BACKGROUND DOCUMENT- UKCGG-CANGENE-CANVAR CONSENSUS MEETING 2021

MODERATE RISK OVARIAN CANCER SUSCEPTIBILITY GENES

Approximately 20% of ovarian cancer occurs due to an inherited genetic susceptibility (1). The majority of inherited susceptibility is due to pathogenic variants in the cancer predisposition genes *BRCA1* and *BRCA2*, which are associated with high lifetime risks of breast and ovarian cancer. Further cases are due to pathogenic variants in the mismatch repair (MMR) genes *MLH1, MSH2* and *MSH6* and a smaller number of cases occur as a result of pathogenic variants in *RAD51C, RAD51D, BRIP1* and *PALB2*.

There are clear and recognised UK clinical guidelines for the management of cancer risks associated with *BRCA1, BRCA2* and the MMR genes. However, no national guidance currently exists for management of cancer risk in carriers of *RAD51C, RAD51D and BRIP1*. For *PALB2*, management of breast cancer risk is addressed under the Public Health England, Very High Risk breast screening guidelines (2) and recent international guidelines (3).

Until very recently in the UK, genetic testing of *RAD51C, RAD51D, BRIP1* and *PALB2* has been relatively limited. *PALB2* is now routinely tested as part of the R208 hereditary breast-ovarian panel according to the National Genomic Test Directory (4). *RAD51C, RAD51D, BRIP1* are currently tested as part of the R207 familial ovarian cancer panel, recommended where there are two or more cases of ovarian cancer in a family.

Recent submitted changes to the National Genomic Test Directory have proposed that *RAD51C, RAD51D, BRIP1* and *PALB2* should be routinely tested in *all* women with non-mucinous high-grade ovarian cancer. Confirmation of the proposed amendment is awaited. If this change is approved, increasing numbers of carriers of pathogenic variants in *RAD51C, RAD51D, BRIP1* and *PALB2* will be identified, necessitating clear guidelines to manage these individuals in clinical practice and ensure evidence based and consistent management across the UK.

As a result, the UK Cancer Genetics Group and the CanGene-CanVar Project have convened a two-day meeting of Geneticists, Genetic counsellors, Gynaecologists, Oncologists, Radiologists and Patient representatives to address specific questions regarding cancer screening and prevention for this patient group with the aim of reaching and publishing a consensus guideline. The focus of the meeting will be on management of breast cancer risk in *RAD51C* and *RAD51D* carriers and management of ovarian cancer risk in *RAD51C, RAD51D, BRIP1* and *PALB2* carriers.

Please read this background document which summarises the relevant information on cancer risks associated with these genes *and* answer the pre-meeting survey to facilitate discussion of key issues at the meeting.

***RAD51C, RAD51D, BRIP1* and *PALB2* ASSOCIATED CANCERS**

The *RAD51C, RAD51D, BRIP1* and *PALB2* genes are all involved in the homologous recombination repair pathway. As such, the associated cancer risks overlap with other genes involved in this pathway such as *BRCA1* and *BRCA2*.

RAD51C

In 2010, six pathogenic *RAD51C* variants were identified in 1100 German families with gynaecological malignancies (5). Multiple studies have been published since then describing associated cancer risks. The largest and most recent study of tubo-ovarian and breast cancer risk in *RAD51C* carriers analysed data from 6178 families, and included 215 women with *RAD51C* pathogenic variants from 125 families (6). An association with breast and ovarian cancer susceptibility was confirmed for *RAD51C*. This and other studies have demonstrated that for breast cancer the association appears strongest for triple negative or ER-negative breast cancer and for ovarian cancer with high grade serous histology (7–12). An association with predisposition to AML, prostate cancer and stomach cancer have been proposed, but at present the evidence is very limited and clear association with these cancers is not substantiated (13,14).

