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Review

Genetic testing and familial implications in breast-ovarian cancer families

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ABSTRACT

DNA-testing for *BRCA1* and *BRCA2* has become incorporated in the diagnostic procedure of patients with breast and/or ovarian cancer. Since 1994 an immense amount of information has been gathered on mutation spectra, mutation risk assessment, cancer risks for mutation carriers, factors that modify these risks, unclassified DNA variants, surveillance strategies and preventive options. For the patient and family the main determinator still is whether a mutation is found or not. When a pathogenic mutation is detected in an index case, relatives can opt for pre-symptomatic DNA testing. However in the vast majority no mutation, or only unclear mutations are detectable yet. This means that a hereditary cause cannot be excluded, but pre-symptomatic DNA-testing is still unavailable for relatives. Surveillance for both index cases and relatives is based of the family history of cancer. Next generation genetic testing may help to elucidate genetic causes in these families.

Contents

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1. Genetic testing and familial implications in breast–ovarian cancer families

Some 20 years ago the *BRCA1* and *-2* genes were discovered and by now, the consideration of a hereditary cause has become an integral part of the diagnostic workup in breast- and ovarian cancer cases. Extensive media coverage has surely facilitated the fast dissemination of acquaintance with genetic breast cancer (and ovarian cancer) testing, as well as its acceptance in mainstream health care. In this review we will focus on the current application of *BRCA* testing: which patients are tested and what are the implications for these patients and their relatives. We will focus on the consequences when a pathogenic mutation is detected, when an unclear mutation is detected and when no mutation is detectable.

2. Reasons for referral and genetic testing

It is assumed that 5–10% of breast cancers and about 10% of ovarian cancers are mainly due to a hereditary predisposition. Because any single case of breast or ovarian cancer could be hereditary, in clinical practice these hereditary cases are hard to distinguish in the vast number of new breast cancer cases and ovarian cancer cases that are diagnosed annually, i.e. ca. 14,500 (incidence 166/100,000) and 1300 (incidence 14/100,000) respectively, in the Netherlands [1]. Because of financial and logistic restrictions, several algorithms have been developed over the years to select those cases that are most likely to harbor a *BRCA1* or *BRCA2* gene mutation [2–6]. All are based on the general characteristics of hereditary breast–ovarian cancer, e.g. early age at diagnosis, bilaterality of breast cancer, number of female relatives with affected breast and/or ovarian cancer and male breast cancer. Additionally, Jewish descent, early onset prostate cancer, pancreatic cancer and melanoma may be included. However, the differential diagnosis of hereditary breast or ovarian cancer is more extensive than just *BRCA1* and *-2*. This means that other types of cancer, (e.g. thyroid-, colon-, sarcoma and endometrial cancer) and other signs (e.g. macrocephaly, perioral lentigines, vascular malformations) should not be neglected when taking a (family) history [7,8].

The algorithms assign points to the above mentioned (family) characteristics, and estimate the chance of finding a mutation, sometimes indicating whether *BRCA1* or *BRCA2* is the most likely candidate gene. The use of these (online) algorithms and the threshold risks applied differ between countries [9], as well as attitudes toward testing and prevention [10]. Recently it was shown that triple negative breast cancers, i.e. negative for the estrogen, progesterone and Her2 receptors, are more likely to be *BRCA1* related, and this by itself may be reason for genetic testing [11]. Another recent change in the Dutch criteria for testing is that epithelial ovarian cancer at any age is now reason for testing, regardless of family history (www.nvog.nl). The current criteria for referral in the Netherlands are shown in Table 1.

Table 1
Current Dutch guidelines for referral to a clinical genetics/familial cancer outpatient's clinic.

Single cases
• A history of breast cancer diagnosed <35 years
• A history of epithelial ovarian/fallopian tube cancer any age
• A history of bilateral/multiple primary breast cancer, first cancer <50 years
• A history of both breast and ovarian cancer
• A history of triple negative breast cancer <50 years
• A history of breast cancer diagnosed in a male at any age
Familial cases
• 2 first degree relatives with breast cancer, one <50 years
• ≥3 breast cancer cases (one <50 years)
• Breast cancer <50 years and prostate cancer <60 years

Initial estimations of the percentage of familial cases due to *BRCA* mutations have diminished, which is mainly due to the definition of 'familial' or 'hereditary'. In severely affected families with ≥4 cases below age 50, *BRCA* may account for over 60% of families, whereas in 2 sisters with breast cancer at age 65, this may be the case in less than 4% [6]. Usually a threshold of ≥10% pretest estimation of mutation detection is applied for mutation testing in index cases, such as in the NICE guideline (www.guidance.nice.org.uk/cg164), the NCCN guideline (www.nccn.org), and by ESMO [12]. This threshold is arbitrary and may be considered rather high, when compared to that used for DNA testing in other genetic disorders. The initially referred families in the nineties were more alike the research families in which the *BRCA* genes were uncovered through linkage analysis. Over the years referral criteria have indeed become less stringent in the Netherlands and the detection rate in index cases has gradually decreased to 7–9% [13].

This gradual shift in referred population may also affect the estimation of cancer risks, in case a pathogenic mutation is found. It is now well established that many factors, other than the BRCA mutation, influence lifetime cancer risks in mutation carriers, such as family history, birth cohort and a large number of environmental, lifestyle and genetic modifying factors [14–17].

3. When a mutation is detected in the index case

A woman with (previous) breast or ovarian cancer, who is the first in the family to be tested for a *BRCA* mutation, is called the index-case. In some of these women a hereditary cause is *a priori* highly likely because most characteristics of hereditary breast/ovarian cancer are present in the family. Here a genetic diagnosis is merely a confirmation of a presumption already present in the patient as well as her physician. However, in other cases a genetic diagnosis may be highly unexpected, for instance when the family is small, contains very few women or when the family history is not available.

Detection of a pathogenic *BRCA* mutation may change the perspective drastically for the index case and her relatives [18,19]. For the index patient, a pathogenic mutation may have consequences for therapy, for post-operative screening and for preventive options that go beyond the cancer she was diagnosed with. Sometimes the index case is a healthy, unaffected first degree relative of a person with breast or ovarian cancer. This occurs when there is an indication for DNA testing, but no cancer cases are available. In this situation unaffected first degree relatives can be tested in order to detect the familial mutation. For these unaffected index patients, the presence of this mutation will have consequences for preventive measures. And for both affected and unaffected women it may have genetic implications. Interpretation of the consequences may be difficult, because the relevance of subsequent cancer risks should be viewed in the light of the initial diagnosis and more importantly, prognosis. Most data on the age related penetrance of breast- and ovarian cancer in mutation carriers are based on healthy carriers, and their risk of getting cancer [20]. Data on second breast cancers [21–23], on breast cancer after ovarian cancer [24,25] or vice versa [26,27], are less well defined. This means, that the counseling regarding risk reducing salpingo-oophorectomy (RRSO) and risk reducing mastectomy (RRM), should be tailored individually by a multidisciplinary expert team [28,29], which may use available (online) tools to discuss and explain risks and options [30,31].

Of note is the fact that is was shown recently, that especially ovarian cancer patients who have a *BRCA* mutation may benefit from treatment with PARP inhibitors. This has generated an additional reason for DNA-testing in the course of ovarian cancer treatment [32]. Another recent development is the use of rapid DNA testing for women who are diagnosed with breast cancer, in order to