

Mini-Reviews

Hereditary Breast and Ovarian Cancer Syndrome: Should We Test Adolescents?

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Introduction

With the identification of the breast/ovarian susceptibility genes BRCA1 and BRCA2 in the 1990s came the evolution of genetic testing for clinical purposes. Increased awareness of the familial susceptibility to breast and ovarian cancer and the availability of genetic testing for BRCA1 and BRCA2 mutations will undoubtedly result in more requests for genetic testing by adolescents and their parents. Direct consumer marketing for BRCA testing is also likely to contribute to a rise in requests for testing. The American Society of Clinical Oncology has recommended that clinical genetic predisposition testing be offered when: (1) the pretest probability of a positive result is high because of a strong family history of cancer or early age of diagnosis of cancer, (2) the test results can be adequately interpreted, and (3) the results will influence the medical management of the patient or a family member.¹ With these factors in mind, the intent of respecting an adult patient's autonomy figures as one of the most important factors for testing adults, but protecting children and "doing no harm" should be the chief consideration in deciding to test a minor for a genetic cancer syndrome. This review discusses the hereditary breast and ovarian cancer syndrome, the medical justification of testing minors, and some of

the ethical, psychological, and legal implications of genetic testing for adolescents.

Hereditary Breast and Ovarian Cancer Syndrome

Although family history is a significant risk factor for developing breast cancer, at the present time only about 5–10% of women with breast and ovarian cancer have a genetic predisposition. A high percentage of hereditary breast and ovarian cancers arise from mutations in the tumor suppressor genes BRCA1 and BRCA2. Mutations in these two genes account for 70–80% of hereditary breast cancer. Approximately 70% of familial ovarian cancer cases are caused by BRCA1 mutations and 20% by BRCA2. These mutations are inherited in an autosomal dominant fashion. If a woman is a carrier of one of these gene mutations, she has a lifetime risk of developing breast cancer of 85%, and a lifetime risk of ovarian cancer as high as 60%.² Mutations of BRCA are also associated with an increased risk of early onset breast cancer (less than 50 years of age) and risk of cancer in the contralateral breast or ovary. The adolescent daughter of a woman who is a BRCA carrier has a 50% chance of having inherited the gene mutation and, hence, a significant lifetime risk of breast and ovarian cancer.

One of the first and most important steps is to assess the adolescent's risk based on family history.³ This should include a detailed three-generation family pedigree. Genetic counseling is highly recommended. This is an opportunity to assess the adolescent's understanding of the natural history of breast and ovarian cancer, evaluate her risk, and discuss the implications and limitations of mutation testing. It is also important to determine if the adolescent is capable of giving informed consent, a requirement for most DNA-based genetic tests. Genetic testing of adolescents is controversial. Consideration of the patient's risk for cancer

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Synopsis: This review discusses some of the medical, ethical, psychological, and legal implications of offering genetic testing to adolescents with a family history of breast and ovarian cancer.

as well as the medical and psychological benefits of genetic testing to the individual is essential before determining whether testing is appropriate.

Medical Benefits of Testing

For adult women with a known BRCA mutation, preventive strategies including prophylactic surgery, chemoprevention, and increased surveillance are available to decrease their risk of developing breast or ovarian cancer. Mastectomy has been shown to decrease the incidence of breast cancer in women at high risk as well as to reduce breast cancer-related mortality.^{4,5} Similarly, Rebbeck et al showed that prophylactic bilateral salpingo-oophorectomy (BSO) was associated with a large reduction in the risk of coelomic epithelial ovarian cancer. This study also found that 6 of 259 women undergoing surgery had incidental stage I ovarian cancer.⁶ The NIH consensus conference recommended that BRCA1 and BRCA2 carriers consider prophylactic bilateral salpingo-oophorectomy after age 35, or after the completion of childbearing.⁷ A recent prospective study followed BRCA1 and 2 carriers, 98 women elected to undergo prophylactic BSO, and 72 chose surveillance with annual pelvic exams, twice-yearly transvaginal ultrasounds, and twice-yearly CA-125 concentrations. They found that the time to breast cancer or ovarian/peritoneal cancer was longer in the surgery group, with a hazard ratio for developing disease of 0.25.⁸ In a similar study, Rebbeck et al followed 551 women with BRCA mutations for occurrence of cancer, for a minimum of 8 years. They found that breast cancer developed in 21 percent of women who had undergone BSO, and 42% of control women. They also found a reduction in the risk of epithelial cancers with a hazard ratio of 0.04.⁹ In a review of the literature, Eisen et al concluded that both prophylactic mastectomy and oophorectomy were associated with considerable reduction in the risk of those cancers, with an estimated efficacy of 85–90%.¹⁰