RAD51D

In 2011, eight pathogenic variants in *RAD51D* were described in 911 breast-ovarian cancer families (15). Multiple studies have been published since then describing associated cancer risks. The largest and most recent study of tubo-ovarian and breast cancer risk in *RAD51D* carriers analysed data from 6690 families, and included 92 women with *RAD51D* pathogenic variants from 60 families (6). This study confirmed that *RAD51D* is associated with breast and ovarian cancer susceptibility. This and other studies have demonstrated that for breast cancer the association appears strongest for triple negative or ER-negative breast cancer and for ovarian cancer with high grade serous histology (7–12). Clear associations with other cancers have not been reported.

BRIP1

Initial studies suggested that *BRIP1* was a breast cancer predisposition gene (16). Whilst some studies still report an association with breast cancer, particularly for triple negative breast cancer (17,18) the most recent and comprehensive studies demonstrate no significant association of *BRIP1* pathogenic variants and breast cancer predisposition (19–22).

Pathogenic variants in *BRIP1* are predominantly associated with ovarian cancer susceptibility (23). The association appears strongest for the high-grade serous subtype, although other histological subtypes have been reported (20,24).

BRIP1 has also been proposed to be associated with a susceptibility to prostate cancer. However, a clear association has not yet been fully demonstrated (25).

PALB2

PALB2 is now firmly recognised to be associated with breast cancer predisposition. In a recent international study of 524 families with *PALB2* pathogenic variants, the breast cancer risks overlapped with that of *BRCA1* and *BRCA2* carriers (26). Management of breast cancer risk is covered by national "very high risk (VHR) breast screening guidelines" and recent ACMG guidelines (2,3). The management of breast cancer risk will therefore not be a focus of this meeting.

In this same study, the association of *PALB2* with ovarian cancer and pancreatic cancer was described, but a clear association with other cancer types was not reported (26).

BREAST CANCER RISKS

RAD51C* and *RAD51D

The most comprehensive study to date of *RAD51C* and *RAD51D* carriers which analysed data from 6178 families, 125 with pathogenic variants in *RAD51C,* and 6690 families, 60 with pathogenic variants in *RAD51D* using complex segregation analysis. The authors estimated relative and cumulative cancer risk whilst adjusting for the mode of ascertainment in each family and modelled the simultaneous associations of breast and ovarian cancer. The study reported a relative risk of breast cancer of 1.99 (95% CI: 1.39-2.85 P =1.55 x 10^{-4}) for *RAD51C* and 1.83 (95% CI: 1.24-2.72 P =0.02) for *RAD51D* (6). A similar association with breast cancer for *RAD51C* and *RAD51D* was also described in a large analysis of 113,000 women through the Breast Cancer Association Consortium; with a OR of 1.93 (95% CI: 1.2-3.11 P =0.0070) for *RAD51C* and OR of 1.8 (95% CI: 1.11-2.93 P=0.018) for *RAD51D* (8). The risks relate

to truncating variants in these genes and rare missense variants do not seem to be enriched in the breast cancer cohort.

The cumulative lifetime risk of breast cancer (to age 80 years) was determined to be 21% (95% CI:15-29%) for *RAD51C* and 20% (95% CI: 14-28%) for *RAD51D* (6). The study also demonstrated that the lifetime breast cancer risk for *RAD51C and RAD51D* pathogenic variant carriers was modified by cancer family history and could be as high as 44–46% for carriers with two first-degree relatives diagnosed with BC.

Table 1 at the end of this document is taken directly from the Yang *et al* paper and demonstrates the estimated age specific and cumulative breast cancer risks for *RAD51C and RAD51D* carriers. Table 2 presents, for each age, the risk of developing breast cancer in the next 10 years (from personal communication with Yang et al).

OVARIAN CANCER RISKS

It is important to recognise that the risk of ovarian cancer for a woman with a *RAD51C, RAD51D*, *BRIP1* or *PALB2* pathogenic variant can be influenced by multiple other factors, in addition to their carrier status. Factors associated with higher ovarian cancer risk are family history of ovarian cancer, nulliparity, subfertility, endometriosis, high BMI, HRT, whereas factors associated with lower risks are the combined oral contraceptive pill, multiparity and breast feeding. Genome-wide association studies have identified >30 common SNPs associated with epithelial ovarian cancer and the use of polygenic risk scores are recognised to have a role in prediction of ovarian cancer risk for women in the general population (27). Modification of ovarian cancer risk with polygenic risk scores has been observed for *BRCA1* and *BRCA2* carriers (28) and are likely to be relevant for modification of risk for *RAD51C, RAD51D*, *BRIP1* or *PALB2* carriers given the effect of family history on risk.

