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BRCA Mutation: A Review of Breast Cancer

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ABSTRACT

In the present study, we focus on the causes of a major cancer type contributing to the major deaths due to cancer across the world. Breast cancer which accounts for more than approximately 29 to 34% affected to women posing a major cause of death due to cancer. In-situ carcinomas might arise in either ductal or lobular epithelium, but remain confined there, with no invasion of the underlying basement membrane that would constitute extension beyond epithelial boundaries. Approximately 29 to 34% of women with invasive breast cancer will die of their disease. This syndrome presents as skin changes resembling skin condition like redness, discoloration, or mild flaking of the nipple skin. As Paget's disease of the breast advances, symptoms may include skin tingling, itching, increased sensitivity, burning and pain. There may also be discharge from the nipple. Approximately half of women diagnosed with Paget's disease of the breast even have a lump within the breast.

Keywords: Breast cancer, BRCA mutation, BRCA1, BRCA2.

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INTRODUCTION:

Cancer is a group of disease involved in abnormal growth of cell with the potential spread to other parts of the body.[1, 2] Cancer when develops to normal cells in a particular part of the body begin to grow out of control. Cardio vascular disease is the first leading cause of death in the world and Cancer is the second leading cause of death in the world. Generally cancer cells are developed from normal cells due to damage of DNA. Most of the time when ever DNA was damaged, the body is able to repair it, unfortunately in cancer cells, damaged DNA is not repaired. People can also inherit damaged DNA from parents, which accounts for inherited cancers.[3]

Breast cancer:

Cancer that forms in tissues of the breast. It occurs in both men and women, although male breast cancer is rare than female breast cancer. Breast cancer commonly develops in lining of milk duct cells and the lobules that supply the ducts with milk. Cancers developing from the ducts are known as ductal carcinomas. Although the cancers developing from lobules are known as lobular carcinomas.[4,5] Breast cancers are divided into two major types, in-situ carcinomas and invasive(or infiltrating) carcinomas. The in-situ type of carcinomas may arise in ductal or lobular epithelium, but remain confined there, with no invasion of the underlying basement membrane that would constitute **extension** beyond epithelial boundaries.[6]Approximately 29% to 34% of women with invasive breast cancer will die of their disease.[7]

Signs and symptoms:

Signs of breast cancer may include a tumor in the breast, mutation in breast, dimpling of the skin, fluid coming from the breast nipple, a newly inverted nipple, or a red patch of skin. Inflammatory breast cancer is a one type of breast cancer which can pose a actual diagnostic challenge. Symptoms may resemble a inflammation in breast and may include pain, itching, nipple inversion, swelling, warmth and redness throughout the breast, as well as an orange-peel texture to the skin referred to as peau d'orange.[8]Another reported symptom complex of breast cancer is Paget's disease of the breast. This syndrome presents as skin redness, discoloration or mild flaking of the nipple skin. As Paget's disease of the breast advances, symptoms may include burning, itching, enhanced the sensitivity, tingling, and pain. Approximately half of women's are diagnosed with Paget's disease of the breast also has a tumor in the breast.[9]

In rare cases, what initially appears as a fibroadenoma (hard, movable non-cancer lump) could in fact be a phyllodes

tumor. Phyllodes tumors are formed within the connective tissue of the breast and contain glandular as well as stromal tissue. Phyllode breast lumps are not staged in the usual sense; they are classified depends on their appearance under the microscope as benign, borderline, or malignant.[10]Occasionally, breast cancer presents as metastatic disease that is, cancer that has spread away the original organ. The symptoms caused by metastatic breast cancer depend on the location of metastasis. Common sites of metastasis include bone, liver, lung and brain.[11]

Causes of breast cancer:

Genetic causes; Family history has long been known to be a risk factor for breast carcinoma. Both maternal and paternal relatives are important. The risk is highest if the affected relative developed breast carcinoma at a young age, had carcinoma in both breasts or if she is a close relative. First-degree relatives, (mother, sister, daughter) are most vital in estimating risk. Some second-degree relatives (grandmother, aunt) with breast cancer may increase risk. Breast cancer in a male increases the risk for all his close female relatives. BRCA1and BRCA2 are abnormal genes that, when inherited, markedly increase the risk of breast cancer to a lifetime risk estimated between 40 and 8S%. Women who have the BRCA1 gene tend to develop breast cancer at an early age.[12]

Hormonal causes; Alteration in hormonal level may precipitate breast cancer. It could be attended by starting and stopping of periods (Menstrual Cycle), Pregnancy in early age, Hormonal replacement therapy, Use of oral pills, etc.[13]

Life style and dietary cause; Sedentary life style, high dietary intake of fat obesity particularly in postmenopausal women may cause breast cancer. The use of alcohol is also another one cause of breast cancer. The risk increases with the amount of alcohol consumed. Women who consume two to five alcoholic beverages per day have a risk about one and a half times that of nondrinkers for the development of breast cancer.[14,15]

Environmental cause; There is known to be a slight increase in risk in ladies who work with low doses of radiation over a long period of time-for example, X-ray technicians.[14,15]

Pathophysiology:

Breast cancer, like other cancers occurs because of an interaction between an environmental (external) factor and a genetically susceptible host. Mutations that can lead to breast cancer have been experimentally linked to estrogen exposure.[16] Abnormal growth factor signaling in the interaction between stromal cells and epithelial cells can facilitate malignant cell growth.[17,18] In breast adipose tissue, over expression of leptin leads to increased cell proliferation and cancer.[19]

In the United States, 10% to 20% of people with breast cancer and ovarian cancer have a first- or second-degree relative with one of these diseases. The familial tendency to developed cancer is called hereditary breast–ovarian cancer syndrome. The best known of these, the BRCA mutations, confer a lifetime risk of breast cancer of between 60% and 85% and a lifetime risk of ovarian cancer of between 15 and 40 percent. Some mutations associated with cancer, such as BRCA1 and BRCA2, occur in mechanisms to correct errors in DNA. These mutations are either inherited or acquired after birth. Presumably, they allow further mutations, which allow uncontrolled division, lack of attachment, and metastasis to distant organs.[20] However, there is strong evidence of residual risk variation that goes well beyond hereditary BRCA gene mutations between carrier families. This is caused by unobserved risk factors.[21] This implicates environmental and other causes as triggers for breast cancers. The inherited mutation in BRCA1 or BRCA2 genes can interfere with repair of DNA cross links and DNA double strand breaks (known functions of the encoded protein).[22]These carcinogens cause DNA damage such as DNA cross links and double strand breaks that often require repairs by pathways containing BRCA1 and BRCA2.[23,24]Focus of this present review is to study about the breast cancer by gene mutations.

MATERIAL AND METHODS:

Initially, we searched papers using keywords like breast cancer, gene mutation, genetic causes and BRCA. Subsequently the papers are matched such word criteria were fully reviewed and their findings duly noted.

BRCA Mutation:

A BRCA mutation is a mutation in either of the BRCA1 and BRCA2 genes, these are tumor suppressor genes. Different types of mutations in these genes have been identified, some of these determined to be harmful, while others have no proven impact. Harmful mutations in these genes may produce a hereditary breast cancer syndrome in affected persons. Breast cancer cases in women Only 5-10% are reason to BRCA1 and BRCA2 mutations (with BRCA1 mutations being slightly more than BRCA2 mutations), but the impact on women with the gene mutation is more profound.[25] Women with harmful mutations in either BRCA1 or BRCA2 have a risk of breast cancer that is about five times the normal risk, and a risk of ovarian cancer that is about ten to thirty times normal.[26]

Mutations can be inherited from either parent and may be passed through on to both sons and daughters. Each child of a genetic carrier, not regard to sex, has a 50% chance of inheriting the mutated gene from the parent who carries the mutation. As a result, half of the people with BRCA gene mutations are male, who would then pass the mutation on to 50% of their offspring, male or female. The risk of BRCA-related breast cancers for men with the mutation is higher than for other men, but still low.[27]

The BRCA1 and BRCA2 genes are tumor suppressor genes pictured here on their respective chromosomes. BRCA1 has located in 17q21 or the q arm of Chromosome 17 at position 21. BRCA2 has located in 13q12.3 or the q arm of Chromosome 13 at position 12.3. Both BRCA1 and BRCA2 genes are produce proteins that help repair damaged DNA, keeping the genetic material of the cell stable. A damaged BRCA gene in either location can lead to increased the risk of cancer, particularly breast or ovarian in women.

