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Genetics: Breast Cancer as an Exemplar

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Synopsis

Genetic testing for adult onset diseases is now available. One such test is for the mutations present in the BRCA gene which result in a significantly higher risk for the development of breast cancer and/or ovarian cancer. Women who have one of these mutations face difficult choices in terms of increased surveillance and/or prophylactic surgeries. Examining experiences of women with BRCA mutations can serve as an exemplar for other populations at risk for genetically associated adult onset diseases.

Keywords

ethics; genetics; genomics; nursing advocacy; nursing competencies

Genetics of Hereditary Breast Cancer

The progress made in the discovery of disease causing genes accelerated greatly with the initiation of the worldwide Human Genome Project in 1990 [1]. While the number of tests for specific diseases continues to grow, one of the earliest presymptomatic mutation tests was for the disease of hereditary breast and ovarian cancer (HBOC). Breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) are the two major genes associated with HBOC [2]. The BRCA1 gene is on chromosome 17 and the BRCA2 gene is located on chromosome 13 [3, 4]. Mutations in either of these genes significantly increase individuals' risk for both breast and ovarian cancer across their lifespan (70 years): the mean cumulative cancer risks for mutation carriers: breast cancer risk of 57% (95% CI, 47% to 66%) for BRCA1 and 49% (95%CI, 40% to 57%) for BRCA2 mutation carriers; and ovarian cancer risk of 40% (95% CI, 35% to 46%) for BRCA1 and 18% (95% CI, 13% to 23%) for BRCA2 mutation carriers [5]. Risks in identified carriers of either mutation are higher when based on other family members being diagnosed with breast cancer prior to the age 35 years [6].

Everyone has a BRCA1 and BRCA2 gene. These genes are tumor suppressor genes so that if a mutation occurs in such genes then the normal controls on cell growth are lost [7]. The mutations are passed down through generations in a dominant Mendelian pattern, meaning *each* offspring has a 50% chance of inheriting the parental mutation [8]. A genetic test is available to determine if a mutation is present in either gene [9]. It is recommended that a family member with breast

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and/or ovarian cancer be the first tested to determine if a mutation is present in either the BRCA1 or BRCA2 gene [10]. If a mutation is identified in a family member then others who have not been diagnosed with breast and/or ovarian cancer can be tested to determine if they carry the mutation and if they do then they too have an increased risk for cancer development.

The specter of breast cancer in HBOC families is significant. Research shows multiple cases of breast cancer across generations [11, 12]. Women in these families can tell story after story of grandmothers, mothers, aunts, cousins being diagnosed with breast cancer. One research participant from the author's research discussed how her mother had broken the “50 year” barrier:

> Okay my mother is definitely the third generation to have breast cancer in her thirties. My grandmother had breast cancer at 38 and passed away. My mother is 51 now she is the first woman in our family to live past 50 in five generations.

Many young women in HBOC families have experienced the loss of their own mothers, an event that only heightens the risk they feel for themselves:

> Yeah, it's completely different… a lot of people worry about dying from the same things that their parents died from but I guess I have one up on that… it's more than just worrying about dying from what my mom died from it's like I have the genetic code and that makes it a really good possibility.

Genetics is understood as being deterministic [13]. Women without a BRCA mutation overestimate their risk for developing breast cancer [14-16] while those with a mutation express “inevitability” that if they do not make the difficult choices for prophylactic mastectomy and/or oopherectomy they will develop cancer [17 18, 19]. Guidelines have been established to address the issue of genetic risk for breast cancer.

Guidelines for Testing and Management of Genetic Risk for Breast Cancer

The National Comprehensive Cancer Network (NCCN) has established guidelines for testing for BRCA mutations and for the management of individuals who have a mutation in the BRCA1 or BRCA2 genes [10]. Genetic testing is recommended if an individual has one or more of the following familial characteristics:

- Early age (<50 years) onset of breast cancer (consider maternal and paternal sides independently)
- Two breast primaries or breast and ovarian cancer in a single individual or two breast primaries or breast and ovarian cancer in close relatives on the same side of the family
- Clustering of breast cancer with various other cancers such as male breast cancer, thyroid cancer, pancreatic cancer on the same side of the family
- Member of the family with a known BRCA mutation
- Member of a population at risk (e.g. Ashkenazi Jewish)
- Male family member with breast cancer
- One or more cases of ovarian cancer on the same side of the family