RAD51C and *RAD51D*

From the largest study of *RAD51C* and *RAD51D* carriers, for *RAD51C* carriers a relative risk of ovarian cancer is reported as 7.55 (95% CI 5.6 – 10.19) ($p = 5x10^{-40}$) and for *RAD51D*, RR= 7.6 (95% CI 5.61-10.30) ($p = 5x\ 10^{-39}$) (6).

The cumulative lifetime risk (to age 80 years) of developing a tubo-ovarian cancer for a R*AD51C* carrier is estimated to be 11% (95% CI: 6-21%) and 13% (95% CI: 7-23%) for a *RAD51D* carrier, with most risk conferred after age 50 years for both genes. Similar to breast cancer risk, lifetime tubo-ovarian cancer

risk was shown to be modified by family history with a lifetime risk exceeding 30% for carriers with two first-degree relatives diagnosed with tubo-ovarian cancer.

Table 1 at the end of this document is taken directly from the Yang *et al* paper and demonstrates the estimated age specific and cumulative tubo-ovarian cancer risks for *RAD51C and RAD51D* carriers (6). Table 2 presents, for each age, the risk of developing ovarian cancer in the next 10 years (from personal communication with Yang et al).

In a study of *RAD51C* (n=855) and *RAD51D* (n=455) carriers identified through multigene panel testing, the median age at ovarian cancer diagnosis was 62 years for *RAD51C* carriers, and 57 years for *RAD51D* carriers (29). Overall, for *RAD51C* carriers 82.6% were diagnosed after age 50 (119/144) and 77.5% (55/71) after age 50 for *RAD51D.*

BRIP1

Data from a recent meta-analysis that pooled findings of 44 studies published prior to Sept 2019 including 200 *BRIP1* pathogenic variants (71 distinct variants) identified in 22,494 cases calculated an odds ratio of 4.94 for ovarian cancer (95% CI: 4.07–6.00; $p < 0.0001$) (23).

A study of *BRIP1* carriers included in the meta-analysis, calculated a relative risk for all epithelial ovarian cancer of 11.22 (95% CI: 3.22-34.10) and for high-grade epithelial ovarian cancer of 14.09 (95% CI: 4.04-45.02) based on evaluation of 3,236 cases of ovarian cancer from several cohorts in the UK, US, Australia, Germany, and Belarus (24). They calculated a cumulative risk of epithelial ovarian cancer by age 80 years of 5.8% (95% CI = 3.6% to 9.1%) among *BRIP1* mutation carriers.

Similarly, to *RAD51C* and *RAD51D*, most ovarian cancer risk is conferred after age 50. The average age of diagnosis for ovarian cancer among *BRIP1* carriers is 63.8 years (n=30) compared to 58 years in non-carriers (P=0.07) (24). This was replicated in a larger study of 222 women with ovarian cancer and *BRIP1* pathogenic variants (n=1779) with 90% of cases occurring after age 50 with a median age of 65 (29).

PALB2

In a study of 545 *PALB2* families including 852 female *PALB2* carriers from 21 countries a RR for ovarian cancer of 2.91 (95% CI, 1.40 to 6.04; $p= 4.1 \times 10^{-23)}$ was reported (26). Age-specific absolute risks were calculated by applying RR to cancer incidence in the UK population. The lifetime risk of ovarian cancer (to 80 years) was calculated to be 5% (95% CI: 2-10%). However, it was suggested that risk can be modified by family history and other factors, such that risks for a *PALB2* carrier with a close family member affected by ovarian cancer are more likely to approach/exceed the 10% risk threshold. For a

female whose mother and sister developed ovarian cancer at 50, the lifetime risk was reported to be 16% (95% CI: 8–28%).

