

Genetic predisposition to breast and ovarian cancer

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Introduction

BRCA1 and BRCA2 are the main genes involved in the hereditary breast and ovarian cancer syndrome with an autosomal dominant mode of inheritance. The frequency of germ-line BRCA1/BRCA2 pathogenic variants is about 1:400 to 1:800 among healthy women from the Western non-Jewish white population. Carrying a germ-line mutation in BRCA1 or BRCA2 is associated with 40% to 75% cumulative risk of developing breast cancer and 15% to 60% cumulative risk for ovarian cancer by age 70 years [1]. About 3-5% of all breast cancer and 10-15% of unselected invasive ovarian cancer cases are BRCA-related [2]. Other rare high- to moderate-risk inherited syndromes can associate breast or ovarian cancer [3, 4].

The rapid translation of next generation or massively parallel sequencing technology in diagnostic labora-

tory has opened impressive perspectives by allowing to test for multiple genes in a single assay (gene panel or exome) with substantial reductions both in costs and turn-around time. Some important issues have also been raised by this technological revolution, e.g. clinical validity or clinical utility of several genetic results, or identification of multiple variants of uncertain clinical significance [5, 6].

In Switzerland, testing for genetic predisposition to hereditary breast/ovarian cancer, particularly BRCA1/BRCA2, is available in a clinical setting. Cancer risk assessment and genetic counseling are mandatory before and after genetic testing (i.e. pre- and post-test counseling). This genetic analysis is covered by health insurances only after formal genetic counseling and informed consent according to the KVL/OPAS/OPre art. 12d, let. f [7]. Twenty-five centres throug-

hout Switzerland are currently doing risk-assessment and counseling individuals with an increased risk for hereditary breast/ovarian cancer syndromes [cf. Annex]. Routine BRCA1 or BRCA2 testing is not recommended [4, 8-10]. Only individuals with a personal history or whose maternal or paternal family history is suggestive of an increased risk of pathogenic variants in high-risk cancer predisposition genes should be referred for counseling and considered for genetic testing, if they agree with this procedure. Targeted medical interventions such as intensive screening, prophylactic surgery, or chemoprevention can be recommended according to the individual risk situation, and particularly to unaffected family members identified as carriers of pathogenic genetic variants [2, 4, 10, 11].

Swiss guidelines for genetic counseling and testing for breast and ovarian cancer predisposition

The present paper summarises the Swiss guidelines for genetic counseling and ultimately testing individuals with an increased probability for carrying mutations in high-risk breast/ovarian cancer predisposition genes, particularly BRCA1/BRCA2. Risk-assessment is mainly based on some particular personal and/or family history patterns on both side of the family, including:

- early-age of onset of breast cancer;
- number of breast cancer cases across generations;
- bilateral breast cancer;
- ovarian cancer: of note, peritoneal and fallopian tube cancers should be considered as part of the spectrum of the hereditary breast/ovarian cancer syndrome;
- ethnic origin: currently limited to Ashkenazi Jews in our population.

Adapted from recently published guidelines [3, 4, 8, 10, 12], it is reasonable to refer individuals with the following personal and/or family history for genetic counseling and considering testing for high-risk predisposition genes, particularly BRCA1/BRCA2 (see box on the right).

Swiss guidelines for referral individuals for risk assessment, genetic counseling and testing for breast/ovarian cancer predisposition syndrome.

I. Individuals with a close relative¹ with a known pathogenic variant in BRCA1 or BRCA2, or in another gene conferring high risk for breast and ovarian cancer.

II. WOMEN with a personal history of BREAST CANCER and one of the following:

- Age at diagnosis < 40 years;
- Triple negative (estrogen receptor, progesterone receptor and HER2 negative) breast cancer ≤ 60 years;
- Age at diagnosis ≤ 50 years, with ≥ 2 close relatives¹ with breast cancer at any age or with only 1 close relative¹ with breast cancer ≤ 50 years;
- Bilateral breast cancer, if the first cancer was diagnosed ≤ 50 years;
- Bilateral breast cancer at any age, with ≥ 1 close relative¹ with breast cancer [if only one relative affected, then age at diagnosis ≤ 50 years];
- Diagnosed at any age, with ≥ 1 close relative¹ with ovarian² cancer at any age;
- Diagnosed at any age, with ≥ 2 close relatives¹ with breast cancer [particularly if ≥ 1 breast cancer diagnosed ≤ 50 years or if bilateral breast cancer];
- A close male relative¹ with breast cancer (any age);
- A personal history of ovarian² cancer;

III. Women with a personal history of OVARIAN² CANCER and one of the following:

- Non-mucinous epithelial subtypes, particularly high grade serous histology, at any age;
- A personal history of breast cancer;
- One or more close relatives¹ with ovarian² cancer (any age);
- One or more close female or male relatives¹ with breast cancer, particularly if breast cancer diagnosed ≤ 50 years;