Although it may seem quite premature to address these issues in adolescence, some mature young women at risk for breast and/or ovarian cancer may inquire about the efficacy of future surgical interventions. Physicians caring for adolescents at risk for breast and ovarian cancer should be knowledgeable about prevention strategies and the current recommendations. In most cases, they can reassure their patients that surgical intervention is not indicated until they are 35 years or older, and have completed childbearing.

Medical therapy such as tamoxifen, a selective estrogen receptor modulator, has been shown to reduce breast cancer incidence in healthy at risk women. King et al found a 62% reduction in the incidence of breast cancer in healthy BRCA2 carriers who used tamoxifen

at age 35 or older but no reduction was seen among BRCA1 carriers.¹¹ Although the optimal age to begin chemoprevention in women at risk for breast cancer has yet to be determined it is not considered a reasonable option for adolescents at this time.

One exception may be oral contraceptives (OC). Oral contraceptives have been shown to reduce the risk of ovarian cancer in the general population.¹² In a comparison of women with BRCA mutations who had been diagnosed with ovarian cancer to their cancer-free sisters, one third had confirmed BRCA mutations, Narod et al showed that OCs may reduce the risk of ovarian cancer. They demonstrated decreasing risk with longer use, and a 60% reduction in risk after 6 or more years of use.¹³ This case-control study did not address the specific dosage, formulation, or the age to begin treatment to optimize risk reduction. Furthermore, since the study group did not include deceased patients, the authors acknowledge that their results might exaggerate the protective effect of OCs, if they were instead responsible for a higher fatality rate in ovarian cancer. In contrast, a study of a population of Israeli Jewish women with BRCA mutations concluded that oral contraceptives do not protect against ovarian cancer.¹⁴ The observed differences between these studies may be attributed to the population studied, the duration of OC use, and/or the choice of control group. While OCs did not significantly decrease ovarian cancer risk in some groups of individuals with BRCA mutations, they have not been shown to cause an increased risk. The use of OCs in adolescents at risk for ovarian cancer for the sole purpose of “chemoprevention” is still unclear.

Parents of adolescents with a strong family history of breast cancer are often opposed to OC use due to their concerns of a possible association with breast cancer. Although some studies suggest that OC use may increase the risk of breast cancer in some individuals, other studies show no increase in risk. In a matched case-control study of 1311 pairs of women, Narod et al found an increased risk of early-onset breast cancer among BRCA1 carriers who first used oral contraceptives prior to 1975, before age 30, or for 5 or more years.¹⁵ They did not find this association for BRCA2 carriers however, the data was limited. Grabrick et al performed a historical cohort study of 426 families of breast cancer patients diagnosed between 1944 and 1952.¹⁶ Through telephone interviews they determined the breast cancer incidence among the sisters, daughters, granddaughters, nieces, and marry-ins of the probands. Controlling for other factors including age, educational level, parity, smoking, age at menarche and menopause, the authors found a significant correlation between ever-use of oral contraceptives and breast cancer in sisters and daughters. The risk