Another study reporting on ovarian cancer risk for *PALB2* carriers report ORs of 2.6 (95% CI: 1.45 to 4.64; p=0.0013) for epithelial ovarian cancer and 3.01 (95% CI 1.59 to 5.68; p=0.00068) for high grade serous ovarian cancer and present a cumulative risk estimate to age 80 of 3.2% (95% CI 1.8-5.7) (30). Both these studies report a cumulative ovarian cancer risk of <1% before age 50.

Table 3 at the end of this document presents estimated age-specific cancer incidences and absolute cancer risks for *PALB2* pathogenic variant carriers (26).

BREAST CANCER SURVEILLANCE AND RISK REDUCING SURGERY

No studies have evaluated the most effective form of breast surveillance for *RAD51C or RAD51D* carriers.

Based on the available risk figures from the Yang et al paper, breast cancer lifetime risk for a *RAD51C* or *RAD51D* carrier would at least reach the NICE moderate risk category for surveillance (annual mammograms 40-49 years before entering the NHSBSP, based on ≥17% lifetime breast cancer risk or 10 year risk of 3-8% 40-50 years) (6). However, for those *RAD51C* or *RAD51D* carriers with significant family histories of breast cancer, the high risk categories (≥30% lifetime breast cancer risk or 10 year risk >8% 40-50 years) or very high risk may be reached (≥40% lifetime breast cancer risk or 10 year risk ≥ 8% age 25-29 or 30-39, or ≥12% 40-49). Similarly the NICE recommended threshold for consideration of bilateral risk reducing mastectomy (≥30% lifetime breast cancer risk) may be reached for carriers with a family history.

Updates to the CanRisk tool are anticipated later this year which will allow calculation of personalised lifetime breast cancer risk for *RAD51C* and *RAD51D* carriers (https://canrisk.org/) and will help facilitate risk assessment and appropriate surveillance for this patient group.

OVARIAN SURVEILLANCE

At present ovarian surveillance has not yet been demonstrated on a population screening level to reduce mortality and as such general population screening is not currently recommended (31).

There is no current NHS ovarian cancer surveillance program for women at increased risk. The UKFOCS study reported that ROCA-based screening (screening with CA-125, interpreted using the risk of ovarian cancer algorithm (ROCA), and transvaginal sonography (TVS)) for women at high risk of tubo-ovarian cancer demonstrated a stage shift. However, it remains unknown whether this screening would improve survival in screened high-risk women (32). The results of the ALDO study which has evaluated the utility of ROCA in *BRCA1* and *BRCA2* carriers is awaited. No studies to date have specifically evaluated ovarian surveillance for *RAD51C, RAD51D, BRIP1* or *PALB2* carriers.

RISK REDUCING OVARIAN/FALLOPIAN TUBE SURGERY

RISK REDUCING BILATERAL SALPINGO-OOPHORECTOMY

Historically in UK practice a lifetime ovarian cancer risk of 10% has been used as the threshold of risk for recommendation of referral for risk reducing bilateral salpingo-oophrectomy (RRBSO). However, prior to comprehensive risk assessment models for women both with and without a recognised causative gene in a family, calculation of individualised risk has been complex. As a result, most typically referral for RRBSO has been based on either a genetic diagnosis in a family or clinically based criteria e.g., two or more cases of ovarian cancer in a family. However, UK based studies have demonstrated that RRBSO is cost-effective above a 4-5% lifetime OC risk threshold and have suggested that women who fall above this level of risk should be offered the opportunity to discuss their options regarding RRBSO (33,34).

Whilst there is no dispute that risk reducing surgery reduces ovarian cancer risk, there are also a number of potential long-term morbidity sequelae of RRBSO if undertaken prior to natural menopause (typically age 50–51 years), that need to be considered when making recommendations. These sequelae can include depression, anxiety, dementia and cognitive decline, parkinsonism, glaucoma, chronic kidney disease, stroke and multi-morbidity. Some of these outcomes are attenuated by the use of HRT; however, the risk is not eliminated by HRT for some sequelae including depression, anxiety, parkinsonism, glaucoma and chronic kidney disease (35–42).

It is standard practice to recommend HRT (if no prior breast cancer diagnosis) for women undertaking RRBSO prior to the age of natural menopause. HRT compliance is necessary to minimise the detrimental consequences of premature menopause. However, poor compliance rates varying from 25–60% have been reported in some studies.

