BRCA Gene Mutation

December 19th, 2020

Outline

- What is the BRCA 1/2 gene?
  - How is it mutated?
- Who is at risk?
  - How women are affected
    - Types of cancer involved
  - How men are affected
    - Types of cancer involved
  - Types of cancer that affects men and women
- How is the mutation detected?
  - Genetic testing
  - Types of testing
- What can be done for preventative care?
  - Risk reduction
  - Imaging for BRCA1/2
  - Risk reducing measures for men
- My family story

Learning Objectives

1. Understand the BRCA gene mutation
2. Explain the type of cancers can be caused from this mutation
3. Describe the types of screening can be done for these mutations
4. Discuss the types of imaging can be done

Abstract

The BRCA1 and BRCA2 gene mutation affects about 0.1-0.2% of the general population[4], but with todays population that is quite a few people. These gene mutations can affect both men and women. They can increase the chances of breast, ovarian, pancreatic, prostate, other pelvic organs, and potentially melanoma cancers. These mutations are detected by genetic testing. Patients with these mutations need to have a lot of communication with their doctors to determine what works best for them. Most doctors will encourage them to get imaging, such as mammogram or MRI, to watch for potential cancers. Screening while having these mutations, is one of the most important preventative care patients can do.

Introduction

According to The Center for Disease Control and Prevention, breast cancer is the second most common cancer among women in the United States, following closely behind skin cancer. Although it is rare, about 1 in 100 breast cancer cases are found in men.[1] Most breast cancers are sporadic, which means they happen by chance. When breast cancer is detected, some of them have a strong tendency of having to do with inheritance. The most common inherited genes that affect breast cancer are the BRCA1 and BRCA 2 pathogenic variants.[2] Along with breast cancer, BRCA1 and BRCA2 can cause other cancers, such as ovarian, prostate, pancreatic, and melanoma, which will be addressed later in this paper. Imaging, such as magnetic resonance imaging (MRI) and mammography, play a very important role as it helps identify potential cancers associated with these gene mutations.

BRCA Gene

BRCA stands for BReast CAncer gene indicating its relevance in breast cancer pathogenesis. The BRCA1 and BRCA2 are gene mutations that were discovered in 1994 and 1995. Respectively, BRCA1 gene was discovered by Doctor Mary-Claire King. Her discoveries lead some of her colleagues, Michael Stratton and Richard Wooster, to map out an analysis on the BRCA2.[3] BRCA 1 and BRCA2 are known as the breast and ovarian cancer predisposition genes. BRCA1 is located on the chromosome 17q21 and has 24 exons.[4] It's code for a protein consisting of 1863 amino acids. BRCA2 is located on chromosome 13q12 with 27 exons with a protein consisting of 3418 amino acids.[4] There are more than 1,600 variants for BRCA1 and

1,800 known variants for BRCA2, the majority of which lead to missense or non-functional proteins.[2] Due to these genes being so large, more than 400 mutations have been reported.[4]

Every person contains the BRCA1 and BRCA2 genes, but only some patient's genes are mutated, which in turn increases the risk for breast and ovarian cancers. BRCA genes play an important role not only in DNA repair, but also in transcriptional regulation, cell growth control, and conversion of genomic integrity.[4] When these genes are unaffected and normal, their function is to be a tumor suppressor gene. When the BRCA1 and BRCA2 genes are mutated, it can cause irregularities in DNA synthesis which means the cells are more likely to develop additional genetic alterations that can lead to cancer. This leads to the p53-dependent DNA breakdown which may lead to cell cycle arrest and apoptosis, also known as cell death. Mutations in exon 13 of BRCA1 gene and exon 11 of BRCA2 gene have been associated with ovarian cancer.[4] Despite the intensive research focus on these two genes, their role in cell biology and cancer are still being explained.[3] Inherited breast cancer is an autosomal dominant genetic condition. This means both male and female children of a parent who has the mutation have a 50-50 chance of inheriting it as well. Luckily, according to the Mayo Clinic, the BRCA gene mutations cannot skip generations, meaning if your parents have it and it skips you, you cannot pass it on to your own children.[5]

Who is at risk?

Both BRCA1 and BRCA2 gene mutation can affect both men and women since it is a hereditary gene and can be passed down. Although this can affect both, about only 0.1-0.2% of the general population are carriers of the gene mutation. That may seem low, but that equates to 780 million people with the current US population. 2-3% of all breast cancers cases have detected BRCA1 and BRCA2 genes.[4] Each family may present with specific mutations of the gene and this may be caused by things such as geographical locations and ethnicity. It is said that Ashkenazi Jews carry these mutations at higher rates than most. BRCA associated cancers tend to progress directly to invasive disease without development of a precancerous component.[4]

According to Mayo Clinic, you may have a BRCA gene mutation risk if you have had breast cancer or bilateral breast cancer before the age 50, ovarian cancer, both breast and ovarian cancer, fallopian tube cancer or primary peritoneal cancer, pancreatic cancer, and two or more close relatives with breast, ovarian, or pancreatic cancer. There are some indications that you

may have a BRCA gene mutation due to your family health history. Some of those include, two or more close relatives with breast or ovarian cancer at a young age, close male relatives with breast cancer, close relatives with breast and/or bilateral breast cancer, two or more close relatives with pancreatic cancer, or a relative with a known BRCA1 or BRCA2 gene mutation.[5]

Both genes, when not mutated, act as tumor suppressor genes. People who have inherited these mutations tend to develop breast and ovarian cancers at younger ages compared to those who don't have the mutation.[6] Studies have shown that patients with BRCA1/2 mutant high grade serous ovarian cancer (HGSOC) have improved survival compared to those with BRCA wild type HGSOC.[7] If a patient has certain BRCA2 mutations inherited from both parents, it may cause a rare form of Fanconi anemia. This is a syndrome that is associated with childhood solid tumors and development of acute myeloid leukemia.[8]

How women are affected

Clinically, 4-7% of women tested in large studies using multi-gene analyses presented with BRCA1 and BRCA2 mutations. These are done in large studies, so keep that in mind when performing the genetic testing to avoid missing a mutation. According to the National Comprehensive Cancer Network, individuals with mutations in BRCA1 have a condition called Hereditary Breast and Ovarian Cancer syndrome also known as HBOC.[4]

Breast cancer

Women with HBOC have an elevated risk for breast cancer that is greatly increased over the 12% lifetime risk for women of the general population in the United States.[5] Women with HBOC also have a higher risk of ovarian, fallopian tube, primary peritoneal cancer, and pancreatic cancer. For patients with the BRCA1 gene, the breast cancer risk is 60-80% compared to the 12% for the general population.[9] Second female breast cancer is up to 20% within 5 years versus 1.5%.[9] In a recent large study, which showed that about 72% of women who inherit a harmful BRCA1 mutation, and about 69% of women who inherit BRCA2, will develop breast cancer by the age of 80.[8] BRCA1 breast cancers are also commonly diagnosed with higher histologic grade, proliferative rate, and show predominance of triple negative pathology compared to sporadic tumors.[4] Approximately 75% of BRCA1 pathogenic variant breast cancers are invasive ductal carcinomas and 10% are atypical medullary cancers.[2] In BRCA2 pathogenic

variant breast cancer, lobular or ductal with lobular types are more frequent.[2] Some studies have shown evidence that women who carry these mutations are more likely to develop a second cancer in either the same breast or the opposite breast than a woman who does not carry these mutations.[8]

Ovarian cancer

BRCA2 carries an increased ovarian cancer risk, but it's not as high of a risk as BRCA1. BRCA germline mutations are reported in 15-17% of high grade serous ovarian cancer versus 6% of somatic mutations.[8] The risk for ovarian cancer is increased to 33-44% for both BRCA1 and BRCA2, while there is only a 1-2% risk for the general population.[4] Serous adenocarcinoma is the main cancer in ovarian cancer patients who carry the BRCA1/2 mutation.[4] The BRCA2 mutation also affects these cancers but at different rates. The risk for breast cancer is 50-70%, the second round of female breast cancer is up to 12% within 5 years, and ovarian cancer is 12-20%.[9]

How men are affected

It is not nearly as common, but men can also be affected by BRCA1 and BRCA2 gene mutations. They are still considered to have HBOC syndrome, excluding the ovarian cancer. Men who have BRCA1 have an elevated risk for breast and pancreatic cancer. The general population has a 0.1% chance for breast cancer and those with BRCA2 have a 7% chance for breast cancer.[9,10] For men who have familial pancreatic cancer, BRCA1 and BRCA2 are the most common genetic mutations linked to this cancer.[6] Those with BRCA1 have a 2-3% risk and with BRCA2 have a 3-5% risk for pancreatic cancer.[9,10]

Prostate cancer

Prostate cancer is the most common cancer diagnosed in the United States. Those with BRCA2 have a 20-30% increased risk for prostate cancer.[10] BRCA2 mutation has been associated with early onset and aggressive prostate cancer with poorer outcomes.[6] Patients may also have an increased risk for prostate cancer more significantly at younger ages. BRCA2 mutations are found in about 5-10% and BRCA1 in approximately 1%.[6] In Ashkenazi Jews, BRCA mutations are found in 5.2% of unselected patients with prostate cancer.[6]

Other cancers

There is not as much information about melanoma being linked to the BRCA1/2 mutations due to it being a common type of cancer. Studies have shown those who have the BRCA2 mutation have a 3-5% increased risk for melanoma compared to 1-2% in the general population.[10] Colon cancer risk is also increased in carriers of BRCA1. Some very rare types of gallbladder and biliary tract tumors may be associated with BRCA2.[4] People with BRCA1/2 mutations also have an increased risk of pancreatic cancer. Approximately 10-15% of pancreatic cancers are attributed to a genetic cause.[6] While the BRCA1/2 plays a role in pancreatic cancer, there are more genes that may also be involved, such as CDKN2A and PALB2.[6]

Detecting a gene mutation

When patients find out they may have a BRCA gene mutation they should talk to a genetic counselor and get a plan for them specifically. Before meeting with a genetic counselor, a personal health history, including any past genetic tests, should be documented. It is important to gather as much family history as possible, including previous cancers and/or surgeries they have done to help prevent cancer. A genetic counselor will discuss the benefits, risks and limitations of genetic testing. Testing may be costly for some patients; the United States now offers patient pay prices of $250-400 for panel tests not billed to insurance.[6] Only 20-30% of eligible patients are referred for testing or have access to it. It is estimated that 97% of carriers in the population remain unidentified and end up missing opportunities for prevention.[11]

Genetic testing

Previously, genetic testing was only done on pancreatic cancer patients with a family history. But several studies have shown that while doing that, it will fail to identify up to 50% of patients with known pancreatic cancer genes.[9] According to the American Society of Clinical Oncology, they recommend that genetic testing should be offered to affected and unaffected patients with familial pancreatic cancer, families with three or more diagnoses of pancreatic cancer, and those who meet the testing criteria for genetic syndromes with an increased risk of pancreatic cancer. Along with that, the National Comprehensive Cancer Network (NCCN) said the breast and ovarian cancer guidelines were updated in 2019 and now offer genetic counseling and testing to all patients diagnosed with pancreatic adenocarcinoma and those with metastatic

prostate cancer.[6] Some researchers also advocate for genetic testing in all women with a new diagnosis of high-grade serous ovarian cancer. There are professional societies that do not recommend children under the age of 18 undergo genetic testing because there are no risk reduction strategies meant for children and the risk for developing a cancer type with BRCA1/2 is extremely low.[8]

When the genetic test is performed, it is usually done by blood test. In some cases, saliva may be collected as well. Today, multi gene panels including broad genomic rearrangements may be chosen for a higher affordability in risk assessment. For those patients who have a family member with a specific mutation, a single site targeted mutation analysis may be done. Once the test is done, it may take a few weeks before test results are available. If a patient has a test result come back positive it does not mean that the patient will develop cancer. Those who receive a negative test may not necessarily be in the clear. If they have a strong family history of this gene mutation, this negative may not be accurate. There is a very low chance that genetic testing would miss the BRCA1/2 mutation, but it could happen. Moreover, scientists continue to discover new BRCA1/2 mutations that have not been identified, so potentially that negative result could be one that is not yet identified.[8]

Risk-reduction

Although it is hard to prevent every type of cancer relating to the BRCA gene mutation, there are some preventative measures that can be taken to help lessen the chance. There are surgeries, imaging, and other types of risk-reducing measures that can be done. When someone is diagnosed with the BRCA1 or BRCA2 gene mutation, they will set up a plan with either their doctor or their genetic counselor. Each patient's plan will be different depending on which mutation they have and family history. The US National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology have published recommendations on how to go about living with this gene mutation. The NCCN states one should have an annual breast MRI and biannual clinical breast exam starting at age 25, annual mammogram starting at age 30, risk reducing salpingo-oophorectomy at age 35-45, consideration of anti-estrogen therapy to reduce breast cancer risk, and consideration of a prophylactic mastectomy.[6] It is said that prophylactic surgery, which is intended to prevent disease, does not guarantee that cancer

will not develop because not all at risk tissue can be removed by these procedures. Therefore, they are considered risk-reducing instead of preventative.[8]

While those are all recommended, each patient may be different depending on what their doctor recommends. Chemoprevention such as tamoxifen and raloxifene may be used to reduce the risk of breast cancer for women who choose not to or cannot undergo surgery.[8] There are some risk-reducing surgeries that can be done to help lower the risk of breast cancers presented by BRCA1/2 gene mutations. As stated above, one surgery that can be done is a salpingo-oophorectomy. This can enable protection from cancer development in up to 90% of patients and breast cancer chance is reduced by 50% with this procedure.[4] Another surgery that can be done is a bilateral mastectomy. A mastectomy increases protection from cancer development by 96%.[4] It has been said that these protective surgeries can only be recommended for suitable cases in conjunction with a genetic counselor.[12] One of the main concerns in surgical treatment of BRCA1/2 pathogenic variant breast cancer, is whether the treatment outcome of breast conserving surgery combined with radiotherapy is equivalent to that of a radical mastectomy. There has only been one study done to compare this and the study showed no significant difference.[2]

Imaging for BRCA1/2

Along with risk-reducing surgeries, there are also imaging procedures that can be done. Enhanced imaging and screening may increase the chance of detecting breast cancer at an early stage, which can lead to better treatment. Patients who present with BRCA1 and BRCA2 are recommended to undergo yearly mammograms and breast MRIs alternating every 6 months after the age of 25, or 10 years before the earliest age at which the cancer was detected in the family.[4] MRI has shown to detect earlier stage cancers and has a higher sensitivity in BRCA carriers than mammography, ultrasound, and clinical breast exams.[12] Although MRI may be better to find tumors, mammography can also identify some breast cancers that are not identified in MRI. MRI may be less specific than mammography.[8] Those patients who have dense breast tissue have a risk of breast cancer that is about 1 ½ to 2 times that of women with average breast tissue. Unfortunately, dense breast tissue also makes it harder to detect cancers on mammograms.[13] The newest type of mammogram is known as breast tomosynthesis or digital breast tomosynthesis. This allows the doctors to see the breast tissue more clearly in three dimensions. Many studies

have found that 3D mammography lowers the chance of being called back for follow up testing.[14]

Ovarian cancer is one of the hardest cancers to detect at an early stage. Only about 20% of ovarian cancers are found at an early stage.[15] Because of this, there has been a lot of research to develop a screening tests for ovarian cancer, but there hasn't been much success so far. As stated above, a salpingo-oophorectomy can be done to help reduce the risk for ovarian cancer along with breast cancer. Doctors can perform a pelvic exam to feel the ovaries for size, shape, and consistency. Although this may help, most early ovarian tumors are difficult or impossible to feel, because early ovarian cancers often cause no symptoms. A type of imaging that can be done is a transvaginal ultrasound detect ovarian cancer. Besides a transvaginal ultrasound, patients with a new epithelial ovarian cancer are routinely imaged with CT, but unfortunately it is unknown if the presence of BRCA can be reliably recognized on a CT.[8] Potentially an easier way to help decrease the risk of ovarian cancer is using oral contraceptives. According to the American Cancer Society, women who used oral contraceptives for 5 or more years have about a 50% lower risk of developing ovarian cancer compared to those who don't take it. Although this helps lower ovarian cancer risk, it may slightly increase the breast cancer risk.[16]

