Risk management for a female ATM (c.7271T>G) mutation carrier

ID: 1610 v.4 **Endorsed**

Related pages:

- Informing family members about hereditary cancer
- Genetic testing for the (c.7271T>G) mutation in the ATM gene
- Facts for people and families with a faulty ATM gene

Summary

Familial breast cancer predisposition due to a germline mutation in the ATM gene is an autosomal dominant condition. Mono-allelic mutations in ATM have been estimated to confer a two-to threefold increased risk of breast cancer.[1, 2]

A specific ATM (c.7271T>G) mutation confers a higher risk of breast cancer similar to that associated with a germline BRCA2 gene mutation.[1, 2]

This risk management guideline has been developed for individuals who have **NOT** been diagnosed with a relevant cancer/tumour. The care of **affected** individuals should be individualised based on their clinical situation, and the monitoring they need as part of their treatment and post-treatment follow up.

Target group

- unaffected known or obligate female ATM (c.7271T>G) mutation carrier
- 50% risk of being ATM (c.7271T>G) mutation carrier.

Exclusion criteria

Not suitable for:

- a female carrier of another ATM mutation
- a female ATM mutation carrier affected by breast cancer
- individuals with a mutation in another breast cancer predisposition gene
- high risk breast cancer family with uninformative genetic test result or no DNA testing available
- high risk breast and ovarian cancer family with uninformative genetic test result or no DNA testing available.

Lifetime risk of cancer

Cancer	ATM (c.7271T>G) mutation carrier up to age 70 yrs	General female population by age 85 yrs**
Breast	47% (95% CI - 17% to 89%)[1]*	12.5%
Pancreas	May be increased [1, 3]	1.3%

**This information has been calculated by the author (Goldgar 2014) from unpublished data and is published here with permission.*

***Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. [Accessed September 2017]*

Cancer risk management guidelines

Cancer type	Recommendations***		
Breast	**Surveillance**	**Age to begin**	**Strategy and frequency**
		in families with breast cancer diagnosed under age 35 years individualised screening recommendations may apply. Otherwise screening should start at age 30 years.	
		between age 30-50 years	annual MRI + mammogram (+/- US)
		over age 50 years	annual mammogram +/- US + CBE
		pregnant	no MRI or mammogram, consider US
	Surgical		offer bilateral risk-reducing mastectomy followed by self surveillance of breast area. The greatest benefit would be predicted when surgery occurs at age ≤40 years.
	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.
Pancreas			no evidence of benefit from surveillance.

Abbreviations: US - ultrasound, CBE - clinical breast examination, MRI - magnetic resonance imaging.

****the impact of lifestyle on cancer risk should be discussed e.g. recommend regular exercise, maintain healthy weight, have a healthy diet, limit alcohol intake, do not smoke.*

Management of associated health problems

N/A

Evidence for risk management guidelines

At the present time, and while there is no specific evidence related to ATM (c.7271T>G) mutation carriers, these guidelines are based on those that apply to management of breast cancer risk in BRCA2 mutation carriers.

Breast

Surgical

Bilateral risk reducing mastectomy reduces breast cancer risk by at least 90%[4, 5] (depending on the operation performed). Statistically significant survival benefit associated with bilateral risk-reducing mastectomy compared with surveillance is yet to be demonstrated.

Risk reducing oophorectomy (RRSO) reduces breast cancer risk by 53% in BRCA2 carriers.[6] Although no specific studies have been done, a similar breast cancer risk-reduction would be expected from RRSO for women with a ATM (c.7271T>G) mutation.

Surveillance

MRI+MMG is the preferred screening technique due to its high sensitivity. MRI 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 prognosis and survival in ATM mutation carriers. Despite this lack of evidence, surveillance is strongly recommended for women who decide not to have risk reducing surgery.

Risk-reducing medication

Tamoxifen and raloxifene have been shown to reduce the risk of breast cancer in high risk women. To date studies have not included enough ATM mutation carriers to determine if it is effective for primary prevention in this population. In view of the potential side effects associated with tamoxifen/raloxifene, 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

Pancreas

There is currently no effective surveillance that detects early pancreatic cancer.

Support and information

First degree blood relatives (parents/brothers/sisters/children) are at 50% risk of having inherited the ATM (c.7271T>G) mutation. First degree relatives should be referred to a local family cancer clinic.