The acceptability of RRBSO to patients has also been evaluated. General population surveys demonstrate that women are willing to undertake ovarian cancer risk based interventions including surgery/RRBSO following risk stratification (43–45). Population intervention studies on personalised ovarian cancer risk estimation show acceptability of the 5% risk threshold in decision making (46).

At present no UK specific guidelines for management of ovarian cancer risk for *RAD51C, RAD51D, BRIP1 or PALB2* are published**.** As a comparison NCCN (National Comprehensive Cancer Network) guidelines recommend consideration of RRBSO from age 45-50 for *BRIP1, RAD51C and RAD51D* carriers taking into consideration relevant family history.

For *PALB2* NCCN do not recommend risk reducing strategies based on carrier status alone, and suggest the patient should be managed based on family history. More recent ACMG guidelines for *PALB2* suggest RRBSO should be considered in a non-directive counselling process taking additional risk and protective factors into consideration as outlined above. If a decision is made in favour of RRBSO, performing the procedure at or after menopause is considered appropriate, considering that the risk before this is very small (3).

RISK REDUCING SALPINGECTOMY WITH DELAYED OOPHORECTOMY

It is now recognised that the fallopian tubes play a key role in pathogenesis of ovarian cancer. Therefore, the possibility of a two-step process of salpingectomy with delayed oophorectomy may be a novel risk-reducing intervention for women at increased risk of ovarian cancer, with the benefit of delaying or avoiding a surgically induced menopause.

A recent non-randomised multicentre study from Holland that included 577 *BRCA1* and *BRCA2* carriers who had undergone either risk reducing salpingectomy or RRBSO with HRT replacement, compared menopause related quality of life after the two procedures and demonstrated that patients have a better menopause-related quality of life after risk reducing salpingectomy compared to RRBSO regardless of HRT (47).

In the UK, the PROTECTOR study is currently evaluating the option of risk reducing salpingectomy with delayed oophorectomy for women at increased lifetime risk of ovarian cancer (48). Women who are carriers of a pathogenic variant in *BRCA1, BRCA2, PALB2, BRIP1, RAD51C, RAD51D* and women assessed to be at increased familial risk are eligible to participate in this research study.

Supplementary Information

Table 1. Estimated age-specific cancer incidences and cumulative cancer risks for *RAD51C* and *RAD51D* pathogenic variant carriers. Taken directly from Yang et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst 2020;112(12):1242–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32107557

	RAD51C pathogenic variant carriers		RAD51D pathogenic variant carriers	
Age, y	BC	TOC	BC	TOC
Estimated incidences per 1000 person-years (95% CI)*				
30	0.4 (0.2 to 0.5)	0.05 (0.01 to 0.2)	0.3 (0.2 to 0.5)	0.03 (0.007 to 0.1)
40	2 (1 to 3)	0.3 (0.2 to 0.8)	2 (1 to 2)	0.3 (0.1 to 0.7)
50	5 (3 to 6)	2 (1 to 3)	4 (3 to 6)	2 (1 to 3)
60	6 (4 to 9)	7 (4 to 11)	6 (4 to 9)	6 (4 to 8)
70	7 (5 to 10)	3 (1 to 8)	7 (4 to 10)	5 (2 to 9)
79	8 (5 to 11)	1 (0.2 to 8)	7 (5 to 11)	3 (0.9 to 12)
Estimated cumulative risks, % (95% CI)*				
30	0.1 (0.08 to 0.2)	0.02 (0.02 to 0.02)	0.1 (0.07 to 0.2)	0.02 (0.02 to 0.02)
40	1 (0.7 to 1)	0.2 (0.08 to 0.4)	0.9 (0.6 to 1)	0.1 (0.06 to 0.3)
50	4 (3 to 6)	1 (0.6 to 2)	4 (2 to 5)	0.8 (0.5 to 2)
60	9 (6 to 12)	4 (3 to 7)	8 (6 to 12)	4 (3 to 7)
70	15 (11 to 21)	9 (6 to 14)	14 (10 to 20)	9 (6 to 14)
80	21 (15 to 29)	11 (6 to 21)	20 (14 to 28)	13 (7 to 23)

*Assuming the UK population calendar and cohort-specific incidences for an individual born between 1950 and 1959. Mortality is not accounted for absolute risk estimates. BC = breast cancer; CI = confidence interval; TOC = tubo-ovarian carcinoma.

