RAD51C Pathogenic Variant Carriers: Management Guidelines for Healthcare Professionals

General information

- Germline pathogenic variants (GPV - including class 4 likely pathogenic and class 5 pathogenic variants) in *RAD51C* are associated with an increased risk of tubo-ovarian cancer (TOC) and breast cancer (BC)[1,2], following an autosomal dominant inheritance pattern.
- **The risk varies with extent of cancer family history.**
- There is a suggestion that GPV in *RAD51C* are more strongly associated with triple negative (ER, PR and HER2 receptor negative) BC or oestrogen receptor (ER) negative BC[3,4]. However, this has not been substantiated in all literature[3].
- The cancer risks are associated with truncating GPV in these genes. An association has not been demonstrated for missense variants[5].

Associated risks

Breast cancer[2] (risk varies with family history of BC)	Lifetime risk: 21% (95% C.I. 15-29) (female carriers without a significant family history of BC) Lifetime risk: 46% (95% C.I. 6-56) (two first-degree relatives affected with BC) Relative risk 1.99 (95% C.I. 1.39-2.85) For individual patients we recommend use of tools such as CanRisk* to generate personalised age-specific risks to direct surveillance and risk reducing strategies (see below).
Tubo-ovarian cancer[2] (risk varies with family history of TOC)	Lifetime risk: 11% (95% C.I. 6-21) (female carriers with no family history) Lifetime risk: 32% (95% C.I. 20-50) (two first-degree relatives affected with TOC at 50 years) Relative risk 7.55 (95% C.I. 5.60-10.19) TOC risk peaks between 50-69 years of age (although age specific results were based on small numbers). Individualised age-specific risk scores can be obtained through tools such as CanRisk*.

Management recommendations

Surveillance[5]	**Breast:** Should be based on individualised risk assessment using tools such as CanRisk*, and in accordance with NICE guidelines on familial breast cancer (CG164). -Moderate risk surveillance (lifetime risk of 17-29%): annual mammograms 40-49 years then NHSBSP -High risk surveillance (lifetime risk of ≥30% but <40%): annual mammograms 40-59 years then NHSBSP -Very high-risk screening (lifetime risk of ≥40% and 10-year risk of 8% 25-29 yrs, 30-39 years or 12% 40-49 years): refer to VHR breast screening programme
	Tubo-Ovarian: Not currently recommended. No evidence-based screening programme. Should be offered only as part of an ethically approved research study
Risk reducing surgery[5]	**Breast:** Consider discussion of risk-reducing mastectomy if lifetime risk ≥30%, in conjunction with an individualised risk assessment* and appropriate counselling
	Tubo-Ovarian: For *RAD51C* carriers with ≥5% lifetime risk, RRSO should be considered from 50 years. It can be considered in carriers younger than 50 years following individualised risk assessment*, including assessment of menopausal symptoms and shared decision making. Risk reducing early salpingectomy with delayed oophorectomy should currently only be offered in the context of a research study
Lifestyle advice	-Provide information about regular self-breast examination and 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 *RAD51C* 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

(1) Breast Cancer Association Consortium, Dorling L et al. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. N Engl J Med. 2021 Feb 4;384(5):428-439. doi: 10.1056/NEJMoa1913948. PMID: 33471991

(2) Yang X, et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in *RAD51C* and *RAD51D*. J Natl Cancer Inst. 2020 Dec 14;112(12):1242-1250. doi: 10.1093/jnci/djaa030. PMID: 32107557

(3) Li N, et al. Combined tumor sequencing and case/control analyses of *RAD51C* in breast cancer. J Natl Cancer Inst. 2019;111(12):1332–1338. doi: 10.1093/jnci/djz045 PMID: 30949688

(4) Shimelis H, et al. Triple-negative breast cancer risk genes identified by multigene hereditary cancer panel testing. J Natl Cancer Inst. 2018;110(8):855–862. doi: 10.1093/jnci/djy106 PMID: 30099541

(5) Hanson H, et al. UK consensus recommendations for clinical management of cancer risk for women with germline pathogenic variants in cancer predisposition genes; *RAD51C, RAD51D, BRIP1* and *PALB2*. JMG Published Online First: 21 November 2022. doi: 10.1136/jmg-2022-108898

*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
- Target Ovarian Cancer "Hereditary Ovarian Cancer" https://targetovariancancer.org.uk/about-ovarian-cancer/hereditary-ovarian-cancer
- Coppafeel https://coppafeel.org/

Version 1. 13/12/2022 HH & MS