Link to information sheet on Informing family members about hereditary cancer.

Website resources

Centre for Genetics Education NSW Health
Genetic Alliance Australia
Breast Cancer Network Australia (BCNA)
Gene Support Connect Programme
Cancer Australia
Cancer Council Australia - Position statement - Combined oral contraceptives and cancer risk

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.

Further References

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

References

1 Goldgar, D. E., S. Healey, JG. Dowty, et al. 2011. "Rare variants in the ATM gene and risk of breast cancer." Breast Cancer Res 13(4):R73.

2 van Os, N. J., N. Roeleveld, C. M. Weemaes, et al. 2016. "Health risks for ataxia-telangiectasia mutated heterozygotes: a systematic review, meta-analysis and evidence-based guideline." Clin Genet 90(2):105-117.

3 Bartsch, D. K., T. M. Gress and P. Langer. 2012. "Familial pancreatic cancer--current knowledge." Nat Rev Gastroenterol Hepatol 9(8):445-453

4 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

5 Rebbeck, T. R., T. Friebel, H. T. Lynch, et al. 2004. "Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group." J Clin Oncol 22(6):1055-1062.

6 Rebbeck, T. R., N. D. Kauff and S. M. Domchek. 2009. "Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers." J Natl Cancer Inst 101(2):80-87.

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History

Version 4

Date	Summary of changes
26/03/2014	Discussed at October 30 2013 & March 5 2014 reference committee meetings and approved for publication. • review second yearly
31/07/2015	AGSA link updated to Genetic Alliance Australia.
07/01/2016	Sentence added to Risk Management template: "The impact of lifestyle on cancer risk should be discussed".
14/04/2016	Sentence added to Risk Management template: "This risk management guideline has been developed for individuals who have NOT been diagnosed with a relevant cancer/tumour. The care of affected individuals should be individualised based on their clinical situation, and the monitoring they need as part of their treatment and post-treatment follow up".
11/07/2016	Discussed at March 2016 reference committee meeting and the following changes made: • 7271T>G changed to c.7271T>G throughout document. • Evidence for cancer risk management guidelines for breast cancer updated. Review second yearly.
28/09/2016	'Unaffected' removed from title.
31/05/2017	Transferred to new eviQ website. Version number changed to V.3.
	Further references used to develop this protocol: Phillips, K. A., R. L. Milne, M. A. Rookus, et al. 2013. "Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers." J Clin Oncol 31(25):3091-3099 Rebbeck, T. R., T. Friebel, H. T. Lynch, et al. 2004. "Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group." J Clin Oncol 22(6):1055-1062 Rebbeck, T. R., N. D. Kauff and S. M. Domchek. 2009. "Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers." J Natl Cancer Inst 101(2):80-87 Chen, S. and G. Parmigiani. 2007. "Meta-analysis of BRCA1 and BRCA2 penetrance." J Clin Oncol 25(11):1329-1333 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 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 Rebbeck, T. R., T. Friebel, T. Wagner, et al. 2005. "Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group." J Clin Oncol 23(31):7804-7810 Antoniou, A., P. D. Pharoah, S. Narod, et al. 2003. "Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies." Am J Hum Genet 72(5):1117-1130. Heemskerk-Gerritsen, B. A., M. B. Menke-Pluijmers, A. Jager, et al. 2013. "Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis." Ann Oncol 24(8):2029-2035. Kriege, M., C. T. Brekelmans, C. Boetes, et al. 2006. "Differences between first and subsequent rounds of the MRISC breast cancer screening program for women with a familial or genetic predisposition." Cancer

Date	Summary of changes
	106(11):2318-2326 Moorman, P. G., L. J. Havrilesky, J. M. Gierisch, et al. 2013. "Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis." J Clin Oncol 31(33):4188-4198. 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. Warner, E., K. Hill, P. Causer, et al. 2011. "Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging." J Clin Oncol 29(13):1664-1669 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. Tracey E, Kerr T, Dobrovic A, Currow D et al 2010 "Cancer in New South Wales: Incidence and Mortality Report 2008". Sydney: Cancer Institute NSW, August 2010
19/09/2017	Discussed at May 2017 reference committee meeting and formally reviewed after with the following changes made: • Lifetime risk of cancer figures updated • Minor wording change throughout document • Version number changed to V.4. For annual review.

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