Hereditary Breast Cancer: Part I. Diagnosing Hereditary Breast Cancer Syndromes

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Abstract: Hereditary breast cancer (HBC) accounts for as much as 10% of the total BC burden. Most of these cases will be found to be due to a BRCA germline mutation. An estimated additional 15–20% of those affected with BC will have one or more first- and/or second-degree relatives with BC. Therefore, when these numbers are combined, familial BC risk accounts for approximately 20–25% of the total BC burden. However, because of the often limited information on family history in the etiologic assessment of BC, this may be an underestimate. Confounding factors include its phenotypic and genotypic heterogeneity, given the association of HBC with a plethora of differing cancer syndromes. Its most common occurrence is its association with ovarian cancer in the so-called hereditary breast-ovarian cancer syndrome due to BRCA1 and BRCA2 mutations. More rarely, it occurs in the Li-Fraumeni syndrome, caused by a p53 germline mutation, in which markedly early-onset BC is found in association with brain tumors, sarcomas, leukemia, lymphoma, malignant melanoma, and adrenal cortical carcinoma. Importantly, the age-adjusted incidence of BC in women in the United States fell sharply, by 6.7%, in 2003, when compared with the rate identified in 2002. We postulate that increasing knowledge about the genetics of BC may have partially contributed to the identification of high-risk patients who thereby may have benefited significantly from early diagnosis.

Key Words: BRCA1, BRCA2, genotypic and phenotypic heterogeneity, hereditary breast cancer, hereditary breast-ovarian cancer

Hereditary breast cancer (HBC) accounts for approximately 10% of the total BC burden, while an estimated additional 15–20% of those affected with BC will have a positive family history of this disease (1). In a previous study (2) of 328 consecutively ascertained BC patients, where family history was intensively pursued, findings were remarkably similar, showing 23% to be familial, that is, one or more first- and/or second-degree relatives of the proband with BC, and 9% to be putative hereditary. Predictably, a subset of familial BCs, and even some so-called “sporadics,” will, with rigorous family history assessment and/or discovery of new low-penetrant germline mutations (3,4), turn out to be hereditary. Clearly, intensive family history documentation in patients with BC should provide the potential for improved cancer control gain through the identification of candidates for highly organ-targeted surveillance and management measures. The advent of BRCA mutation testing, which became available in the mid-1990s (2), now allows a much more precise estimation of high-risk candidates for targeted surveillance and management (5).

A significant portion of HBC-prone families are characterized by the more common hereditary breast-ovarian cancer (HBOC) syndrome and carry BRCA1 and BRCA2 mutations which, in fact, account for at least 30% of all HBC. Therefore, about 70% of the HBC burden lacks these mutations (6,7). In spite of an intensive search at many centers throughout the world for identification of additional mutations predisposing to HBOC (3,4), results have remained elusive (8,9).

Walsh et al. (6) have called attention to the mutation spectra of BRCA1 and BRCA2, which include “…many high-penetrance, individually rare genomic rearrangements. Among patients with BC and severe family histories of cancer, who test negative (wild
type) for BRCA1 and BRCA2, approximately 12% can be expected to carry a large genomic deletion or duplication in one of these genes, and approximately 5% can be expected to carry a mutation in CHEK2 or TP53."

Easton et al. (4) investigated genome-wide association studies in the search for common alleles in FGFR2 (rs2981582), TNRC9 (rs3803662), and MAP3K1 (rs889312), which were shown to pose increased risk to carcinoma of the breast.

In spite of meticulous attention given to the compilation and interpretation of family history, its findings and interpretation may nonetheless be obfuscated by factors which may explain an underestimate of the percentage of BCs that are otherwise deemed familial/hereditary: (a) incomplete family history assessment; (b) unavailable medical records; (c) small family size; (d) early death of informative relatives from causes other than cancer; (e) failure to investigate extra-BC that could be integral to a HBC syndrome, such as ovarian, colon, pancreas, melanoma, or prostate cancer; (f) false paternity; (g) limited disclosure of vital information because of fear of insurance and/or employment discrimination; (h) emotional distress, including fear that knowledge of the family history will potentially result in alienation from progeny and siblings.

Our purpose is to describe those strategies involved in the identification of HBC with its phenotypic and molecular genetic diversity, which, in turn, will guide the screening, management, and genetic counseling of individuals who are at high risk for this disease.

Decrease in Breast Cancer Incidence in the United States

Using data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Registries, Ravdin et al. (10) found that the age-adjusted incidence rate of BC in women in the United States fell sharply, by 6.7%, in 2003 when compared with the rate identified in 2002. However, this decrease was identified only in those women who were 50 years of age or older, and the findings were more evident in cancers that were estrogen receptor (ER)-positive as opposed to those that were ER-negative. The reason for this decline remains elusive, although the authors speculate that the data “...are most consistent with a direct effect of hormone-replacement therapy on preclinical disease, but this conclusion does not rule out some contribution from changes in screening mammography...” While not evidence based, we postulate that increasing knowledge about the genetics of BC may have partially contributed to identification of high-risk patients, who thereby have benefited from early diagnosis.

History of Hereditary Breast Cancer

Historically, the first family prone to carcinoma of the breast that was extensively studied was reported by Broca (11), the famed French surgeon and Renaissance man of his time, in the 1860s. This was about the time that Gregor Mendel was completing his treatise on genetic factors in garden peas. Interestingly, Broca was led to this family through the happenstance occurrence of early-onset BC in his wife. His compilation of her pedigree led to the identification of four generations with BC, including one of his wife’s sisters as well as her mother (Fig. 1). Of keen interest was the likely integral association with gastrointestinal tract cancer, from which Broca astutely considered “the possibility of the inheritance of a general diathesis for cancer in this family.”

Colorectal cancer (CRC) was more recently found to be integrally associated with BC in a family (12); this phenomenon has been further elucidated by evidence at the molecular level related to the 1100delC mutation in the CHEK2 gene (13) (discussed subsequently), which has been identified as being responsible for a subset of families with the combination of BC and CRC.

More than a century after Broca’s report, descriptions of pedigrees consonant with a variety of HBC-prone syndromes, characterized by differing tumor combinations, began appearing in the literature (Fig. 2); the most common of these is the HBOC syndrome, first published in the early 1970s (12,14). [See Lynch et al. (15) for a review.]

Prior to the availability of gene testing, high-risk individuals received genetic counseling based upon their having a 50% cancer risk if they were the first-degree relative of a patient with a hereditary syndrome cancer, in an autosomal dominant setting such as HBOC. The discovery of the molecular genetic basis for HBOC through the BRCA1 and BRCA2 germline causal mutations has given a high level of certainty to its diagnosis (16,17). However, there will be situations in which an informative HBOC family member may not be available. In a limited number of these cases, BC tissue blocks, when available, may be...
a source for DNA extraction and molecular genetic testing for a BRCA mutation (18).

**BRCA mutation status derived from formalin-fixed and paraffin-embedded tissue**

It is not uncommon to encounter patients from HBOC kindreds where all of their genetically informative cancer syndrome affected relatives are either deceased or otherwise unavailable, causing an immediate limitation to collection of DNA that could lead to the identification of the family's BC-causing mutation (18). Therein, the absence of knowledge about a pathogenic mutation that may be segregating in the family poses an etiologic, diagnostic, and cancer control barrier to progeny and/or siblings from such a putative HBOC pedigree, thereby limiting their receipt of accurate genetic counseling in concert with highly-targeted surveillance and management. In these clinical settings, particularly when coupled with fear and anxiety, patients often focus upon their dread of “When will I get cancer?” In some such families, as a consequence of small family size and/or death of key informative family member(s) due to HBOC syndrome cancers, there may not be any surviving informative family members for DNA testing. Some of these high-risk family members may, in the absence of knowledge of their BRCA mutation status, elect to undergo intensive surveillance, or even surgical prophylaxis.

This serious lack of potentially vital DNA for germline mutation testing, with potential for hereditary cancer syndrome diagnosis, however, may be circumvented in a small percentage of families (limitations are discussed subsequently) by identifying a BRCA mutation in archival tissue from a deceased breast and/or ovarian cancer-affected family member (18).

**Figure 1.** Pedigree of the family of Paul Broca’s wife, based upon Broca’s original report of this family in the French medical literature (11).

**Figure 2.** Circle graph showing relative frequencies of sporadic, polygenic (familial), and hereditary breast cancers. (Reprinted with permission from Lynch and Lynch. In: Breast Cancer, 2nd edn. Winchester et al., editors. B.C. Decker, 2006. pp. 61–82.)
This knowledge could then be effectively applied through testing all consenting at-risk unaffected family member(s).

How can this important strategy be accomplished? An answer has been offered by Adank et al. (18), who extracted DNA from formalin-fixed paraffin-embedded (FFPE) morphologically normal tissue of 161 blindly, coded samples from Ashkenazi women who had been found, through testing of lymphocyte-derived DNA, to be carriers of one of the three Ashkenazi Jewish BRCA founder mutations. Multiplex polymerase chain reaction followed by denaturing polyacrylamide gel electrophoresis produced concordant results with those of the lymphocyte-derived DNA. It was concluded that this method “...reliably detected BRCA founder mutations in archival DNA derived from FFPE tissue...” Therefore, this feat should prove to be useful in genetic counseling, and ultimately diagnosis and management, through the study of DNA from archival BC specimens, with the possibility of achieving certainty about patients’ BRCA mutation status, i.e., are they carriers or non-carriers of a deleterious mutation. These results would then enable those with wild type BRCA results to avoid unnecessary intensified surveillance or risk-reducing prophylactic surgery; those who are mutation carriers can then undergo more intensive surveillance and may even consider risk-reducing prophylactic surgery.

In theory, this could work for any mutation. However, the rate-limiting step is obtaining enough tissue specimens with the mutation of interest in order to validate the primers and DNA testing methodology. This concern has led Adank et al. (18) to suggest that current use of the technique should be focused on founder mutations. A laboratory should validate results on each specific mutation with FFPE samples.

**Hereditary Breast Cancer: Phenotypic and Genotypic Heterogeneity**

Prior to when molecular genetic diagnostics came of age more than a decade ago, a comprehensive family history was the sole basis upon which a patient’s risk for familial BC could be estimated. Now that cancer-causing pathogenic BRCA1 and BRCA2 mutations have been identified in the HBOC syndrome, a major question arises: “Who do we send for genetic testing?” (19) In order to answer this question, the first step continues to be the compilation of a comprehensive family history/pedigree, preferably of four generations, which will include the proband’s siblings, progeny, both parents, second-degree relatives, namely maternal and paternal aunts and uncles, and, whenever possible, both sets of grandparents. Reports of cancer of all anatomic sites must be compiled and, whenever possible, pertinent medical and pathology data should be retrieved for verification of the specific cancers. Findings in older family members will be especially pertinent as, being older, they will have passed through the typical age of cancer onset and hereby become highly genetically informative. This then becomes the patient’s “nuclear pedigree” (Fig. 3). Evaluation of this pedigree will, in certain cases, lead to a presumptive HBC syndrome diagnosis, and therein may become a candidate for DNA mutation testing following genetic counseling. When a BRCA mutation is identified in an informative relative, ideally one affected by early onset of breast and/or ovarian cancer in the HBOC syndrome, that individual’s first-degree relatives will then become highly informative candidates for BRCA testing. Those who are found to harbor the pathogenic BRCA mutation will then become candidates for intensive screening and management, to be discussed in Part II of this series. When the presence of the BRCA mutation has been confirmed to be segregating in the family, relatives in the direct genetic lineage of an individual who tests negative for the BRCA mutation will not need to be tested; such individuals will then revert to general population surveillance and management recommendations. Conversely, those who test positive for the mutation will require intensive screening and management. For example, Watson et al. (20) evaluated data from a cohort of 10,910 individuals belonging to either HBOC or Lynch syndrome families, 1,408 of whom had been tested for a hereditary cancer syndrome mutation and learned their test result. Carrier risk changes from uncertainty to certainty, namely to carrier or noncarrier status, accounted for 89% of risk changes resulting from testing. In addition, 60% of persons with a carrier risk status change were not themselves tested, but had a change in their risk status because of a relative’s test result. Those deemed to be BRCA-negative based on the absence of the mutation in a relative in the direct line of descent, would therefore not need to be tested. They would, therefore, derive significant economic benefit. Moreover, they would have reduction in fear and anxiety, although some might experience survival guilt, i.e., “Why was I spared the mutation when many of my relatives were
found to have the mutation and a number of them have manifested cancer.”

