Referral to Clinical Genetics

- It is recommended that all patients identified as carriers of a germline pathogenic variant (GPV – i.e. class 4 – likely pathogenic variant, or class 5 -pathogenic variant as determined by ACMG/AMP guidelines) in BRCA1 or BRCA2 are referred to clinical genetics to receive individualised advice on cancer risks, management of cancer risks, reproductive options and to facilitate cascade testing of at-risk relatives.

General population lifetime cancer risk estimates


Breast, contralateral breast and ovarian cancer cumulative risk estimates

- The estimates presented are from Kuchenbaecker et al., 2017
- This was a prospective cohort study of carriers of PV recruited through 3 consortia. It included 6000 BRCA1 and 3800 BRCA2 GPV carriers. 94% were ascertained through familial cancer clinics and 6% via population-based studies.
- A limitation of this data with respect to ovarian cancer risk is that the study did not include many women of 70 years or older, so the risks artificially appear to plateau at this age.

Breast cancer screening recommendations

- Are presented from NICE Clinical Guideline CG164 (NICE, 2013) and PHE Protocols for surveillance of women at very high risk of developing breast cancer (Dec 2021)
- https://www.nice.org.uk/guidance/cg164

Oral contraception

Early studies on the effect of oral contraceptive use (OCP) on breast cancer risk among carriers of a pathogenic BRCA1/2 variant have reported conflicting data (Narod et al.,2002; Milne et al., 2005; Haile et al., 2006). Conflicting data may be due to differences in study design, differences in risk based on family history or other factor or OCP formulation. Two meta-analyses and a more recent case-control study have showed that OCP use is not significantly associated with breast cancer risk in carriers of a pathogenic BRCA1/2 variant (Lee et al., 2008; Iodice et al., 2010; Moorman et al., 2013). However, larger prospective trials are likely needed to fully understand the impact of OCP on breast cancer risk in BRCA1/2 carriers.

OCP use may reduce the risk of ovarian cancer. Two meta-analyses have demonstrated that OCP use significantly reduced the risk for ovarian cancer for both BRCA1 and BRCA2 carriers (Iodice et al., 2010; Moorman et al., 2013).

We advise that women discuss contraception with their GP to assess the range of available options. OCP use can be considered, providing patients are informed about the need for further data to fully understand impact on breast cancer risk and alternative contraceptive methods have been discussed.
Pancreatic, male breast and other cancer risk estimates

- The estimates presented are from Li et al., 2022 rounded to nearest whole %.
- For pancreatic cancer, whilst the cumulative lifetime risks are similar for BRCA1 and BRCA2, relative risks are slightly higher for BRCA2 (BRCA1; RR 2-3 lifetime risk - 1-4%, BRCA2; RR 3-6 lifetime risk-3-5%). RR was higher for BRCA2 carriers under 65 years. It is important to consider relevant family history and other risk factors e.g. smoking.
- The study also reported a possible association between BRCA1 and BRCA2 GPV and stomach cancer. They reported BRCA1 absolute risks for stomach cancer to age 80 of 1.6% (male) and 0.7% (female); and BRCA2 3.5% (male and female). However, the association between BRCA GPV and stomach cancer remains under considerable debate.

Prostate cancer risk estimates

- The estimates presented are from Nyberg et al., 2020 and Li et al., 2022. rounded to nearest whole %.
- Nyberg (2020) was a prospective cohort study (EMBRACE) of GPV carriers recruited via familial cancer clinics. It included 376 BRCA1 and 447 BRCA2 mutation carriers.
- Li (2022) was a retrospective cohort study of GPV carriers recruited through 26 consortia globally. It included 7281 families ascertained through familial cancer clinics and 337 families via population-based studies (i.e. unselected for family history).
- The Nyberg data when unadjusted for PSA screening effects reported much higher cumulative risks; 29% (17 to 45) by age 85 for BRCA1 and 60% (43 to 78) by age 85 for BRCA2 which are much higher than those presented in Li (2022) and likely explained by the detection of indolent prostate cancers undetectable in the absence of screening. The Nyberg data presented in the table is adjusted for screening effect.
- Other factors may influence prostate cancer risks. Risks for BRCA2 GPV carriers increase with the number of relatives affected by prostate cancer. Prostate cancer risks are also affected by the location of the BRCA2 GPV within the gene. BRCA2 GPV both within and outside the ovarian cancer cluster region (OCCR) are associated with elevated prostate cancer risk compared to the general population. However, carriers of variants within the OCCR may be at comparatively lower risk than carriers of variants outside the OCCR. At present this does not alter surveillance recommendations and the same recommendations are made for all BRCA2 carriers.

Prostate cancer screening recommendations

- BRCA2 recommendations are based on European Association of Urology guidelines (Mottet et al., 2021), and interim results from the IMPACT study (Page et al., 2019)

It is important to manage patients in the context of their family history of cancer.
References: