

Swiss guidelines for counselling and testing

Genetic predisposition to breast and ovarian cancer

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Zusammenfassung

Diese Empfehlungen dienen Allgemeinmedizinerinnen zur besseren Evaluierung jener Personen, die im Kontext individueller oder familiärer medizinischer Vorbelastungen mit genetisch prädisponierter Entwicklung von Brust- oder Ovarialkrebs einer besonderen klinischen Behandlung bedürfen. Eine solche Behandlung umfasst eine onkogenetische Untersuchung, bzw. eine gezielte genetische Beratung, die beispielsweise die Durchführung von Molekularanalysen empfehlen könnte. Letztere dienen der Identifizierung pathogener Varianten in jenen Genen, die sich im Vergleich zur Normalpopulation durch ein erhöhtes Risiko zur Entwicklung von Brust- oder Ovarialkrebs auszeichnen. Für Personen mit einer solchen genetischen Prädisposition stehen besondere Kontroll- und Präventivmassnahmen zur Verfügung, deren Wirksamkeit bereits unter Beweis gestellt wurde.

Die hier genannten Empfehlungen richten sich auch an die Vertreter der obligatorischen Krankenpflegeversicherung gemäss Bundesgesetz über die Krankenversicherung (KVG) im Zusammenhang mit der Übernahme der Kosten für besagte Molekularanalysen in Übereinstimmung mit der geltenden Gesetzgebung.

Im Übrigen gleichen diese Empfehlungen jenen, die in diesem Kontext bereits in anderen Ländern oder anderen internationalen Fachgesellschaften eingeführt wurden.

Der Bereich der Genanalyse unterliegt – vor allem in der prädiktiven Onkologie – einem ständigen Entwicklungsprozess. Die hier genannten Empfehlungen reflektieren den aktuellen Wissensstand per Juli 2016. Sie werden in regelmässigen Abständen aktualisiert und sind frei auf der Webseite der Schweizerischen Arbeitsgemeinschaft für Klinische Krebsforschung zugänglich (<http://sakk.ch/de/die-sakk-bietet/fuer-patienten/genetische-beratung/>).

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 laboratory 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 counselling are mandatory before and after genetic testing (i.e. pre- and post-test

Swiss guidelines for referral individuals for risk assessment, genetic counselling 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 (oestrogen 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;

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.

counselling). This genetic analysis is covered by health insurances only after formal genetic counselling and informed consent according to the KVL/OPAS/OPre art. 12d, let. f [7]. Twenty-five centres throughout Switzerland are currently doing risk assessment and counselling individuals with an increased risk for hereditary breast/ovarian cancer syndromes [cf. Annex online]. Routine *BRCA1* or *BRCA2* testing is not recommended [4, 8]. 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 counselling 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, 8, 9].

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

The present paper summarises the Swiss guidelines for genetic counselling 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 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], it is reasonable to refer individuals with the following personal and/or family history for genetic counselling and testing for high-risk predisposition genes, particularly *BRCA1/BRCA2* (see box on the left).

Comments

- 1) Meeting one or more of these criteria warrants further personalised genetic risk assessment and genetic counselling 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.

Conclusion

Cancer genetic predisposition is a complex clinical and socio-psychological condition which requires harmonisation in medical practice and close interdisciplinary collaboration. An adequate identification of individuals who can potentially benefit from genetic counselling and testing is the essential prerequisite for a positive

risk/benefit ratio. 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 utilisation of health care resources.

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Address and contact information of the Swiss centres that offer genetic counselling 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) are published online: www.saez.ch → Aktuelle Ausgabe or → Archiv → Ausgabe 18. Regular update on <http://sakk.ch/en/sak-provides-for-patients/genetic-counseling>

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