Genetic Counseling

It is imperative that genetic counseling, an essential component of any cancer genetic testing and management program, take place before blood is drawn for collection of DNA in the search for a pathogenic mutation. The patient must have given consent and know that protection of confidentiality will be secure in accord with the regulations of the Health Insurance Portability and Accountability Act (21). The patient must also be fully informed about the multifaceted issues that relate to genetic testing. For example, in the case of HBOC, the patient must be fully apprised of the fact that failure to identify a \textit{BRCA1} or \textit{BRCA2} mutation in the family does not exclude the presence of a hereditary factor as only about 60\% of classical HBOC families may be found to harbor a \textit{BRCA} mutation (5). Therefore, the remainder of such classical HBOC cases will likely be due to yet-to-be-identified germline mutations (6). These high-risk patients must also appreciate the fact that \textit{BRCA} mutations are not fully penetrant.

Phenotypic and Genotypic Heterogeneity

A rather complex diagnostic and management challenge relates to the extensive phenotypic and genotypic heterogeneity that occurs in HBC. Specifically, there are multiple differing hereditary cancer syndromes that predispose to carcinoma of the breast, as shown in Figure 2. Therefore, the genetic counselor, medical geneticist, and/or primary care physician must be cognizant of this marked phenotypic and genotypic diversity of HBC-prone syndromes. They must also be thoroughly familiar with the natural history and molecular genetics of these syndromes. If not, referral to a center with special expertise in hereditary cancer will be warranted.

The sometimes diverse extra-breast/ovarian cancer types found in association with \textit{BRCA} germline mutations must be critically assessed. For example, several genetic epidemiologic studies have noted an increased risk of prostate cancer in \textit{BRCA2} mutation studies. Although investigations dealing with the etiologic role of \textit{BRCA2} mutations in hereditary prostate cancer (HPC) have frequently been consistent, Agalliu et al. (22) in a study of 266 individuals from 194 HPC families who were screened for \textit{BRCA2} mutation found no evidence of an association between \textit{BRCA2} mutations and susceptibility to HPC in men selected from families at high risk for prostate cancer.

A striking example of this broad cancer syndrome heterogeneity is evidenced in the Li-Fraumeni syndrome, which is characterized by Sarcomas, Brain tumors, remarkably early-onset BC, Leukemia,
Figure 4. Pedigrees of seven families depicting evidence of the heterogeneity found in hereditary breast cancer families.
Figure 4. continued.
Lymphoma, and Adrenal cortical carcinoma. This remarkable array of cancer sites led us to coin the acronym “SBLA” for the syndrome (23). Other cancers may be integral to the disorder, such as colorectal and pancreatic cancers; p53 is the culprit mutation in the Li-Fraumeni syndrome.

Given this extensive phenotypic and genotypic heterogeneity, it is diagnostically insufficient for the physician to state, “We have a patient with hereditary breast cancer,” without defining the specific type of syndrome of record; in turn, when relevant, we must relate this information to the molecular geneticist in order to aid in the search for the possible presence of a pathogenic germline mutation, e.g., the p53 mutation in the Li-Fraumeni syndrome, BRCA1/BRCA2 in HBOC, and the list goes on (Fig. 2) (4,6). Clearly, this listing of hereditary disorders wherein BC is an integral lesion will likely continue to expand, commensurate with its increasing clinical and molecular genetic research interest. One example is the mentioned germline mutation first identified in 2002, namely CHEK2*1100delC, which predisposes to early-onset BC and possibly other cancers inclusive of colon, prostate, kidney cancer, and brain tumors (24,25). This provides an additional example of the phenotypic and genotypic heterogeneity of HBC (Fig. 2).