There are also some labs that can be drawn. Serum CA-125 levels can be measured every 6-12 months for ovarian screening starting at age 30 or 5-10 years before the earliest age of the first diagnosis in the family.[4] Unfortunately, checking CA-125 levels has not been found to be as useful as a type of screening. Higher levels of CA-125 are more often caused by common conditions such as endometriosis and pelvic inflammatory disease. Also, those who have ovarian cancer may not have an abnormal CA-125 level, which may cause doctors to repeat the tests again.[15]

Risk-reducing measures for men

For men, there are not a lot of risk-reducing surgery options available. It is recommended that men with HBOC talk to their doctor at the age of 40. Whether a bilateral prophylactic mastectomy reduces breast cancer risk in men with BRCA1/2 is still unknown and it is more considered an experimental procedure.[8] Prostate cancer has a slightly better screening process. Currently the most effective way to screen for prostate cancer is by doing a blood test that looks for the prostate-specific antigen (PSA), which can be done yearly. It is important for men to talk

to their doctors about this because with this test there is possibility for false positives and false negatives. Knowing this information, men may not reach out to their doctor for this reason. Some conditions that may raise PSA levels are; an enlarged prostate with benign prostatic hyperplasia, old age, prostatitis, and certain medicines. If the result doesn't come back normal, doctors may do a percent-free PSA test.

PSA is in the blood in 2 major forms, attached to the blood and circulating. This test measures how much is circulating. The percentage is lower in men who have prostate cancer. When a patient's levels are low, many doctors recommend a prostate biopsy. When the biopsy is done, transrectal ultrasound and/or MRI may be used to help guide the biopsy. If the biopsy comes back positive, an MRI may be done to determine if the cancer has spread to other places. After the first MRI, usually a second one that uses dynamic contrast enhancement is done. The results are reported using the prostate imaging report and data system. CT may be used to determine if the prostate cancer has spread to the lymph nodes. According to the American Cancer Society, if prostate cancer spreads, it often goes to the bones first so additional imaging will be done to determine that. Another type of screening that can be done is a digital rectal exam, where a doctor feels through the rectum for any bumps or hard areas on the prostate.[17]

My family story

The reason I decided to write my paper on this is because I may potentially be part of these statistics. I come from a family history with the BRCA gene. My mom knowingly has the BRCA1 gene mutation and because of this, I have a 50/50 chance of also having the gene mutation. I have not been tested but I have a plan with my genetic counselor. My grandmother died from ovarian cancer at a young age. We aren't sure if my grandmother had the mutation because it has been over 30 years since she passed, and there is no DNA left to test for the gene. My grandmother's niece is also positive for the BRCA1 gene mutation. Her father, my grandmother's brother, has not been tested. My grandmother's other brother has had breast cancer at age 45 and skin cancer. He does not have any kids, so he has chosen not to be tested. We aren't assuming that my grandmother had it, but since the signs of it are prevalent throughout the family, there is a good chance that her mother is who gave my mom the gene. With my grandma, and two great uncles potentially having, it we believe it may have come from my great

grandmother. She had cancer at one point in her life as well, but she has also been gone for too long and there is no DNA to test.

Since my mom has the BRCA1 gene mutation she undergoes a mammogram and a breast MRI, alternating every 6 months, and a clinical breast exam every 6 months as well. Her doctor recommends a prophylactic mastectomy, but she has chosen to continue to do just the testing for now. Since my grandmother died at a young age of ovarian cancer, after my mom was done having kids, she decided to get a total abdominal hysterectomy with a bilateral salpingo-oophorectomy out of precaution. Since she has had this done, she doesn't have as much estrogen and progesterone. This can halt or slow the chance of her getting breast cancer.

