8]

Ovarian

Although there are no specific RRSO studies to date including PALB2 pathogenic variants, evidence suggests that ≥4% lifetime risk of ovarian cancer warrants consideration of RRSO in premenopausal women on the basis of family history of ovarian cancer.[9] The recommendation for surgery is generally after age 50 years.

Pancreas

There is currently no effective surveillance that detects early pancreatic cancer.

Support and information

First degree blood relatives (parents/brothers/sisters/children) are at up to 50% risk of having inherited the PALB2 pathogenic variant . More distant relatives may also be at risk of inheriting the pathogenic variant. Genetic relatives should be referred to a clinical genetics service or familial cancer centre to discuss predictive genetic testing.

Informing family members about hereditary cancer

Website resources

Centre for Genetics Education NSW Health
Genetic Alliance Australia
Breast Cancer Network Australia (BCNA)
Gene Support Connect Programme
Cancer Australia

Research studies

Research is taking place in all aspects of hereditary breast and ovarian cancer. Families may be invited to participate in research trials. Speak to your doctor for more information.

References

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History

Version 5

Date	Summary of changes
14/04/2020	Protocol reviewed by CG reference committee. Discussion continued via email. Protocol approved for publication with the following changes made: • Title changed from "PALB2 – risk management (female)" to "PALB2 – risk management" • Summary: minor wording changes • Target group: ◦ First bullet: "obligate female carrier..." changed to "obligate carriers..." ◦ Second bullet: "Woman at 50% risk..." changed to "Individuals at 50% risk..." ◦ Exclusion criteria ▪ "Male with a loss-of-function PALB2 mutation" removed ▪ "Individuals with a missense variant not verified as loss-of-function" added ◦ Note: "biallelic pathogenic variants cause Fanconi anaemia and are NOT covered by this protocol" moved down from summary section • Lifetime risk of cancer: ◦ All data in table updated. Risk to age 80 years for PALB2 carriers and general population listed (previously listed risk to age 70 and age 85 respectively) ◦ Breast (male) and ovarian cancer added to table • Cancer risk management guidelines table ◦ Breast (female) - Surgical: wording revised. Link to CanRisk added ◦ Breast (female) - Surveillance: wording revised. Age to begin and Strategy and frequency aligned with BRCA2 protocol ◦ Breast (male) - Surgical, Surveillance and Risk reducing medication: added to table, aligned with the BRCA 1 or BRCA2 - risk management (male) protocol ◦ Ovarian - Surgical and Surveillance: added to table ◦ Footnote added: "Encourage participation in clinical trials of pancreatic cancer screening in high risk individuals" • Evidence for cancer risk management guidelines: ◦ Breast (female) - Surgical: paragraph regarding RRSO for breast cancer risk reduction removed ◦ Breast (female) - Surveillance: wording updated, aligned with BRCA2 protocol ◦ Breast (male) - paragraph added, from BRCA1 or BRCA2 - risk management (male) protocol ◦ Ovarian - paragraph added ◦ Pancreas - paragraph added • Protocol template changes applied • "Mutation" changed to "pathogenic variant" throughout document for consistency among eviQ cancer genetics protocols per agreement among the cancer genetics reference committees' chairs. Definition of "pathogenic variant" added as a pop-up. Protocol version number increased to V.5. Protocol to be reviewed in 2 years

Date	Summary of changes
02/07/2020	Protocol edited. Cancer risk management guidelines table underwent minor formatting changes to align with table in BRCA1 or BRCA 2 - risk management (female) protocol.

Version 4

Date	Summary of changes
28/08/2019	Protocol title changed from 'Risk management for a female PALB2 mutation carrier' to 'PALB2 – risk management (female)' in accordance with Cancer Genetics Reference Committees' consensus. Version number increased to V.4.

Version 3

Date	Summary of changes
02/04/2014	Discussed at October 30, 2013 & March 5, 2014 reference committee meetings and approved for publication. • Review second yearly
31/07/2015	Link to AGSA changed to Genetic Alliance Australia.
07/01/2016	Sentence added to risk management template: "The impact of lifestyle of cancer risk should be discussed".
14/04/2016	Sentence added to risk management template: "This risk management guideline has been developed for individuals who have NOT been diagnosed with a relevant cancer/tumour. The care of affected individuals should be individualised based on their clinical situation, and the monitoring they need as part of their treatment and post-treatment follow up".
24/05/2016	Reviewed via email and the following changes made: • Target population - amended • Lifetime risk of cancer table - updated • Cancer risk management guidelines - amended • Evidence for cancer risk management guidelines - updated • References - updated • For yearly review.
28/09/2016	'Unaffected' removed from title.
31/05/2017	Transferred to new eviQ website. Version number changed to V.3.
25/07/2019	• Link in *Cancer risk management guidelines* and *Evidence for risk management guidelines* sections changed from **Cancer Australia Risk-reducing medication resource** to **COSA medication to lower the risk of breast cancer: clinician guide** as per consensus at November 2018 RCM. Version kept at V.3.

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