Comments

- 1) Meeting one or more of these criteria warrants further personalized genetic risk assessment and genetic counseling which will cover explanation of inheritance pattern, available testing options, discussion of disease management, treatment, surveillance and prevention options.
- 2) Consider referral of cases with a weaker history of breast cancer if there is a family history of pancreatic cancer or prostate cancer, particularly at an early age at diagnosis (≤ 60 years), or sarcoma < 45 years, or glioma, or childhood adrenal cortical carcinoma, or complicated patterns of multiple cancers at a young age.
- 3) Particular clinical situations not included in one of the above criteria should be discussed individually, e.g. ductal carcinoma in situ (DCIS) at an early age of onset (< 40 years), small or uninformative families or adoption.
- 4) Borderline ovarian tumour is not considered as part of the spectrum of the hereditary breast/ovarian cancer syndrome.
- 5) Among the Ashkenazi Jewish population, the 3 BRCA1 and BRCA2 founder pathogenic variants (BRCA1: c.68_69delAG, c.5266dupC; BRCA2: c.5946delT) account for 98-99% of mutations identified and are carried by about 2.6% (1/40) of this population.
- 6) When an appropriate affected family member is unavailable, testing of a family relative without a cancer diagnosis should be considered.
- 7) Genetic testing for adult onset diseases, such as BRCA1/BRCA2-related disorders, is not recommended in children < 18 years.
- 8) Genetic testing on formalin-fixed and paraffin-embedded tumoral tissue is yet feasible to identify mutations predictive of response to treatment, e.g. identification of somatic or potentially germ-line BRCA1 or BRCA2 pathogenic variants and decision to introduce platinum-based drugs or poly(ADP-ribose) polymerase inhibitors. Currently, this molecular approach does not replace the search for germ-line pathogenic variants based on a blood sample in the context of a suspicion of genetic predisposition to hereditary breast/ovarian cancer.

IV. MEN with a personal history of BREAST CANCER:

- Particularly, if one or more close male relatives¹ with breast cancer;
- Particularly, if one or more close female relatives¹ with breast or ovarian² cancer;

V. Ashkenazi Jewish heritage:

- Search for the 3 founder BRCA1 and BRCA2 pathogenic variants³ regardless of personal or family history;

VI. Family history only (i.e. unaffected individuals):

- One or more close relatives¹ with breast or ovarian² cancer fulfilling one of the above criteria (points II-IV).

¹ Close relative is defined as a first- or a second-degree relative on the same side of the family.

- first-degree relatives: mother/father, sister/brother, daughter/son;

- second-degree relatives: grandparents, aunt/uncle, niece/nephew, grandchildren.

² Ovarian cancer also includes primary peritoneal cancer and fallopian tube cancer.

³ BRCA1: c.68_69delAG, c.5266dupC; BRCA2: c.5946delT.

Conclusion

Cancer genetic predisposition is a complex clinical and socio-psychological condition which requires harmonization in medical practice and close interdisciplinary collaboration. An adequate identification of individuals who can potentially benefit from genetic counseling and testing is the essential prerequisite for a positive risk/benefit ratio [9]. Health care professionals should therefore be aware of the personal and/or family history patterns that are associated with an increased risk for germ-line pathogenic variants to allow for the most effective management of hereditary breast and ovarian cancer families and the most efficient utilization of health care resources.

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Conflict of interest

None of the authors have any conflict of interest to declare.

References

1. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al., EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst.* 2013;105(11):812-22.
2. Tung N. Management of women with BRCA mutations. *JAMA.* 2011;305(21):2211-20.
3. The American College of Obstetricians and Gynecologists (ACOG). Committee Opinion. Number 634. June 2015. Available from: www.acog.org.
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast and ovarian [v.2. 2016; March 15, 2016]. Available from: www.nccn.org.
5. Easton DF, Pharoah PD, Antoniou AC, Tischkowitz M, Tavtigian SV, Nathanson KL, et al. Gene-panel sequencing and the prediction of breast-cancer risk. *N Engl J Med.* 2015;372(23):2243-57.
6. Thompson ER, Rowley SM, Li N, McInerney S, Devereux L, Wong-Brown MW, et al. Panel testing for familial breast cancer: calibrating the tension between research and clinical care. *J Clin Oncol.* 2016;34(13):1455-9.
7. Verordnung des EDI über Leistungen in der obligatorischen Krankenpflegeversicherung. [updated 2016 May 1]. Available from: <https://www.admin.ch/opc/de/classified-compilation/19950275/index.html>
8. Ordonnance du DFI sur les prestations dans l'assurance obligatoire des soins en cas de maladie. [updated 2016 May 1]. Available from: <https://www.admin.ch/opc/fr/classified-compilation/19950275/index.html>
9. Ordinanza del DFI sulle prestazioni dell'assicurazione obbligatoria delle cure medico-sanitarie. [updated 2016 May 1]. Available from: <https://www.admin.ch/opc/it/classified-compilation/19950275/index.html>
10. Nelson HD, Huffman LH, Fu R, Harris EL. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systemic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;143(5):362-79.
11. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol.* 2010;28(5):893-901.
12. National Institute for Health and Clinical Excellence (NICE). Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical guideline (CG164) 2013. Available from: www.nice.org.uk.
13. Robson M, Offit K. Management of an inherited predisposition to breast cancer. *N Engl J Med.* 2007;357(2):154-62.
14. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol.* 2016;(suppl 5):v103-10.

Annex

Address and contact information of the Swiss centres that offer genetic counseling and evaluation for cancer predisposition gene testing according to the Swiss regulation of the Krankenpflege Leistungsverordnung (KVL)/Ordonnance sur les prestations de l'assurance des soins (OPAS)/Ordinanza sulle prestazioni (OPre) [7]. Regular update on <http://sakk.ch/en/sakk-provides/for-patients/genetic-counseling/>

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