increased with an increased number of affected relatives, while no increased risk was seen in nieces and granddaughters. However, this increased risk was only seen in women who used OCs before 1975, implicating older formulations and higher estrogen-containing pills. This study did not specifically look at the BRCA mutation status among these families. Marcus et al found that African American women who used OCs before 18 years of age had an elevated risk for breast cancer compared to women who had never used OCs (OR = 2.0). There was no significant difference among Caucasian women.¹⁷ The authors did not evaluate BRCA status. The National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study examined the risk of breast cancer in over 4500 women who were current or former users of OCs, ages 35–64, with breast cancer and over 4600 controls.¹⁸ They found no significant increased risk of breast cancer. The risk did not increase with duration of use, estrogen dose, and age at first and last use or relation to first term pregnancy. The results were similar for whites and blacks. Further, they found no increased risk among individuals with a family history of breast cancer. However, BRCA mutation status was not determined. The use of OCs for contraceptive purposes in adolescents at risk for hereditary breast and ovarian cancer syndrome should be individualized and require informed consent including a discussion of these studies and their limitations. Additional studies that specifically address the relative risk of breast cancer in OC users with BRCA mutations may clarify these issues.

Increased surveillance for BRCA carriers is recommended as outlined by the Cancer Genetics Studies Consortium.¹⁹ This includes breast self-exam beginning by age 18–21; frequent clinical examination; annual mammography beginning at age 25 to 35; semiannual to annual ovarian cancer screening with transvaginal ultrasound and CA125 levels, beginning at age 25 to 35. Some studies have begun looking at the role of MRI for periodic cancer surveillance in high-risk women, with promising results of early cancer detection.²⁰

Kodish discussed testing children for cancer genes, formulating the argument that physicians should respect the “rule of earliest onset” and defer testing until the age of first possible onset of disease.²¹ In the case of hereditary breast cancer, the first screening test, a mammogram, is recommended at age 25, though with some trepidation regarding the medical benefit, given the low incidence of malignancies and the high incidence of false positives. Current screening tests have limited clinical utility in younger patients, but this may change with advances in technology and screening, and studies will be needed to determine their validity in young women.

In 1995, the American Society of Human Genetics (ASHG) and the American College of Medical Genetics (ACMG) issued a joint report on the genetic testing of children and adolescents.²² This report points out that the primary goal of genetic testing should be to promote the wellbeing of the child. The primary justification for genetic testing should be timely medical benefit. Testing is acceptable only if there are medical benefits such as preventive measures and therapy. If medical benefits are uncertain or will be deferred until a later time, then there is less justification for testing. The medical benefits from diagnosing BRCA1/2 mutations in adolescents are not firmly established. Additional studies are needed to assess the risks and benefits of oral contraceptives. While studies have shown that prophylactic surgery decreases the risk of cancer in older women, no one has addressed the issue in adolescents. The medical benefit of increased surveillance in adolescent patients has also not been examined. Most of the currently available preventive and screening options with the exception of monthly breast self-exams are not indicated until young adulthood. Presently, there does not appear to be conclusive evidence of a medical benefit to BRCA testing in adolescence.

Impact on Reproductive Decisions

A common reason cited by advocates of testing adolescents is that knowledge of their genetic status may assist them in making reproductive decisions. For example, adolescents and young adults who are BRCA mutation carriers may choose to have children earlier in life with the intent of later opting for prophylactic oophorectomy, or mastectomy. They may wish to discuss the feasibility of this plan with their physicians and partners.

It is now well established that greater parity and earlier age at first pregnancy are protective in the development of breast cancer in the general population. This may not be true for carriers of BRCA mutations.²³ Jernstrom et al compared BRCA carriers who had developed breast cancer by the age of 40 to matched controls, BRCA carriers who were either cancer-free or had developed cancer after age 40.²⁴ They found that women who were carriers of BRCA1 and BRCA2 mutations who had had a full-term pregnancy were significantly more likely than nulliparous carriers to develop breast cancer by the age of 40, with an odds ratio of 1.71. Furthermore, they found that the risk increased with the number of births and did not diminish with time since last pregnancy. They speculated that since the BRCA1 gene is expressed in rapidly proliferating cells and is believed to counteract proliferation and promote differentiation, gene mutations

may make women susceptible to carcinogenesis during periods of high sex-hormone exposure, such as during pregnancy. These data are important for clinicians to include when counseling patients about their risks of developing breast cancer, especially since they contradict the Gail model in which early pregnancy is thought to be a protective factor.

