Risk Management for an Unaffected Female BRCA1 Mutation Carrier

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Information for families with a BRCA1 mutation
Contacting family members about hereditary cancer

Familial breast and ovarian cancer predisposition due to a germline mutation in the BRCA1 gene is an autosomal dominant condition.

Target group

- unaffected known or obligate female BRCA1 mutation carrier
- 50% risk of being BRCA1 mutation carrier

Exclusion criteria

Not suitable for:

- known male BRCA1 mutation carrier
- known BRCA2 mutation carrier
- a female BRCA1 mutation carrier affected by breast or ovarian cancer
- high risk breast cancer family with uninformative BRCA result or no DNA testing available
- high risk breast and ovarian cancer family with uninformative BRCA result or no DNA testing available

Lifetime risk of cancer

Cancer	*BRCA1 mutation carrier up to age 70 yrs	General female population by age 85 yrs
Breast cancer	57% (95% CI, 47% to 66%)[1] **Residual lifetime risk is dependent on age at consultation****	11%
Ovarian and fallopian tube cancer	40% (95% CI, 35% to 46%)[1] **Residual lifetime risk is dependent on age at consultation****	1.2%
Primary peritoneal cancer	< 2.0% (post RRSO***)[2]	<1%

* Estimation of cancer risk and age penetrance varies according to different populations' assessed[1]. Factors which influence risk include age of onset of the proband, family history and whether the proband had unilateral or bilateral breast cancer. No clinically relevant modifier genes for BRCA1 associated cancers have been identified.
** **Suthers, G. K. 2007. "Cancer risks for Australian women with a BRCA1 or a BRCA2 mutation." ANZ J Surg 77 (5):314-319**
*** Risk reducing salpingo-oophorectomy (RRSO)

Cancer risk management guidelines

Cancer type	Recommendations	
Breast	Surgical	▪ offer bilateral risk reducing mastectomy followed by self surveillance of breast area. The greatest benefit is predicted when surgery occurs ≤40 yrs[3] ▪ alternatively in the absence of bilateral risk reducing mastectomy recommend RRSO preferably ≤40 yrs[3]

	Surveillance	▪ in families with breast cancer <35 yrs, individualised screening recommendations may apply ▪ otherwise screening should start at 30yrs ▪ 30-50yrs – annual MRI*+MMG* (+/- US*) ▪ >50 yrs – annual mammogram +/- annual US + CBE* ▪ 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 **Cancer Australia Risk-reducing medication resource**
Ovarian/fallopian tube	Surgical	▪ recommend RRSO from age <40[3] with peritoneal lavage and close histological examination to exclude occult malignancy
	Surveillance	▪ serum CA125 and/or transvaginal ultrasound (TVU) is not recommended as there is no evidence of benefit[5]. The discovery and investigation of abnormal findings can result in unnecessary anxiety and the investigations can carry significant risks. See **Cancer Australia for further information**
All cancers		▪ exercise, maintain reasonable weight, healthy diet, limit alcohol intake, breast feed, avoid the use of combination post menopausal hormonal replacement therapy beyond the age of 50 yrs without specialist advice
*Abbreviations: US – ultrasound, CBE – clinical breast examination, MMG mammogram (digital if available), MRI – magnetic resonance imaging.		

Management of associated health problems and side effects

Management of early menopause

Contraception and fertility

Evidence for cancer risk management guidelines

Breast

Surgical

Bilateral risk reducing mastectomy reduces cancer risk by at least 90% (depending on the operation performed). In the absence of bilateral risk reducing mastectomy, risk reducing salphingo-oophorectomy (RRSO), reduces breast cancer risk by 56% in BRCA1 carriers and is associated with a decrease in both cancer specific and all cause mortality[2]. Maximal risk reduction is achieved by RRSO by age of 40[3].

Surveillance

MRI+/-MMG is the preferred screening technique due to its high sensitivity. This imaging detects tumours which are smaller and more likely to be node negative than mammography. 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 survival in BRCA1 mutation carriers. However, for women who do not choose risk reducing surgery, surveillance is strongly recommended.

The rate of cancers occurring between annual screening (interval cancers) is higher in BRCA1 mutation carriers than other high risk populations[4].

Risk-reducing medication

Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer in high risk women. Current studies have not included enough BRCA1 or BRCA2 mutation carriers to determine if it is effective in this population. Tamoxifen and raloxifene are not PBS-subsidised for primary prevention of breast cancer. These medications are associated with side effects. In view of these potential side effects risk-reducing medications should be discussed with an experienced medical professional to determine the relevant risks and benefits in an individual mutation carrier. See **Cancer Australia**

Risk-reducing medication resource

Ovarian and fallopian tube

Surgical

RRSO reduces the risk of developing ovarian and fallopian tube cancer in BRCA1 mutation carriers by 98%[2].

Surveillance

Annual transvaginal ultrasound (TVU) and serum CA125 levels do not detect ovarian cancers at an earlier stage, nor do they affect outcomes[5]. This is true of women in the general population and women at high risk of hereditary ovarian cancer. The discovery and investigation of abnormal findings can result in unnecessary anxiety and the investigations can carry significant risks.
See **Cancer Australia for further information**

Risk-reducing medication

Although there is evidence that the combined oral contraceptive pill can reduce the ovarian cancer risk, it is significantly less effective than RRSO and it is not recommended for cancer prevention.

Support and information

First degree blood relatives (parents/brothers/sisters/children) are at 50% risk of having inherited the BRCA1 mutation. First degree relatives should be referred to a local Family Cancer Clinic.

Link to an **information sheet on contacting relatives**

Website resources

Centre for Genetics Education NSW Health
Association of Genetic Support of Australasia INC (AGSA)
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.

For further references used to develop this protocol please see the History tab

References

1. **Chen, S. and G. Parmigiani. 2007. "Meta-analysis of BRCA1 and BRCA2 penetrance." J Clin Oncol 25(11):1329-1333.** - **Link to external article**
2. **Domchek, S. M., T. M. Friebel, C. F. Singer, et al. 2010. "Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality." JAMA 304(9):967-975**
3. **Kurian, A. W., B. M. Sigal and S. K. Plevritis. 2010. "Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers." J Clin Oncol 28(2):222-231.** - **Link to external article**
4. **Rijnsburger, A. J., I. M. Obdeijn, R. Kaas, et al. 2010. "BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study." J Clin Oncol 28 (36):5265-5273.**
5. **Woodward, E. R., H. V. Sleightholme, A. M. Considine, et al. 2007. "Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective." Bjog 114(12):1500-1509.** - **Link to external article**

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