**PEDIGREE STUDIES**

The following pedigrees depict a variety of clinical presentations in HBC (Fig. 4).

**Family A**

This is a classical HBOC pedigree with breast and ovarian cancer occurring through four generations. Of special note is individual IV-1, who had bilateral BC with strikingly early onset (at ages 23 and 24). Other evidence for HBOC includes both breast and ovarian cancers in individual III-3 and possibly in the proband’s mother (III-2).

**Family B**

This pedigree depicts a family with the HBOC syndrome occurring in the lineage of both the maternal and paternal portions of the pedigree (both of the proband’s parents and their respective lineages). A deleterious BRCA1 mutation was found on the maternal side of the family and a deleterious BRCA2 mutation was found on the paternal side of the family wherein three male BC have occurred.

**Family C**

This pedigree depicts an example of a highly-extended HBOC syndrome family. Of interest is the large number of ovarian cancer cases in this family, notably in generation III. A deleterious BRCA1 mutation was found in this family.

**Family D**

This pedigree demonstrates a classical HBC syndrome wherein BRCA1/2 testing was performed, but a deleterious mutation was not found after complete sequencing. Another gene, such as the p53, CHEK2, or PTEN, may be the culprit and these possibilities should be explored.

**Family E**

This pedigree depicts a family wherein the proband (III-3) manifested a rather aggressive BC at age 31, and in spite of intensive therapy succumbed at age 36. Her mother (II-3) had BC at age 56 and was living. The mother declined DNA BRCA testing, her reason being “The breast cancer affecting my daughter was too aggressive, and I fear that knowing the mutation would cause great alarm to other members of my family.” While DNA testing of this mother would be of immense value to her entire family, her decision must be accepted and even subtle coercion must not be used. Such emotional barriers as these must always be accepted with the hope that they will be eventually reconciled.

**Family F**

This family depicts carcinoma of the breast at age 53 and ovary at age 56, in the proband’s mother (II-3), who is living and is now age 66. She had her DNA tested with findings of a BRCA2 mutation of undetermined significance. Her identical twin sister (II-4) manifested BC at age 56. Because of these remarkable cancer occurrences in these identical twins, we counseled and examined the 37-year-old proband (III-2). Upon breast examination, which we regularly perform as part of our genetic counseling program, we found a solid nodule in the left breast, immediately lateral to the areola. We ordered mammography with focal compression, identified the lesion, and biopsy proved it to be minimally infiltrating carcinoma of the breast. The proband was tested and found to carry the same BRCA2 mutation as her mother, as does the mother’s cancer-affected identical twin sister. These findings support our belief that
the physician/genetic counselor should always offer breast examination for such high-risk patients.

Family G—Li-Fraumeni with p53 Mutation
This pedigree depicts an abbreviated form of a classical Li-Fraumeni syndrome family with a known p53 mutation. The spectrum of diverse cancers that characterizes this syndrome is readily displayed in this family. Note the extremely early onset of BC in individuals IV-4, III-3, II-1, and III-16, as well as the multiple occurrences of sarcoma, in individuals IV-4, IV-5, V-12, IV-12, IV-23, IV-26, and IV-28. A p53 mutation, present in this classical Li-Fraumeni kindred, will be identified in only about 50% of such classical families; in the future, another mutation(s) may be found to be responsible for such families that lack an identified p53 germline mutation.

DISCUSSION
Before a high-risk individual undergoes gene testing, he/she must receive genetic counseling that imparts a full understanding of the pros and cons of cancer genetic testing, thus enabling the person to provide fully informed written consent. Specifically, the patient must be able to determine whether such DNA testing is acceptable emotionally; he/she must also feel secure regarding issues of confidentiality, which may relate to the patient’s perception of insurance or employment discrimination. Given these concerns, the physician must also carefully appraise, in so far as possible, the individual’s emotional state in terms of his or her ability to accept a positive or negative DNA mutation test result. When the physician lacks expertise in these matters, the patient should be referred to a medical geneticist and/or a medical genetics center experienced in all facets of hereditary cancer.