Marcus et al investigated the relationship between reproductive events in adolescence and subsequent breast cancer risk as part of the Carolina Breast Cancer Study.¹⁷ They interviewed women diagnosed with primary breast cancer about their history of pregnancies, breastfeeding, use of oral contraceptives during their adolescent years (age 10 to 19) and compared them to age-matched controls. They did not report the BRCA status of the subjects in this study. They found that full-term pregnancy before age 18 did not reduce breast cancer risk, but breastfeeding before age 20 was associated with a substantial risk reduction. Neither miscarriage nor abortion in the teenage years conferred an increase in cancer risk.

Ethical Issues

In the absence of an anticipated benefit to the adolescent, testing for cancer susceptibility should be postponed until the adolescent is capable of making this decision, hence preserving her right of autonomy. Bendorff et al looked specifically at patients' attitudes towards autonomy and confidentiality in reference to genetic testing.²⁵ They agreed with previous authors that, in the context of BRCA1/2, autonomy refers to the patient's right to receive information about cancer risk, to choose to be tested, to decide with whom to share the resultant information, and to control the disclosure of the above information. A more controversial aspect of this autonomy is a patient's parental autonomy to obtain tests for minor children or to obtain testing against the recommendation of a physician. The authors recruited and subsequently interviewed 238 study participants who had at least one first-degree relative with breast or ovarian cancer. As expected, almost all respondents felt that genetic testing should be voluntary and that the results should not be disclosed to employers or insurance companies. Of interest, however, was that 95% of the women interviewed thought a person should be able to get a genetic test even if the physician is against it. Many (88%) thought parents should be able to decide if their children under age 18 should have a genetic test. It is important for physicians to be aware of these findings, as they can impact the tone of the discussion with the adolescent patient and her parents, and promote a more open-minded dialogue.

Elger and Harding believe that there is a benefit to granting adolescents the autonomy to make their own choice regarding testing, as they feel this gives them a greater sense of control and may grant them greater self-esteem.²⁶ In terms of conflict between the wishes of the adult parent and the adolescent, they again promote adolescent autonomy and state that the test should be performed if the adolescent gives informed consent in the absence of parental pressure.

Ross argues against allowing minors to act on the principle of autonomy, stating that "lifetime autonomy" should outweigh present-day autonomy, and that adolescents have a high chance of changing their attitudes and regretting previous decisions once they become adults.²⁷ She states that in the case of BRCA1 testing, where no therapeutic interventions can begin in childhood, both the parents and adolescent must consent before testing is done. Others argue that even if some patients later feel regret, this would likely be the case in only a minority of patients, there is no physical harm, and arguably little true mental or social harm.

Wertz et al did an extensive review of the ethical, psychological, and legal implications of genetic testing of children.²⁸ While they focused on diseases such as Huntington's disease, adult polycystic kidney disease, and familial polyposis coli, their conclusions can be applied to breast and ovarian cancer susceptibility genes as well. Using the guidelines described by the authors, testing for BRCA might fall into one of two categories: "the test may detect conditions for which treatment or preventive measures are available..." if the use of OCs is considered; or, "...there are no medical benefits to the minor per se, but testing is possibly of immediate benefit to the minor in making reproductive decisions," if timing of pregnancy is considered. Wertz describes the conclusions of the National Commission for the Protection of Human Subjects, which suggested the term "assent" to distinguish a minor's agreement to treatment or research from an adult's legal "consent." This commission recommended that children need to assent prior to participation in research, under the assumption that minors do have sufficient understanding to assent. The capacity of a child/adolescent is variable. The legal standard for decision making is 18 years of age. However, the President's Commission for the study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended the age of competence for minors be 14, although there is less agreement about this age of cutoff. ASHG/ACMG recommend that as children and adolescent's cognitive and moral development grows, professionals and parents should be attentive to their increasing interest and ability to participate in decisions regarding their own welfare.²²

Psychological Implications

There is concern that individual adults and adolescents, in particular, who undergo genetic testing, may suffer adverse psychological impact. Several studies have looked at the impact of BRCA1/2 mutation testing on individuals' psychological well being, and a few have addressed this same issue in adolescents. The studies described below, which include descriptive data as well as quantified results, do not seem to support such concerns.

