Annex C: Absolute risk for breast and ovarian cancers

This annex summarises the estimated lifetime absolute risk of breast cancer associated with pathogenic variants (PVs) in HBOC syndrome-related genes. The risk estimates in the tables below are primarily for females, for whom more comprehensive gene-specific estimates are available. For males, the absolute risk of breast cancer is substantially lower than females, estimated at approximately 0.2-1.2% for *BRCA1* and 1.8-7.1% for *BRCA2* carriers and population level risk is 0.12%.[1, 2]

Risk estimates are presented as ranges and have been compiled from international guidelines such as NCCN, European Society for Medical Oncology (ESMO), EviQ and American College of Medical Genetics and Genomics (ACMG). As Asian-specific risk estimates are currently limited for many genes, the figures presented are primarily derived from non-Asian populations and should be interpreted accordingly. These risk estimates are intended to serve as a reference to support clinical decision-making and risk discussions with patients. Cancer risk may vary between specific variants within the same gene, and gene-level risk estimates may not apply equally to all variants. Decisions on risk-reducing interventions should therefore consider variant-specific risks, alongside family history and other individual risk factors.

As evidence and variant classifications continue to evolve, users should refer to up-to-date resources such as ClinVar, ClinGen, NCCN, eviQ, for latest information, including variant-specific cancer risks and updates on variants of uncertain significance (VUS).

Category	PVs	Absolute risk for **breast** cancer for females
High risk	*BRCA1*	60-85%[1, 3-5] (local 57-61%)[6]
	BRCA2	40-85%[1, 3-5] (local 43-47%)[6]
	TP53	40-85%[1, 3, 7]
	PTEN	40-80%[1, 3, 8]
	PALB2	32-60%[1, 3, 9, 10]
	CDH1	37-55%[11-13]
	STK11	32-54%[1, 3, 14]
Moderate risk	*ATM*	Typical ~20-25%[15]; c.7271T>G: higher risk 52%[16]
	BARD1	17-30%[1, 3]
	CHEK2	~20-50%[1, 3, 17, 18]
	NF1	20-40%[1, 19]
	RAD51C	20-21%[3, 5, 20, 21]
	RAD51D	~20%[3, 5, 20, 21]
Population level risk	-	11-13%[1, 3, 4]

Category	PVs	Absolute risk for **ovarian** cancer for females
High risk	*BRCA1*	39-58%[1, 4, 22, 23] (local ~ 42%)[6]
	BRCA2	13-29%[1, 4, 22, 23] (local ~20%)[6]
	BRIP1	5-15%[1, 22, 24]
	RAD51C	10-15%[1, 20, 22]
	RAD51D	10-20%[1, 20, 22]
	PALB2	3-5%[1, 9, 22]
Population level risk	-	1.45% (local)[25]

References:

1. National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (Version 3.2026) 2026. cited April 9, 2026. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=2&id=1545
2. 656 v.12-BRCA1 or BRCA2 – risk management (male) [Internet]. EviQ, Cancer Institute NSW. 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/656-brca1-or-brca2-risk-management-male.
3. Sessa C, Balmaña J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(1):33-47.
4. 3814 v.5-BRCA1 or BRCA2 – risk management (female) [Internet]. EviQ. Cancer Institute NSW. 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/3814-brca1-or-brca2-risk-management-female#.
5. National Institute for Health and Care Excellence: Guidelines. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer: National Institute for Health and Care Excellence (NICE); 2023.
6. Ho WK, Hassan NT, Yoon SY, et al. Age-specific breast and ovarian cancer risks associated with germline BRCA1 or BRCA2 pathogenic variants - an Asian study of 572 families. Lancet Reg Health West Pac. 2024;44:101017.
7. 749 v.12-TP53 (Li-Fraumeni) – risk management (adult) [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/749-tp53-li-fraumeni-risk-management-adult#cancer-tumour-risk-management-guidelines.
8. 546 v.13-PTEN (PTEN hamartoma/Cowden) – risk management [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/546-pten-pten-hamartoma-cowden-risk-management.
9. 1609 v.10-PALB2 – risk management [Internet]. EviQ. Cancer Institute NSW 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/1609-palb2-risk-management.
10. Tischkowitz M, Balmaña J, Foulkes WD, et al. Management of individuals with germline variants in PALB2: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1416-1423.
11. O'Reilly C, McGarry JL, Zaborowski AM, et al. Risk-Reducing Bilateral Mastectomy and Mortality in Carriers of BRCA1 and BRCA2 Variants: A Systematic Review and Meta-Analysis. JAMA Surg. 2026;161(3):260-267.
12. Woo J, Gwak G, Park I, et al. Preoperative diagnosis of BRCA1/2 mutation impacts decision-making for risk-reducing mastectomy in breast cancer patients. Sci Rep. 2021;11(1):14747.
13. 1090 v.11-CDH1 – risk management [Internet]. EviQ. Cancer Institute NSW 2021 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/1090-cdh1-risk-management.
14. 395 v.11-STK11 (Peutz-Jeghers) – risk management [Internet]. EviQ. Cancer Institute NSW 2026 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/395-stk11-peutz-jeghers-risk-management.
15. Pal T, Schon KR, Astiazaran-Symonds E, et al. Management of individuals with heterozygous germline pathogenic variants in ATM: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27(1):101243.
16. 1610 v.11-ATM (monoallelic pathogenic variants) – risk management [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/1610-atm-monoallelic-pathogenic-variants-risk#evidence-for-risk-management-guidelines.
17. Hanson H, Astiazaran-Symonds E, Amendola LM, et al. Management of individuals with germline pathogenic/likely pathogenic variants in CHEK2: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(10):100870.
18. 3701 v.6-CHEK2 – risk management [Internet]. EviQ. Cancer Institute NSW 2024 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/3701-chek2-risk-management-female.
19. 752 v.13-NF1 (Neurofibromatosis type 1) – risk management [Internet]. EviQ. Cancer Institute NSW 2025 [cited 27 March 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/752-nf1-neurofibromatosis-type-1-risk-manageme.

20. 4117 v.1-RAD51C or RAD51D − risk management (female) [Internet]. EviQ. Cancer Institute NSW 2026 [cited 10 June 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/4117-rad51c-or-rad51d-risk-management-female.
21. Ngeow J, Chiang J, Astiazaran-Symonds E, et al. Management of individuals with heterozygous germline pathogenic variants in RAD51C, RAD51D, and BRIP1: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2025;27(11):101557.
22. Cancer Service Lin Development (CSLD) Workgroup. Cancer Service Lin Development (CSLD) Workgroup for Cancer Genetics of National Cancer Centre Singapore (NCCS) version 2. 2023. 2023.
23. Chen J, Bae E, Zhang L, et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. JNCI cancer spectrum. 2020;4(4):pkaa029.
24. 4118 v.1-BRIP1 − risk management (female) [Internet]. EviQ. Cancer Institute NSW 2026 [cited 26 June 2026]. Available from: https://www.eviq.org.au/cancer-genetics/adult/risk-management/4118-brip1-risk-management-female.
25. Singapore Cancer Registry (Health Promotion Board). Singapore Cancer Registry Annual Report 2022 [Internet]. 2024 [cited 2026 Jun 15]. Available from: https://www.nrdo.gov.sg/docs/librariesprovider3/default-document-library/scr-ar-2022_web-report6c6e8522-cf39-416f-9390-5fe903065927.pdf?sfvrsn=3712e8bb_1.