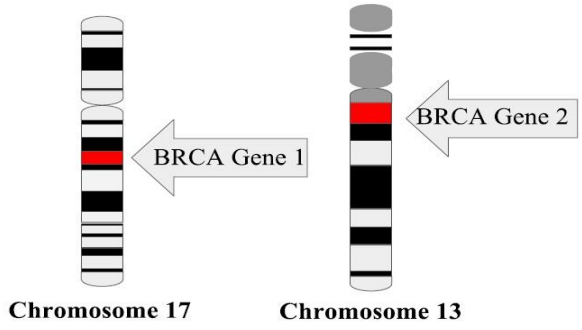

Fig. 1: Location of BRCA Gene

Survival impact: [28]

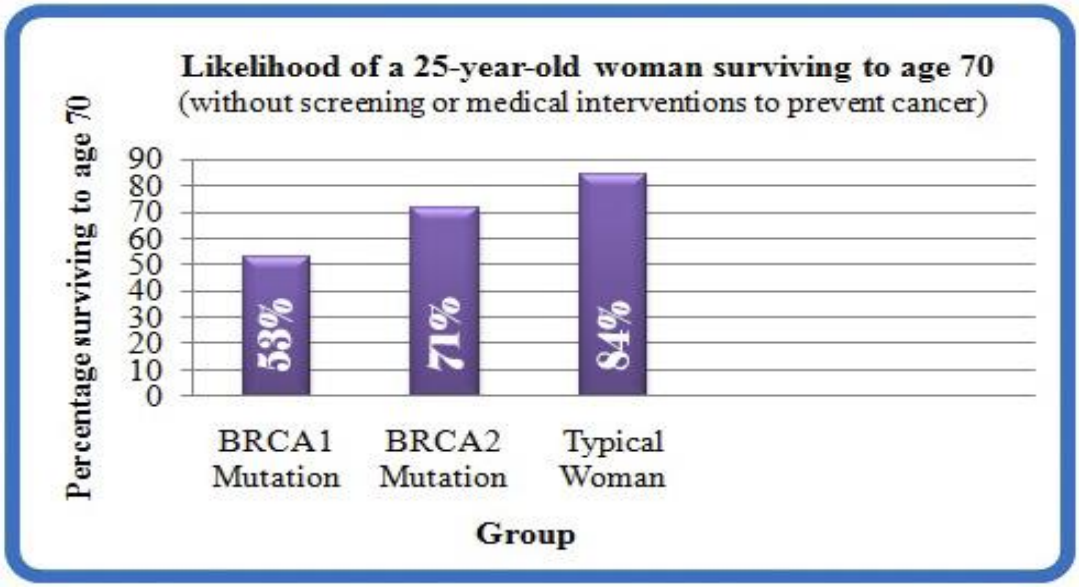

Fig. 2: Likelihood of a 25-year-old woman surviving to age 70

A 25-year-old woman with no mutation in her BRCA genes has an 84% probability to reach at least the age of 70. Of those not surviving, eleven percentage die from either breast or ovarian cancer, and 89% from other cancers. Compared to that, a woman with a high-risk BRCA1 mutation, if she had carcinomas in breast tissues screening but no prophylactic medical or surgical intervention, would have only fifty nine percentage chance to reach age 70, twenty five percentage points lower than normal. Of those women not surviving, twenty six percentage would die of breast cancer, forty six percentage of ovarian cancer and twenty eight percentage of other causes.

Women with high-risk BRCA2 mutations, with screening but with no prophylactic medical or surgical intervention, would have only seventy one percentage chance to reach age 70, thirteen percentage points lower than normal. Of those not surviving twenty one percentage would die of breast cancer, twenty five percentage of ovarian cancer and fifty four percentage of other causes. The likelihood of surviving to minimum age 70 can be improved by several medical interventions, notably prophylactic mastectomy and oophorectomy.