A descriptive study by Lynch et al collected data on hereditary breast and ovarian cancer syndrome relative's motivations for undergoing genetic testing, and their subsequent emotional reaction to the results.²⁹ The most common (56%) reason for seeking risk assessment was concern about children or family. Not surprisingly, of those who tested BRCA1 positive, 36% appeared to be sad, in contrast to the relief/happiness apparent in 80% of those who tested negative. In this high-risk group, 43% of those tested were found to be BRCA1 positive. So, a greater number of patients receive good news and feel subsequent relief. The authors also provided interesting anecdotes of parents who strongly desired testing for their minor children, despite discouragement by physicians and counseling that no earlier interventions would be done.²⁹ While this qualitative study is consistent with results obtained from similar evaluations, most studies using standardized measures of psychological distress have not shown clinically significant adverse psychological effects of genetic testing. Also, previous studies have shown that psychological distress and morbidity of people who receive genetic testing are not higher than in the general population.³⁰

Schwartz et al measured cancer-specific distress and general life distress with the use of standardized scales designed to test for intrusive thoughts and feelings, as well as to assess for the presence of anxiety and depression.³¹ They interviewed women previously diagnosed with breast and/or ovarian cancer whose family cancer history placed them at high risk for carrying a BRCA mutation, as well as their relatives. Among these relatives, they found psychological benefit from a negative test result, as evidenced by a decrease in all the distress scores tested, while those who received positive or uninformative test results did not seem to exhibit increased psychological distress 6 months after the disclosure of mutation status.

In a prospective cohort study, Lerman et al set out to define predictor variables of those who chose to be genetically tested, and then evaluated outcomes of their participation in a genetic testing program.³² The study participants, aged 18 years and older, all attended educational sessions prior to testing, and received a counseling session at the time of results' disclosure. They

found that women were twice as likely to request testing as men, those who had insurance four times as likely to request testing as those without insurance. Those who were more knowledgeable about hereditary cancer syndromes and thought the benefits of testing outweighed the risks were more likely to get tested. Again, the benefit of BRCA1 testing rated as most important was to "learn about my children's risks." Depression symptoms and functional health status was measured with standard, previously validated scales at baseline and at 1-month followup. Non-carriers exhibited significantly greater reduction in depression than carriers and those who declined testing. At the same time, those who were identified as carriers did not show an increase in depression or functional impairment 1 month after disclosure of results. Perhaps learning one's BRCA genetic status may reduce uncertainty and set forth a plan of action, consequently improve a person's quality of life, regardless of the result. The authors concede, however, that they obtained these encouraging results in the context of a research protocol, with pretest education and genetic counseling, both of which may have contributed to the psychological benefits. They caution that outside a controlled research environment, the potential for adverse psychological outcomes may be greater, and they called for further studies examining more subtle effects of testing, such as feelings of guilt, anger, or relationship strain.

One multi-center group set out to determine the psychological consequences among genetic testing participants using a newly developed questionnaire specifically targeting this population.³⁰ The Multidimensional Impact of Cancer Risk Assessment found that individuals who were BRCA1 negative, whether or not they already had a diagnosis of cancer, all had good overall mental health and limited concerns specific to genetic testing. Conversely, of those subjects who tested positive, more did score high on the scales of distress, but the authors acknowledge the uncertainty of what this means clinically and what bearing this may have on people's lives. Although self-report measures may overestimate the psychological morbidity, these types of assessments are thought to be able to identify those individuals who are more psychologically vulnerable and who might benefit from extra support and counseling interventions.

