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Breast and Ovarian Cancer and the BRCA Gene

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Abstract: Genetic cancer is important to gain knowledge in how to battle certain gene mutations in Ovarian and Breast cancers. It is interesting to see what kind of mutations and proteins are inherited, seeing that BRCA1 or BRCA2 is inherited in more than 16% of Ovarian Cancer patients. This scientific paper is trying to address inherited mutations and exactly which ones are the cause of cancer, specifically Ovarian and Breast Cancer with Breast Cancer being the most common cancer in Women and Ovarian cancer estimating 5% of cancer related deaths in Women. Current unanswered questions; how to stop the mutations, is it possible to stop the gene mutation from being inherited, as well as do these Ovarian inherited mutations cause Breast cancer without causing Ovarian cancer first. Included are studies that worked on establishing the difference in BRCA1 and BRCA 2 in the country of Belarus, the study of inherited inflammation and its association to Ovarian Cancer, a study of the specific modifiers of BRCA1/2, and research into the tumor suppressor causing Ovarian Cancer. This paper will be a summary of BRCA1 and BRCA2 mutation genes as well as the connection of Breast and Ovarian Cancer. It will also go into detail of the mutations and tumor suppressors found in Ovarian Cancer and what they cause.

Introduction

Breast cancer is the most common cancer within women. Breast cancer can be traced to being a very genetic cancer as women with a close relative with breast cancer are two times more likely to develop breast cancer than those without a familial relative. (Reference 1) This BRCA1 and BRCA2 gene is mainly found among those with ovarian cancer, which can further lead to breast cancer. The risk of breast cancer by 80 years old is 72% for BRCA1 mutations and 69% for those with BRCA2 according to a cohort study. (Reference 1) The same study also demonstrated breast cancer risk for these mutation carriers varies by family history of breast cancer in first and second degree relatives.

Ovarian cancer has been found to be the leading lethal gynecological cancer and has most often been diagnosed in the later stages. It has been studied and observed to be 5% of cancer related deaths. (Reference 2) There is a current 5-year survival rate among those with ovarian cancer, with new research into proteins and RNA there is a new good outlook on where to begin fighting ovarian cancer. Because of deficiency in early detection procedures and the rapid progression of the disease, more than 70% of the ovarian cancer patients are diagnosed at an advanced stage. A study in Belarus has shown the two BRCA mutations account for 80% of BRCA1 and BRCA2 mutations in these cancer families. They also observed that more than 16% of ovarian cancer patients are carriers of one of the two BRCA genes. Of the women in the Belarus study, 25.2% of them with ovarian cancer were detected to have 1 of these 2 genes. (Reference 3) Through the Belarus study, there has been many

other factors and statistics found about these 2 mutated genes.

Recent Progress

Genetics play a large part in risk associated with cancer development. Breast cancer is a prime example of cancer risk derived from genetic relation. 15-20% of all breast cancer familial risk is linked to two genetic mutations: BRCA1 and BRCA2 (Reference 1). These genetic mutations increase the likelihood of contracting breast cancer, and therefore the risk, especially in combination with the presence of SNPs and INDELs. SNPs are single nucleotide polymorphisms and INDELs are small insertions or deletions. There is combined 179 of these two polymorphisms common in breast cancer identified through genome-wide association studies. (Reference 1) These risk alleles at each SNP are associated with modest increase in breast cancer risk, and it has shown they combine with other SNP or INDELs to generate a higher risk. Multiple of these two polymorphisms create a substantially higher risk of breast cancer.

BRCA1 and BRCA2 have been shown in more than 50 of the 179 variants. Showing a connection in the mutations in BRCA gene and a higher risk of breast cancer. These genes along with more SNPs or INDELs shows the substantial increase in risk for those carrying either of these 2 genetic mutations.

Today's high rates of cancer deaths make it clear that there is still room for research in finding a way to mitigate said cancer; 5% of cancer deaths are caused by ovarian cancer (Reference 1&3). Despite these numbers, limited progress has been made in utilizing advanced methods to prevent and treat ovarian cancer. The study of variants of breast cancer related to genetic mutations is an example of a way to detect cancer related to genes and familial risk, improving the overall risk predicted for the patient. This specific study did a case comparing 7,257 BRCA1 and 5,097 BRCA2 mutation carrier breast cancer cases with 60,212 breast cancer cases from the Breast Cancer Association Consortium. (Reference 1) This provided an insight into SNPs and the two mutations. Association between 2 variants for BRCA1 and 3 for BRCA2 were identified.