It is recommended that any individual meeting one of the above criteria be referred to a professional genetic counselor for assessment. If the woman tests p[positive for one of the BRCA mutations, the National Comprehensive Cancer Network [10] has published guidelines health care providers should follow for these women: Recommended management of individuals that have been identified as carrying a BRCA mutation includes the following:

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- Self-breast exam monthly starting at age 18 years
- Clinical breast exam, semiannually, starting at age 25 years
- Annual mammogram and breast MRI starting at age 25 years or based on earliest age of onset in family
- Prophylactic oopherectomy between ages 35 and 40 years or upon completion of childbearing
- For individuals not electing a prophylactic oopherectomy, concurrent transvaginal ultrasound and CA125 levels semiannually starting at age 35 years or 5-10 earlier than the first diagnosed case of ovarian cancer in the family
- Consider chemoprevention options (e.g tamoxifen)
- Consider research studies testing investigational imaging and screening options. Clearly, such recommendations are meant to lower the woman's risk or identify a cancer as early as possible in the development of the disease.

Risk Across the Lifespan

One of the corresponding experiences of following these screening guidelines is that a woman is in frequent interaction with health care providers across her lifespan. If she is a young woman who has not received a breast cancer diagnosis, she faces the choice between breast and ovarian screening and a prophylactic mastectomy and/or prophylactic oopherectomy. It has been shown that a prophylactic oopherectomy reduces the risk of breast cancer in women with BRCA mutations by 50% or more [20, 21]. The recommendation is that women have this surgery by the age of 40 years or when childbearing is completed [10]. While the screening guidelines recommend the decision on a prophylactic mastectomy be considered by individual case it has been shown that a prophylactic mastectomy reduces the risk of breast cancer in women with a BRCA1/2 mutation by approximately 90% [22]. While mammography and breast MRI may identify breast cancer very early, the screening for ovarian cancer is much less efficient and not considered adequate for this at risk population [23]. If a woman chooses to follow the screening guidelines but chooses against surgical interventions, she will interact with various health care providers at least four times each year, significantly more than a typical healthy young woman.

An aspect of having a genetic risk for a disease is that even when the disease is not present it affects the individual's life [24-27]. One result of this risk is that the “disease” is present across the lifespan of the woman. Even if a woman has no cancer diagnosis, she becomes a “patient” which can occur as young as 18 years of age when as an adult she may choose to have the presymptomatic genetic test. The cumulative risk for breast cancer increases across the lifespan. For example, a 30 year old woman with a BRCA1 mutation has a 3.2% risk, a 40 year old with a BRCA1 mutation has a 19.1%, while a 70 year old woman with BRCA1 reaches the cumulative risk of 85% [28].

Research with young women (ages 18-39 years) [11, 24] has shown that for some women who have genetic testing for the BRCA mutation, life changes in that they cannot “undo” the knowledge they received. For some this is comforting, for example this 32 year old explained it this way:

> I definitely have a feeling of gratitude that I live in a time where I can have this information to do with as I see fit, to reduce my risk or increase my surveillance or put my head in the sand -- my mother and grandmother never had that alternative. Some women have made the analogy that knowing you carry a BRCA mutation is like having a “ticking time bomb” inside you -- frankly, I would rather hear the ticking,

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> be able to do what I could to prepare for the explosion, than just have it silently counting down, while I'm ignorant of its existence.

Others however, do not find knowing easy to live with even if they do not question their decision to have the BRCA mutation genetic test:

> For the last couple of years, or even several years, knowing about my genetic mutation has colored my general outlook on life. I do believe we all carry certain genetic mutations and that most diseases are probably genetically based, but knowing for certain that I have BRCA1 and that I have a very high risk of another breast cancer, or possibly other certain cancers, certainly "hangs" over my head in my daily life. I'm glad I was informed, because there are certain choices I can make and certain things I can do to closely monitor myself. At the same time, knowing this has made me more pessimistic regarding the opportunity for a long and healthy natural lifespan.

Kenen [26] introduced the idea of living with chronic risk to assess how individuals who had attended a high risk breast cancer clinic in the United Kingdom but who do not know their mutation status. These participants used various coping strategies "to get on with their lives" but even not knowing if they carried a mutation, they found it difficult not to be concerned that they too might develop cancer. Living with the actual knowledge of genetic risk is a relatively new phenomenon. While prior to the availability of presymptomatic genetic tests for diseases like breast cancer, individuals, such as those in Kenen's study [26] might have thought they had a higher risk because of their family history, the knowledge of an actual mutation appears to create a sense of inevitability of developing breast cancer. It was no longer a matter of "if" but "when" as one research participant described: "As I recall, I felt it was inevitable that I would die of breast cancer one day, and that played a part in how hopeless and awful I felt." The experience of daily living with BRCA genetic test results has not been well documented. Some studies report a sense of loneliness and social separation in individuals with BRCA mutations [27, 29] Others document the barriers to disclosing genetic test results to family [30-33].