Table 2. For each age, the risk of developing the cancer in the next 10 years. (Source: Personal communication Yang et al.)

	Age	10-year risk	10-year risk
Breast cancer		*RAD51C*	*RAD51D*
	20	0.1%	0.1%
	30	0.9%	0.8%
	40	3.0%	2.7%
	50	5.2%	4.8%
	60	6.8%	6.3%
	70	7.0%	6.4%
Ovarian cancer		*RAD51C*	*RAD51D*
	30	0.1%	0.1%
	40	0.9%	0.7%
	50	3.4%	3.5%
	60	4.9%	5.2%
	70	2.0%	3.8%

Table 3. Estimated age-specific cancer incidences and absolute cancer risks for *PALB2* pathogenic variant carriers. Taken directly from Yang et al. Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families. J Clin Oncol [Internet]. 2020;38(7):674–85. Available from http://www.ncbi.nlm.nih.gov/pubmed/31841383

TABLE 2. Estimated Age-Specific Cancer Incidences and Absolute Risks for Persons With *PALB2* Pathogenic Variants

Age (years)	Female Breast Cancer	Ovarian Cancer	Male Breast Cancer	Female Pancreatic Cancer	Male Pancreatic Cancer
Estimated Incidence (per 1,000 person-years) for Persons With *PALB2* Pathogenic Variants (95% CI)[a]					
30	2 (1 to 3)	0.09 (0.04 to 0.2)	0.002 (0.0004 to 0.01)	0.006 (0.003 to 0.01)	0.007 (0.004 to 0.01)
40	9 (7 to 11)	0.3 (0.1 to 0.6)	0.02 (0.004 to 0.1)	0.03 (0.01 to 0.05)	0.04 (0.02 to 0.09)
50	18 (14 to 22)	0.7 (0.3 to 1)	0.07 (0.01 to 0.4)	0.1 (0.06 to 0.2)	0.2 (0.1 to 0.4)
60	20 (16 to 25)	1 (0.6 to 3)	0.2 (0.03 to 1)	0.4 (0.2 to 0.8)	0.6 (0.3 to 1)
70	19 (14 to 25)	2 (0.8 to 4)	0.4 (0.07 to 2)	1 (0.5 to 2)	1 (0.6 to 2)
79	17 (11 to 25)	2 (1 to 4)	0.6 (0.1 to 3)	2 (0.8 to 3)	2 (1 to 4)
Estimated Absolute Risk (%) for Persons With *PALB2* Pathogenic Variants (95% CI)[a]					
30	0.7 (0.5 to 1)	0.02 (0.02 to 0.02)	0.0001 (0.0001 to 0.0001)	0.0009 (0.0009 to 0.0009)	0.002 (0.002 to 0.002)
40	5 (4 to 7)	0.2 (0.1 to 0.4)	0.009 (0.002 to 0.05)	0.01 (0.008 to 0.03)	0.02 (0.01 to 0.04)
50	17 (13 to 21)	0.6 (0.3 to 1)	0.05 (0.008 to 0.3)	0.07 (0.04 to 0.1)	0.1 (0.06 to 0.2)
60	31 (26 to 38)	2 (0.8 to 3)	0.2 (0.03 to 0.9)	0.3 (0.2 to 0.6)	0.5 (0.2 to 0.9)
70	44 (37 to 52)	3 (1 to 6)	0.4 (0.07 to 2)	1 (0.5 to 2)	1 (0.7 to 3)
80	53 (44 to 63)	5 (2 to 10)	0.9 (0.2 to 5)	2 (1 to 4)	3 (2 to 5)

[a]Assuming population calendar and cohort-specific incidences for an individual born between 1950 and 1959. Mortality is not accounted for in absolute risk estimates.

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