Spread of Knowledge to High-Risk Relatives
Who tells the rest of the family of their need for testing (19)? Ideally, patients who have become knowledgeable about “their” HBC disorder, and may have already been tested for a mutation, will be the best emissaries for this mission. Alternatively, with the patient’s permission, the primary care physician and/or genetic counselor(s) should inform family members about their potential high risk through correspondence or at a family information service (FIS) (26). An FIS is a planned but informal gathering of multiple family members who are at risk for a particular hereditary cancer-prone syndrome. The meeting is conducted by a team of health care professionals, ideally comprising an oncologist/cancer geneticist, an informed family physician, a genetic counselor, and/or a Registered Nurse. The primary focus of an FIS is to reach the maximum number of at-risk relatives and provide them with pertinent information about their hereditary cancer syndrome, DNA testing options, and targeted cancer surveillance and risk management. This should take place in an informal and friendly setting where family members can ask questions more freely and can garner support from each other (26). In short, the FIS, in our experience, often provides a “group therapy” type of experience for the family.

Economic and other Personal Concerns
DNA testing has significant economic dimensions, as commercial testing may be extremely expensive, and in many cases out of reach for a high-risk patient (27,28). From the patient’s standpoint, payment may be made “out of pocket” because he or she may be concerned about the potential for insurance discrimination or does not have health insurance coverage for genetic testing. Some individuals may be reluctant to be tested because of a variety of other personal reasons, foremost of which is fear and anxiety about their own cancer destiny should they be carriers of a deleterious germline mutation. A parent may also experience feelings of guilt for possibly passing the deleterious mutation to his or her children. Conversely, a high-risk family member may harbor feelings of hostility and even alienation toward the parent who transmitted a deleterious mutation to him or her. Collectively, these factors may deter a patient from being tested for a deleterious mutation or even prevent him/her from relating this knowledge to close relatives, even though they might benefit from this testing.

Although genetic testing is extremely valuable for designating which patients will require highly-targeted cancer control measures (those who are mutation positive) versus those who will not require such intensive management (mutation negative, thereby reverting to general population screening guidelines), this knowledge is often not fully utilized (see Part II of this series). For example, Murff et al. (29) showed that of six high-cancer-risk candidates for DNA testing, only one was referred for BRCA testing. Furthermore, Guttmacher et al. (30) noted that only 17% of patients who would be considered as candidates for genetic testing were referred for germline mutation testing.
Physicians, in concert with genetic counselors, play an important role in the management of patients with hereditary forms of BC. This management strategy has been significantly abetted by discoveries in the area of hereditary cancer syndrome delineation, with particular attention to the disorder’s natural history, including those “at the bench” in molecular genetic laboratories. Collectively, this strategy will not only impact upon hereditary cancer syndrome diagnosis, but it will also play an important role in management, including the potential for gene-targeted therapy (5,31,32).

The entire impact upon hereditary cancer syndrome diagnosis and its ultimate management starts with our strong emphasis on a well-orchestrated family history. Research into the cost-effectiveness of this entire process is needed, very possibly using a decision model similar to that used for the Lynch syndrome (33). This type of cancer control program, if it shows cost benefit, could significantly impact health insurance coverage for screening and management of high-risk patients. For example, ongoing studies suggest that prophylactic mastectomy and/or oophorectomy can enable cost-effective cancer risk reduction, although quality-of-life questions may impact their use (34). Prophylactic oophorectomy in BRCA mutation carriers may also lead to as much as a 50% reduction in BC (35). Significant gains in life expectancy can also be realized for BRCA mutation carriers who are diagnosed with early-stage BC, and then undergo prevention strategies which may involve tamoxifen chemoprevention, prophylactic oophorectomy (35,36), and prophylactic contralateral or bilateral mastectomy (37,38).

In conclusion, knowledge of the clinical and molecular genetic facts that are crucial for the diagnosis and interpretation of most forms of hereditary cancer and, in particular, the HBC-prone syndromes, the subject of this article, will then be shown to benefit cancer control for patients at increased cancer risk. Needed, however, is a knowledgeable physician who is ready to listen intently to his/her patient’s account of the family history, which can then be embellished through the help of additional informative family members.

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