Most studies of the HBOC population that have used standardized measures of distress, anxiety, depression, and cancer worries support the emerging consensus that women who have a BRCA mutation do not experience major mental health risks [34-36]37 38. It has been shown however that women who reported higher levels of distress at baseline continued to report higher distress as long as six months after receiving BRCA mutation test results [38]. A recent study comparing pre-test psychological distress of women having the BRCA mutation testing with comparative healthy controls showed that the high-risk women reported higher distress levels than the controls [39]. d'Agincourt [40] in a qualitative study found that a subset of her participants experienced a loss of agency after genetic testing and felt less control over their future health. The author's longitudinal study of women who know they carry a BRCA mutation but have not had a cancer diagnosis indicates a hypervigilance over a four year span, where the next screening exam could "be the one" that finds cancer [41]. Women who live with the knowledge of a BRCA mutation that significantly increases their risk of breast cancer do so in a new world of genetic health care and while research provides some information, the long-term consequences of having genetic risk knowledge is still largely an uncharted domain.

BRCA testing as an exemplar for genetic healthcare

Four autosomal dominant cancers for which there is clinical presymptomatic genetic testing are HBOC; two forms of colon cancer, hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), and multiple endocrine neoplasia [42]. While all cancers have a genetic component, these four have been identified to have specific mutations that are inherited in families in a Mendelian dominant pattern. For the purpose of this article, the BRCA associated breast cancer will be used as an exemplar of genetic medicine. Quotations

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from Hamilton's research with women who have a BRCA mutation [11, 24, 41, 43] will be used to illustrate the experience from the woman's perspective.

Genetics is Familial

It has been argued that "genetic information is different" [42, 44] because of the nature of that information. First of all, genetics is familial. That means that while a woman, exercising her own autonomy, may decide to have a presymptomatic BRCA test, the knowledge she receives potentially impacts other family members whether or not they were consulted prior to the testing. While most families do share genetic test results [32, 33, 45], not all family members are willing participants in the genetic testing process. One research participant spoke of the differences with her sisters:

> I think the way we've handled it in all the four sisters has been very, very different. Um, my sisters don't like to talk about it, don't want to deal with it, the two sisters that have chose not to be tested. And that's very difficult for me because I need to talk about this…and that's my way of coping. By their not dealing with it I definitely felt a sense of isolation and it, just pretending… like we have to pretend that somehow this is all OK when it's not.

Others [46] have also found that in families genetic test participants often feel a strong sense of responsibility to inform immediate and extended family members of the potential risk they face. Women describe going to great lengths to contact aunts, uncles, and cousins: "So I found it really hard to, to make these contacts with all the family, to try to pull together the information and like it was a huge responsibility." Those who test first feel not only a responsibility to inform but to somehow set a standard as to how to deal with this information:

> It sucks to be first. I feel like I always have to have the answers and be the voice of reason. So even though I'm a basket case to my sweet husband- to my brothers and sisters I feel like I have to be at peace with all of this. If I'm not, how can I expect them to be? I don't want them to live scared because of this.

Genetic information sets up many complex communications and interactions within families. Health care providers benefit from being aware of potential barriers as well as expectations faced by their patients.

Genes are "Passed Down"

The definition of genetics implies the fact that what a parent has may be inherited by their offspring. This basic fact is important in understanding how individuals and families may react to information gained from genetic testing. Studies report the guilt parents feel when their daughters test positive for a BRCA mutation [19, 47, 48]. Younger women who are considering their reproductive choices also ponder and worry about the possibility of passing on the mutation, but only one of over 80 research participants decided not to have children based on that issue alone (Hamilton, unpublished data). Most participants acknowledge the risk but believe medicine will have found a cure by the time their offspring may face an actual cancer diagnosis:

> As far as worrying about my (future) daughters carrying the mutation, I think breast cancer is something that has become more preventable and treatable, and is becoming even more so with advances in modern medicine. So I don't worry about that.

While young women may not change their plans to have children there is an acknowledgment that life is different because of the nature of a genetic risk for a specific disease:

> My family is no longer as lighthearted as we once were. Genetic discussions happen all the time. I feel like there is absolutely no escaping this disease. And I know that

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> the chances of having to watch someone I love go through this are high and that breaks my heart.