Childbearing and fertility effects:

The dilemma of whether or not to have children is a significant source of stress for women who learn of their BRCA mutations during their childbearing years.[29]There is likely little or no effect of a BRCA gene mutation on overall fertility,[30]although women with a BRCA mutation may be more likely to have primary ovarian insufficiency.[31,32] BRCA mutation carriers may be more likely to give birth to girls than boys,[33] however this observation has been attributed to ascertainment bias.[34,35]If both parents are carriers of a BRCA mutation, then pre-implantation genetic diagnosis is sometimes used to prevent the birth of a child with BRCA mutations. Inheriting two BRCA1 mutations (one from parent) has never been reported and is believed to be a lethal birth defect. Inheriting one BRCA1 mutation and one BRCA2 mutation have been reported occasionally; the child's risk for any given type of cancer is the higher risk of the two genes like BRCA1 and BRCA2. (e.g., the risk of ovarian cancer from BRCA1 gene and the risk of pancreatic cancer from BRCA2 gene). Inheriting two BRCA2 mutations produces Fanconi anemia. [36]:82-85

Each pregnancy in genetically typical women is associated with a significant reduction in the mother's risk of developing carcinomas in breast tissues after age of 40.[29] The young woman is at the time of her first birth and the more protection against breast cancer she receives. Breastfeeding for more than one year protects against breast cancer.[36]:113–142 Pregnancy also protects against ovarian cancer in genetically typical women.[29]

Although some studies have produced different results, women with BRCA mutations are generally not expected to receive these significant protective benefits.[36]:113–142 Current research is too limited and imprecise to permit calculation of specific risks.[29]

However, the following general trends have been identified:

- For women with a BRCA1 mutation, the woman's age when she first gives birth has no association with her risk of breast cancer. Childbearing provides no protection against breast cancer, unless the woman has five or more than five full-term pregnancies, at which point she receives only modest protection. Similar to genetically typical women, pregnancy protects against ovarian cancer in BRCA1 gene women. Breastfeeding for more than one year considerably protects against breast cancer.[29]This effect may be as high as 19% per year of breastfeeding, which is much higher than that seen among genetically typical women.[37] The effect, if any, of long-term breastfeeding on ovarian cancer is unclear.[29]
- For women with a BRCA2 mutation, each pregnancy is paradoxically associated with a statistically significant increase in the risk for breast cancer. Unlike genetically typical women or women with BRCA1 gene mutations, breastfeeding has no effect on either cancer in women with BRCA2 gene mutations. Limited and conflicting data suggest that, also unlike other women, pregnancy does not decrease the ovarian cancer risk significantly in women with a BRCA2 gene mutation and might increase it.[29]

BRCA1:

Breast cancer type 1 susceptibility protein is a protein that in humans is encoded by the BRCA1 gene.[38] Orthologs are most

common in other mammalian species.[39] BRCA1 is a human tumor suppressor gene[40, 41](also known as a caretaker gene) and is responsible for repairing DNA.[42]BRCA1 combines with other tumor suppressors, DNA damage sensors and signal transducers to form a large multi-subunit protein complex known as the BRCA1-associated genome surveillance complex (BASC).[43] The BRCA1 protein associates with RNA polymerase II, and through the C-terminal domain, also interacts with histone deacetylase complexes. The role of this protein is transcription, and DNA repair of double-strand DNA breaks[44] ubiquitination, transcriptional regulation as well as other functions.[45]

BRCA1 has 24 exons, including 2 non-translating exons, encoding a protein of 1863 amino acids, which is characterized by a zinc-binding RING finger domain at the amino terminus and BRCA1carboxyl-terminal (BRCT) domain at the carboxylterminus.BRCA1 is classified as a tumor suppressor geneand plays an important role in surveillance of cell cycle and repair of DNA damage. Evidence shows that BRCA1 is phosphorylated by the check point kinase ataxia telangiectasia mutated (ATM) protein after ionizing radiation.[46]

Gene location:

The human BRCA1 gene is located on the long (q) arm of chromosome 17 at region 2 band 1, from base pair41,196,312 to base pair 41,277,500 (Build GRCh37/hg19) [47]