Conclusion

BRCA stands for BReast CAncer gene indicating its relevance in breast cancer pathogenesis. BRCA1 was discovered in 1994 and BRCA2 was discovered in 1995. Every person has these genes, but only some are mutated increasing the risk for breast and ovarian cancers. When these genes are mutated, patients have a higher chance of having breast and ovarian cancer, and a lower chance of pancreatic and prostate cancer. Both men and women can inherit this gene. Women can be affected by having a higher risk of breast and ovarian cancer. Men with this mutation have a higher risk of breast, pancreatic, and prostate cancer. Those who have a strong family history are encouraged to speak with their doctor and genetic counselor to work out a plan. If a patient has a positive genetic test, there are risk reducing measures they can do such as; risk reducing surgeries, lab testing, medications, and imaging. Some common risk-reducing surgeries that can be done are a mastectomy and a salpingo-oophorectomy. These are considered risk-reducing because there is still a chance for cancer to reappear in these areas. Labs that can be checked are CA-125 levels for ovarian cancer and PSA for prostate cancer. Imaging plays a big part in screening for these mutations. Imaging that is used is usually MRI, mammography, and sometimes CT. Screening patients who have the BRCA1/2 mutation is very important to catch potential cancer in early stages.

References

1. Breast Cancer in Men. Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/breast/men/index.htm. Published August 11, 2020. Accessed November 19, 2020.

2. Lee A, Moon BI, Kim TH. *BRCA1*/*BRCA2* Pathogenic Variant Breast Cancer: Treatment and Prevention Strategies. *Ann Lab Med*. 2020;40(2):114-121. doi:10.3343/alm.2020.40.2.114

3. Hurst JH. Pioneering geneticist Mary-Claire King receives the 2014 Lasker~Koshland Special Achievement Award in Medical Science. *J Clin Invest*. 2014;124(10):4148-4151. doi:10.1172/JCI78507

4. Varol U, Kucukzeybek Y, Alacacioglu A, et al. BRCA genes: BRCA 1 and BRCA 2. *J BUON*. 2018;23(4):862-866.

5. Mayo Clinic. Hereditary Breast and Ovarian Cancer: Assessing Your Risk. Published 2012.

6. Pilarski R. The Role of BRCA Testing in Hereditary Pancreatic and Prostate Cancer Families. American Society of Clinical Oncology Educational Book. 2019;(39):79-86.

7. Nougaret S, Lakhman Y, Gönen M, et al. High-grade Serous Ovarian Cancer: Associations Between BRCA Mutation Status, CT Imaging Phenotypes, and Clinical Outcomes. Radiology. 2017;285(2):472-481.

8. BRCA Mutations: Cancer Risk and Genetic Testing Fact Sheet. National Cancer Institute. https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet. Published 2018. Accessed November 19, 2020.

9. BRCA1. Patient Library. https://www.geneticsupport.org/genetics-cancer/breast-cancer/hboc/brca1/. Published April 23, 2020. Accessed November 19, 2020.

10. BRCA2. Patient Library. https://www.geneticsupport.org/genetics-cancer/breast-cancer/hboc/brca2/. Published August 28, 2019. Accessed November 19, 2020.

11. Sun L, Brentnall A, Patel S, et al. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer [published online ahead of print, 2019 Oct 3]. *JAMA Oncol*. 2019;5(12):1718-1730. doi:10.1001/jamaoncol.2019.3323

12. Pilewskie M, Zabor EC, Gilbert E, et al. Differences between screen-detected and interval breast cancers among BRCA mutation carriers. *Breast Cancer Res Treat*. 2019;175(1):141-148. doi:10.1007/s10549-018-05123-6

13. The American Cancer Society medical and editorial content team. Breast Cancer Risk Factors You Cannot Change: Genetic Risk Factors. American Cancer Society.

https://www.cancer.org/cancer/breast-cancer/risk-and-prevention/breast-cancer-risk-factors-you-cannot-change.html. Published 2019. Accessed November 19, 2020.

14. Mammogram Basics: How Does A Mammogram Work? https://www.cancer.org/cancer/breast-cancer/screening-tests-and-early-detection/mammograms/mammogram-basics.html. Published 2020. Accessed November 19, 2020.

15. How to Check for Ovarian Cancer: Ovarian Cancer Screening. (2020). Retrieved November 19, 2020, from https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/detection.html

16. How to Prevent Ovarian Cancer: Oral Contraceptives & Ovarian Cancer. (2018). Retrieved November 19, 2020, from https://www.cancer.org/cancer/ovarian-cancer/causes-risks-prevention/prevention.html

17. Screening Tests for Prostate Cancer. (2019). Retrieved November 19, 2020, from https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/tests.html