The sense that genetic risk will always be present adds to the burden some participants feel after genetic testing both for themselves and their offspring. Unlike other diseases that may have a contributing genetic component along with environmental influences, diseases such as HBOC cannot at this time be altered to any significant degree by health behavior choices. While a smoker can stop smoking, an individual with a BRCA mutation may live a healthier lifestyle and shift the age of onset of breast cancer but not alter the actual risk of breast cancer development [49]. There is an "inescapability" component to HBOC that is described by women with the mutation:

> It suddenly makes the possibility of cancer for the siblings - and their children - a real possibility. And with BRCA it is not just about breast cancer - but also ovarian cancer - and to a lesser extent other cancers like pancreatic cancer, prostate cancer. My two sisters all have sons so the latter is a factor. With BRCA, it just doesn't stop in the female line - it affects the males as well. A huge can of worms and worries was opened with my test results.

The very characteristic of genetics being something that is passed down through the generations creates varied and complex issues for families having such knowledge.

Genetics and Decision Making

Usually through examining the family pedigree, individuals and family members may become aware that they potentially carry a BRCA mutation; these family members face many decisions. The first decision is whether to have the genetic test or not. If individuals choose to have the test and receive a positive result (e.g. they have a mutation in the gene), then the follow-up decision is either to increase screening or consider prophylactic surgery (see Guildelines Section). An individual who receives a positive BRCA mutation test knows that her risk of breast cancer onset is significantly higher than the general population [5]. Individuals may decide not to have the test. If this is the decision, depending on the woman's age, she may find it more difficult to get insurance to pay for increased screening without a genetic test result. For example, a 30 year old woman who decided not to have the test may not be covered for a mammogram because the recommended screening guidelines do not recommend mammograms before the age of 40 years [50]. Young women who are potentially at risk for carrying a BRCA mutation who choose not to test are unlikely to be offered early screening exams. If the young woman does indeed have a BRCA mutation she risks not identifying a cancer early in its progression. If an individual has the test and tests negative for a known family mutation, her risk is the same as the general population. However, a significant proportion of women who have the genetic test receive what is called a variant of unknown clinical significance (VUCS). Such a change in the DNA may or may not represent deleterious mutation [10, 51]. BRCA mutations account for only 20% to 25% of familial aggregation of breast cancers [52], meaning the majority of women who have testing will receive a VUCS result. Data from the Breast Cancer Information Core (http://research.nhgri.nih.gov/bci) estimates that 32% and 53% of all detected BRCA1 and BRCA2 mutations, respectively, are VUCS [51] It is unclear whether this population has a risk equivalent to those with an identified mutation or equivalent to the general population. For this group, the National Comprehensive Career Network (NCCN) [10]guidelines recommends offering these women opportunities to participate in research studies that work to identify risk associated with VUCS mutations and/or provide individualized recommendations based on family history. For example, if a woman's genetic test indicated a VUCS but she had a sister that developed breast cancer in her early 30's, then recommendations would be that the unaffected sister have intensive surveillance starting in her early to mid-20's.

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Interestingly, some research suggests that women who have had a breast cancer diagnosis but who test negative or VUCS doubt their results: “I often wonder if my cancer is still genetic - and that there are other markers besides BRCA 1 & 2 - and could my type be worse?” A recent publication [53]indicated that women who receive VUCS and who entered the genetic testing process with a higher perceived risk of carrying a mutation continued to report higher levels of genetic testing distress over a year's time. In an early study by Lerman et al [54], 30% of women ages 25-39 years who were noncarriers of a BRCA mutation and had no breast cancer diagnosis continued to have follow up mammograms one year after genetic testing. Because this group of women is not recommended to have mammograms until age 40, this activity suggests that they are not completely reassured by their negative BRCA test. Similar results have been reported with individuals who test negative for the FAP gene which significantly increases risk for colorectal cancer [55]. It is unclear why a negative test result is not reassuring though indications of the impact of family experiences with breast cancer suggest that women who have lived through the experience of multiple family members with breast cancer frame their risk perceptions on the family experience and not only the BRCA mutation test result [11]37.