Most studies have examined the psychological impact of testing in adult women. Elger and colleagues argue that there is not enough evidence that testing is harmful or psychologically detrimental for mature adolescents, ages 14 to 17.²⁶ Based on previous studies which had determined that consent skills of older adolescents are comparable to those of adults, they advocate for allowing adolescents in this age group who are members of families with a known BRCA mutation to decide autonomously about genetic testing. They

recommend that adolescent's decisions should only be overridden by adults in cases of very dangerous or experimental treatments. They stress that children younger than age 13–14, who are comparatively immature, are not able to give consent, and should not be tested. Elger's group cites literature similar to that discussed above, that reduction of uncertainty through disclosure of BRCA status actually lessened distress and psychological impairment in adults. The authors speculate that mature adolescents who are already cognizant of their 50% chance of having inherited their families' BRCA mutation would react similarly.

From the psychological standpoint, Wertz's group warns about possible hazards of strained family dynamics, sibling rivalry, or damage to the child's "self-concept."²⁸ They point to theories of children's cognitive development to caution medical professionals about disclosing results to children before they have reached the stage of formal operational thought. Likewise they remind professionals that even well-informed and articulate children are not necessarily prepared to think about future illness or death.

Legal and Financial/Insurance Issues

There has been an increasing trend to recognize the concept of the "emancipated minor," in lieu of the historical trend of paternalism in decision-making. As Wertz et al describe, courts have begun to acknowledge that mature minors are able to make decisions about medical treatment, and have generally regarded age 15 as the age when minors can consent to medical interventions without parental consent.²⁸ Many states permit adolescents to consent to medical treatment, typically on issues revolving around sexual and reproductive health. In the event of dissent of opinion between parents and physicians regarding medical treatments, courts have ruled in favor of mainstream medical therapy. Since they have not specifically addressed genetic testing, it is unclear whether cases of religiously motivated parents refusing traditional treatments can be equated with accepting or declining genetic testing on behalf of minor children. Furthermore, there is yet no clear consensus of when and if minors should be tested, so therefore no "mainstream" guidelines can be followed.

While there are concerns of insurance discrimination associated with genetic testing, individuals considering testing should be reassured that recent federal legislation prohibits employment and health insurance discrimination because of genetic information. The Health Insurance Portability and Accountability Act of 1996 prevents insurers from using genetic information in underwriting health care insurance. The Genetic

Information Nondiscrimination Act of 2003 protects the privacy of genetic information. It provides individuals with protection against genetic discrimination in the workplace and insurance coverage.

Conclusion

The availability of genetic testing for mutations in the two genes associated with hereditary breast and ovarian cancer, BRCA1 and 2, may prompt adolescents, their parents, and/or physicians to consider testing. The American Society of Clinical Oncology recommends that genetic testing be offered to individuals with a strong family history or early age at diagnosis of cancer, but just how early should testing be done? Consideration of the patient's risk for cancer as well as the medical and psychological benefits of genetic testing to the individual is essential before determining whether testing is appropriate. Genetic testing of adolescents is controversial, especially in the absence of a direct medical benefit. Current surgical and medical options to reduce the risk of breast and ovarian cancer do not apply to adolescent women. The medical benefit of increased surveillance in adolescent patients has not been examined. Current screening tests have limited clinical utility in younger patients, although this may change with advances in technology. Additional studies on the impact of oral contraceptive use in adolescence on the risk of ovarian and breast cancer, specifically in BRCA1 and 2 carriers, are needed. For some mature adolescents, there may be significant psychological relief from knowing their mutation status and they may be capable of using this information for reproductive and health decisions. It is important for the parents and adolescent to understand that testing is voluntary, confidential, and requires informed consent; there should be no evidence of parental coercion. Testing adolescents for BRCA 1 and 2 mutations can be done on an individual basis but only with the appropriate support and genetic counseling.

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