Throughout the previous study only 57,725 cases were comparable with 5,097 BRCA2 mutation cases. This study only included Women with European ancestry with 60.9% coming from European countries, 31.1% from the USA, 6.1% from Australia, and 1.7% from Israel. This included with women with an average age of 40.9 years for BRCA1 and 44.1 years for BRCA2. (Reference 1) This study resulted in finding 59 SNPs were associated with BRCA1 mutation carriers, however only four of these were truly associated. The other 55 SNPs are associated with ER-negative breast cancer cases. Among BRCA2 cases, 43 SNPs were associated with the gene mutation. Although, only 3 were truly associated when comparing to ER-negative breast cancer cases. (Reference 1) This showing the relation between SNPs and BRCA genes is only seen in a few variants. The found SNPs connected with the BRCA genes creates a substantially higher risk of contracting breast cancer.

With Ovarian cancer accounting for 2.5% of female cancer occurrences and 5% of cancer deaths, it is a large and much needed subject to study. Preventative measures have included organ removal and lifestyle changes, which are not as effective or advanced compared to treatments for cancers like renal cell carcinoma, which is treated with miRNA inhibitors. Most of what is known about ovarian cancer treatment today is reactive rather than proactive. Current treatments used include cancer removal via surgery, chemotherapy, radiation, and PARP inhibitors. A recent study of ovarian cancer treatment using miRNA is the first study to utilize this means of treatment with evidence of inhibiting ovarian cancer growth. (Reference 2) This study has opened the door for more effective treatment of ovarian cancer, levels above current common treatments.

MicroRNAs are a class of small noncoding RNAs consisting of 20-22 nucleotides and have a pivotal role in tumor invasion by binding to untranslated regions of target genes. Evidence shows miRNAs have a special function in regulating cell migration, invasion, proliferation, and differentiation in various tumors. Contrary to normal tissue, ovarian cancer tissue has shown differential expression of miRNA. (Reference 2) A study over miRNA, specifically miR-363-3p, it showed a lower expression of this specific miRNA.

The miRNA miR-363-3p was shown to repress cell proliferation, invasion, and migration in vitro and vivo. It was also identified this miRNA repressed ovarian cancer proliferation by directly combining with it and regulating SERPINE1, a mRNA-binding protein. This study used ovarian cancer cell lines OVCAR3, CAOV3, HO-8910, and SKOV3 and normal human ovarian cell line IOSE80 obtained from the American Type Culture Collection. A dual-luciferase reporter assay was used to assess the effects of miR-362-3p on the expression of the SERBP1 protein. (Reference 2)

This study showed the expression of ovarian cancer-related miRNAs may have a role in ovarian cancer tumorigenicity, the tendency for cultured cells to give rise to either benign or malignant growth tumors. The findings demonstrated that miR-362-3p in ovarian cancer tissue was significantly downregulated compared to that of normal tissue. (Reference 2) This causing a lack of correspondence of miR-362-3p with protein SERBP1 and a lack of regulation. Allowing more ovarian cancer cells and less direct combination of the miRNA with cancer cells.

This study also yielded the miRNA was expressed significantly more in the HO-8910 cells than in all ovarian cancer cell lines tested. Among the four cancer cell lines, CAOV3 cells had the lower expression of miR-362-3p. Due to these results, a mimic made of miR-362-30 and an miR-363-3p were individually tested in both samples. Resulting in miR-362-3p possibly playing a vital role in ovarian cancer. (Reference 2)

The results yielded expression of miR-363-3p was significantly higher in the mimic group and significantly lower in the inhibitor group than a controlled group of both cell line samples. (Reference 2) This data, assuming miR-363-3p plays a major role in ovarian cancer, shows an inhibitor is unable to express the miRNA enough to make a difference in the ovarian cancer cells. Though, with introduction of more cells, even only a mimic version, the expression of the miRNA is greatly increase. This allows us to assume an introduction of more miR-363-3p would slow down and stop ovarian cancer cells from reproducing.

Cell cycle analysis of the inhibitor showed the significantly suppressed promoted the migration of cells and analysis of the mimic showed significant suppressed migration and wound healing. (Reference 2) This shows the significantly different effects the two had on CAOV3 and HO-8910. The inhibitor increased migration which is unexpected considering it is an inhibitor.