If a woman tests positive for a BRCA mutation she is then faced with decisions about surveillance and/or prophylactic surgery(ies). The recommendation is for alternating mammogram and breast MRI and ovarian surveillance with CA125 levels and transvaginal ultrasound every six months. It has been reported that breast MRI is more sensitive but less specific than mammography resulting in a higher false positive rate leading to three times as many unneeded biopsies [56]. Women describe the difficulty of the experience of biopsies on suspicious findings on a MRI:

> In addition to mammography, I have been given the option to have routine breast MRIs. There is a high rate of “false positives” or abnormal breast tissue anomalies which ultimately trigger additional biopsies. I have had three I think. This has been very challenging emotionally.

The other aspect of surveillance is the women's worry about being told at their next appointment that breast cancer has been identified:

> It's almost like a time bomb…. I don't know when, but I'm pretty sure it will “go off” before I am age 40. It's the anxiety I feel each time I know I have an appointment coming up and wonder… will this be the time they find something?

Women describe not being able to live with this sense of anxiety over the next surveillance appointment and so they decide to go ahead with prophylactic surgeries:

> More and more I would hear about young women in their late 20's and early 30's getting diagnosed with the cancer. I would think about the possibility of me being diagnosed as if it was going to happen that day or the next or in the next week. Finally, in May 2005 I elected to get a prophylactic bilateral mastectomy and reconstruction. (24 year old BRCA1+)

Some women cannot tolerate the idea of having any cancer, so the prospect of “catching it early” as is the case with the intensive surveillance is simply not good enough:

> However, when I got the BRCA+ result, and was truly faced with such a high risk of breast cancer, and since my sister already had it, I figured it was just a matter of time before I got breast cancer, so all of a sudden early detection wasn't good enough. I DO NOT want breast cancer and the best way to reduce my risk the most is to have preventive mastectomy, thus I am planning it for July/August of 2006 (about 1 year, 3 months after receiving my BRCA+ results)

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The choice to have a prophylactic oopherectomy is an issue of great concern for younger women largely due to reproductive concerns, sexuality changes, and early onset of menopause [11, 57, 58]. Young women speak of a sense of urgency to make decisions about the timing of having children:

> I feel very pressured to have children soon in fact my doctor has told me that I have to have a full hysterectomy and oopherectomy by the time I am 35. I plan on having children before then but I also feel very limited you know I don't feel like “oh I can't have children because I may pass on the gene” but I feel like, you know, I am 24 now, I am married, I feel like I should start having children soon but I don't know if I am ready for that.

While high risk women report relief from the fear of ovarian cancer after a prophylactic oopherectomy, they also report concerns about loss of libido, body image changes and dealing with early-onset menopause [59, 60]. The choices women face after finding out they have a BRCA mutation are difficult and involve multiple aspects of their lives and their families' lives.

Summary

Women's health is and will continue to be in increasing numbers of ways affected by the advances in genetic healthcare. Not only are women most likely to be the keepers of health histories in families but they also tend to be the communicators of risk [33, 46, 61]. Because the BRCA mutations were among the earliest mutations identified in cancer risk assessment, women have also been pioneers in both genetic testing and decision making after genetic testing. In some ways the BRCA affected population has been one large experimental group as researchers and health care providers discover what women want; what they need; how they react to knowledge of genetic risk; what procedures lower or eliminate the genetic risk; the aftermath, both psychological and physical, of choosing one procedure over another; and the impact on quality of life for the individual and her family. While our knowledge continues to grow, only time will allow an examination of the long-term effects such as the physical sequelae of prophylactic surgeries in young women; the psychological impact on offspring of women identified with a mutation; the impact on family coherence and communication; and the interaction of this at-risk population with their health care providers.

Examining the experiences of women with a BRCA mutation provides a window into considering issues that may arise with genetically based cancers that present in adulthood. At present genetic testing for cancers for which individuals have a 50% risk of inheriting from a parent with the mutation include hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), and multiple endocrine neoplasia. Similar issues such as disclosure of test results, psychological distress and follow-up care after testing have been reported in the HNPCC population. [62-66] As more cancer and other disease type mutations are discovered, the knowledge gained from the BRCA population may assist health care providers in providing knowledgeable and sensitive care to patients.

Genetics is increasingly considered an essential science for all areas of health care [67]. Nurses must be knowledgeable of the science of genetics and have skills to engage patients who are in different stages of their encounters with genetic risk and follow-up. Beyond that, nurses must also understand the complexities that may arise for individuals and families when a genetic diagnosis occurs. Because the nature of genetics is familial the idea that an individual is singular in her concerns does not apply in genetic healthcare. Fortunately, nursing has a strong commitment as a practice discipline to view a patient holistically and this history of practice will serve nurses well in the evolving age of genetic healthcare.

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