The clinical implications of genetics. BRCA1- and BRCA2-positive: how do I proceed? Implications for ovarian cancer prevention

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Introduction: defining high risk

The life-time risk of a woman to develop ovarian cancer has been estimated to be 1.1% [1]. However, women with a hereditary elevated risk of ovarian cancer have a much higher chance of developing cancer. Approximately 5% of all ovarian cancer cases are hereditary, mostly due to a mutation in the BRCA1 or BRCA2 gene. BRCA1/2 mutation carriers have a high life-time risk of developing ovarian cancer, reportedly up to 46% for BRCA1 and up to 27% for BRCA2 at the age of 70 [2, 3]. Although these highest risk estimates have not been confirmed by other studies, risks generally are calculated to be 40% and 20%, respectively.

These risks definitely warrant preventive measures. To decrease the mortality of ovarian cancer, BRCA1/2 mutation carriers are currently being counseled for gynecological screening or prophylactic bilateral salpingo-oophorectomy (BSO).

Based on the family history a risk profile can be made, indicating whether DNA testing would be indicated. In about half of the women from high-risk families DNA testing will be able to show or exclude a BRCA mutation. This low figure of definitive risk assignment is partly due to the fact that not yet all mutations can be found, in particular not in women from families where there are no affected members alive for testing. Also (young) women might decide not to opt for DNA testing for socio-psychological reasons or to avoid insurance problems.

In those patients where DNA testing has not been possible or has resulted in an inclusive result, risk may be calculated on the basis of the family history, also allowing a decision on a preventive strategy.

Finally, questions may arise regarding reproductive genetic counseling, as prenatal diagnosis and pre-implantation genetic diagnosis (PGD) are currently feasible. Based on the scarce discussions and descriptive studies one may conclude that (i) prenatal diagnosis and subsequent selective abortion in case of carriership cannot as such be regarded as ethically unacceptable, and (ii) both genetic and ethical counseling should always precede antenatal diagnosis [4].

In conclusion, high-risk women may be identified by both family history analysis and mutation detection. A large proportion of presumably high-risk women will, however, not have a documented carrier status. Antenatal diagnosis is feasible but still remains controversial. Counseling on preventive strategies cannot be based solely on mutation carrier status.

Screening for ovarian cancer

No precancerous lesions, if they exist at all in the ovary, can be detected. Screening for ovarian cancer is therefore aimed at the detection of cancer at an early stage, which would still carry a favorable prognosis. Screening is usually done by (semi-)annual measurement of the tumor marker CA125 in serum and transvaginal ultrasonography (TVU).

The role of serum CA125 as a screening tool for early detection of ovarian cancer in high-risk women is largely unknown. Single measurements of serum CA125 lack adequate sensitivity (<50%) or sufficient positive predictive value (PPV < 13%) [5]. To achieve a higher performance of gynecological screening TVU has been combined with serum CA125 measurements. This so-called multimodal screening for ovarian cancer has been adapted as the best approach for early detection of ovarian carcinoma resulting in a markedly improved PPV of 40% [6, 7].

While the efficacy of prophylactic BSO has been demonstrated [8], efficacy of gynecological screening with (bi-)annual TVU and the serum tumor marker CA125 is still unclear.

To summarize the literature on well-defined high-risk populations, in nine cohort studies (three prospective and six retrospective) the value of screening was assessed. TVU and CA125 screening was performed in a total of 4104 women. Of the 30 screen-detected cases only nine were detected in an early stage and an additional seven interval cancers, which had not been picked up by screening, were found [9]. Also in a recent survey of screening in the Netherlands, none of the screen-detected cancers appeared to be in an early stage [9]. Since cancer is not detected at an early stage, screening may not be expected to improve survival, although this latter effect has not yet been addressed in any of the screening studies.
In conclusion, screening cannot be advised as the primary preventive measure in women at high risk for ovarian cancer, but it should still remain an option for those women who cannot or will not yet decide for prophylactic surgery.

**prophylactic surgery**

Prophylactic BSO should include removal of both the Fallopian tube and the ovary, as Fallopian tube cancer occurs relatively frequently in BRCA-mutation carriers and may even be the primary cause of hereditary adnexal cancer [10]. Since most of these Fallopian tube cancers occur distally, it is not necessary to also remove the intramural part of the Fallopian tube [11].

BSO results in at least a 90% protection against ovarian cancer [12]. If performed under the age of 50 years BSO carries a residual risk of peritoneal carcinomatosis of 4% [13, 14].

BSO also partially protects against breast cancer, with a risk reduction of up to 70% if performed under the age of 40 [8, 15, 16].

Occult cancer was found in 2.3% of adnexal specimens removed at BSO. Reported percentages in the larger studies varied from 1.6% [9] to 9% [17], but rarely is occult cancer found in women under the age of 40.

In conclusion, for prophylaxis both Fallopian tubes and ovaries should be removed and meticulously examined. In general it seems safe to postpone prophylactic surgery until the age of 40.

**coping with hormonal withdrawal symptoms**

As prophylactic BSO will usually be performed before natural onset of the menopause, women will prematurely suffer from peri-menopausal symptoms. All of these can theoretically be treated at one time by providing hormonal replacement therapy (HRT). Unfortunately, a recent study has shown that only ~30% of women will experience alleviation of symptoms [18]. For this reason, alternatives should and will be available, also because one should consider treating the large variety of post-menopausal complaints symptom by symptom, rather than using a panacea.

Hot flushes may be treated with clonidine hydrochloride, gabapentin or a specific serotonin reuptake inhibitor (SSRI) such as venlafaxine, vaginal dryness by using lubricant jelly, osteoporosis by dietary measures and/or a bisphosphonate such as alendronic acid.

All of these alternatives, however, are not a substitute for HRT for reasons of cancerogenic risk of hormones. A lot of discussion on HRT use in the general population has been elicited by the reports on the Million Women Study [19] and the Women's Health Initiative (WHI) [20] studies, which indicated an elevated relative risk (RR) for HRT users, although the absolute increased number of breast cancer cases was still extremely low. This discussion obviously also raised concerns with women at high risk for particularly breast cancer. First, the data from these studies in patients >50 years of age cannot be extrapolated to relatively young women before the age of menopause; secondly, hereditary carcinogenesis is most probably different from sporadic carcinogenesis.

Recent studies have shown that there is indeed a slightly higher risk in long-term HRT users, which is in addition to the already >60% life-time risk in this group of women. It was, however, shown that overall survival was not affected [21]. Likewise, oral contraceptive use in this high-risk group of women did not convey an additionally elevated risk of breast cancer [22].

In conclusion, HRT is (also) safe in women at high risk of breast and ovarian cancer, especially when prescribed before the age of 50 at the time of prophylactic BSO. Alternative therapies that differentiate between the various perimenopausal complaints are available and advisable.

**conclusion**

In view of the uncertainties regarding prevention of hereditary ovarian cancer, it would be advisable to counsel women at (possible) risk in clinics with special multidisciplinary expertise. Geneticists, surgeons and gynecologists should be available to advise women on the options available. Coordinated arrangements on prophylactic surgery and screening, as well as psycho-social support, are much appreciated and help women to cope with the already manifold dilemmas and uncertainties that come with the diagnosis ‘hereditary high risk of cancer’, without the availability of adequate tools to protect them against such risk.

**disclosures**

No significant relationships.

**Table 1. Brief summary**

| Family history and mutation carrier status both important for counselling |
| Antenatal diagnosis feasible but controversial |
| Screening only for those who cannot (yet) opt for prophylactic adnexectomy |
| For prophylaxis both Fallopian tubes and ovaries should be removed |

**references**