Looking specifically at the SERBP1 protein and mRNA expression in all 5 ovarian cancer cell lines, it was noted that the protein and mRNA expression was significantly lower in IOSE80 cells than other ovarian cells. This showed a reverse trend when compared to the expression of the miRNA. It was also found that SERBP1 protein and mRNA expression was significantly inhibited by the mimic and promoted when the miRNA was silenced. This shows that miR-362-3p could negatively regulate SERBP1 expression by binding to it. (Reference 2)

A study done specifically on ovarian cancer patients from Belarus aimed to gather details on BRCA1 and BRCA2. Ovarian cancer is them ost aggressive gynecological tumor. Deficiency in early detection procedures and rapid progress of the disease causes more than 70% of patients to be diagnosed at an advanced stage. (Reference 3) There still remains a 5-year survival rate is still under 40% despite advances in treatment. In 2018, the age-standardized rate of ovarian cancer per 100,000 cases was 15.4 in Belarus, which is 3rd highest in the world. (Reference 3)

Ovarian cancer patients from Belarus are characterized by a high proportion of a limited number of mutations in the BRCA1 gene. Two BRCA1 founder mutations, c.5266dupC and c.4035delA, account for 80% of all detectable BRCA1 and BRCA2 mutations in breast and ovarian cancer families. More than 16% of ovarian cancer patients carry of these two mutations. (Reference 3) These two genetic mutations are a large part of Ovarian cancer. Learning to control and manage these two genes will be a large part in treating ovarian cancer patients.

BRCA1 or BRCA2 gene mutations were detected in 54 of the 214 women affected with epithelial ovarian cancer, caner that forms in the tissue covering the ovary, from the Belarus study. The study found that a mutation was found significantly more in women diagnosed with cancer at or under the age of 50. Along with 54 of the ovarian cancer patients with a BRCA1 mutation, only 28 reported a first or second relative with breast or ovarian cancer. (Reference 3) In this and all other studies, the BRCA1 mutation c.5266dupC was the most common and accounted for 49-60% of all detected mutations. This gives a specific gene and mutation for treatment to be

focused on. Further research could grant treatments targeting these specific mutations to fight ovarian cancer in patients.

Discussion

Current research into ovarian cancer shows many different mutations to genes and mutations in ovarian cells. Two genetic mutations are BRCA1 and BRCA2 genes which lead to Ovarian and Breast cancer. These two genetic mutations create malignant cells and tumors that spread from the primary ovarian region to the breast region. Knowing these two types of mutations gives researchers specific areas to target for future treatments. The main areas further detailed into mutations than BRCA1 and BRCA2 are, the mutation c.5266dupC and the miRNA-362-3p.

With ovarian cancer making up 5% of all cancer deaths in women and a life expectancy of 5 years, treatments are needed. There are few treatments beyond chemotherapy and organ removal and surgery that are used as treatment for ovarian cancer. Even with recent minor improvements, survival rate is still only a 40% survival rate. The treatments for Ovarian and Breast Cancer are a major need and subject that needs to be worked on. With specific mutations like the genes BRCA1 and BRCA 2, we now have a research focus of what to treat to eliminate ovarian cancer. Though these two genes only make up 16% of cases, it is still a large percentage of cases. Focusing on this known area will drastically increase the survival rate and increase life expectancy.

The study done in Belarus showed the amount of ovarian cancer cases in the country, with population around 10 million, as well as the percentage of those with a BRCA1 or BRCA2 gene. They were also able to use the study to detect specific mutations among the BRCA genes. We do not know the ability to target these specific mutations yet. They were able to find and specify which mutations were in their BRCA1 mutations in the Belarus population study, but this information has yet produced treatments. We do not yet know what can attack or prevent these proteins. It might be possible to find a way to make these mutations dormant and not be genetically passed down. This would stop future generations from having the BRCA1 and BRCA2 genes genetically from past relatives.

With miRNAs being a major factor in tumor invasion, miRNA-362-3p has acted as a strong tumor suppressor by targeting SERBP1. Therefore, miRNA-362-3p has been shown to fight and inhibit Ovarian cancer, currently we do not know if we will be able to use this as a near future solution. There are current inhibitors used and given to patients to attempt to inhibit different proteins in DNA but there are no current inhibitors being used to target SERBP1. It has been lab tested to see if the miRNA-362-3p attacks SERBP1 and inhibits Ovarian Cancer, but no current human use. There is no current knowledge if this works in women Ovarian cancer patients.

The SERBP1 protein is a protein that stops ovarian cancer cells from spreading. Through a study we know the miRNA-362-3p suppresses ovarian cancer when in Vivo, when inside the body. Using this knowledge, we should be able to work towards making treatments around miRNA-362-3p. Currently there is no research on treatments for this miRNA. There are limited studies and only 1 that has gone into detail about miRNA-362-3p. To this point there is no detail on possible treatment, but through the study it looks promising that this will be a good miRNA to focus on and create treatment to enhance this. Hopefully future treatments can stem from this research and increase the life expectancy to higher than 5 years.

With further research into these mutations, BRCA1, BRCA2, and the miRNA-362-3p, maybe we can make progress in the near future to work with what has been found in these studies to produce treatments. This could double life expectancy and increase the survival rate. This would at least create treatments for the 16% of cases that include BRCA1 and BRCA2. As well as help prevent Breast Cancer that stems from malignant tumors in Ovarian Cancer.

References

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