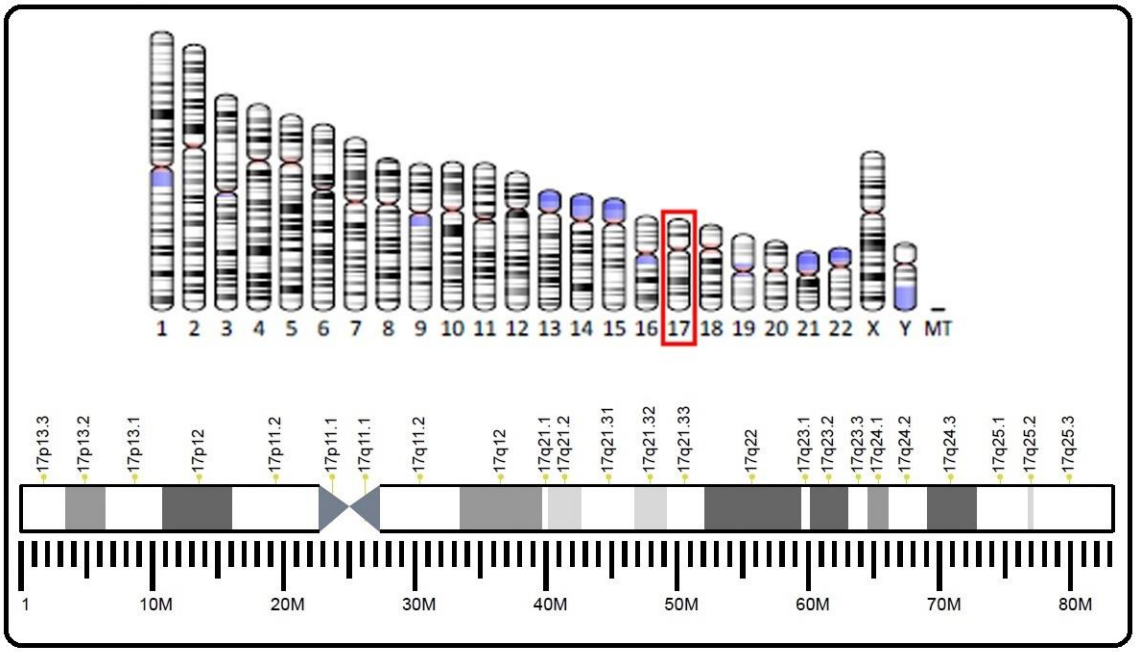

Fig. 3: BRCA1 Gene location (Human)

Mutations and Cancer risk:

Certain variations of the BRCA1 gene lead to an increased risk for breast cancer as part of a hereditary breast and ovarian cancer symptoms. Researchers have identified more than hundred mutations in the BRCA1 gene, many of which are associated with an increased risk of cancer. Females with an abnormal BRCA1 or BRCA2 genes have up to an 80% risk of developing carcinomas in breast tissues by age 90; increased risk of developing ovarian cancer is about 55% for females with BRCA1 mutations and about 25% for females with BRCA2 mutations.[48]

These mutations can be changes in a small number of DNA base pairs (the building-blocks of DNA), and can be identified with PCR and DNA sequencing. Some cases large segments of DNAs are rearranged. Those large segments, also called large rearrangements, can be a deletion of one or several exons in the gene. Classical methods for mutation detection (sequencing) are unable to reveal these types of mutation.[49] Other methods have been proposed: traditional quantitative PCR,[50] Multiplex Ligation-dependent Probe Amplification (MLPA),[51] and Quantitative Multiplex PCR of Short Fluorescent Fragments (QMPSF).[52] Newer methods have also been recently proposed: hetero-duplex analysis (HDA) by multi-capillary electrophoresis or also dedicated oligo-nucleotides array based on comparative genomic hybridization (array-CGH).[53]Some results suggest that hyper-methylation of the BRCA1 promoter, which has been reported in some cancers, could be considered as an inactivating mechanism for BRCA1 expression.[54]

BRCA1 mRNA 3' UTR can be bound by an miRNA, Mir-17 microRNA. It has been suggested that variations in this miRNA along with Mir-30 microRNA could confer susceptibility to breast cancer.[55]In addition to breast cancer, mutations in the BRCA1 gene also increase the risk of ovarian and prostate cancers. Moreover, precancerous lesions (dysplasia) within the Fallopian tube have been linked to BRCA1 mutations. Pathogenic mutations anywhere in a model pathway containing BRCA1 and BRCA2 greatly increase risks for a subset of leukemias and lymphomas.[44]

Females who have inherited a defective BRCA1 or BRCA2 gene are greatly elevated risk to develop breast and ovarian cancer. Their risk of developing breast and ovarian cancer is high, and specific to those cancers, that many mutation carriers choose to have prophylactic surgery. There has been more conjecture to explain such apparently striking tissue specificity. Major determinants of where BRCA1 and BRCA2

hereditary cancers occur are associated to tissue specificity of the cancer pathogen, the agent that causes chronic inflammation or the carcinogen. The target tissue may having the receptors for the pathogen, may become selectively exposed to an inflammatory process or carcinogen. An innate genomic deficit in a tumor suppressor gene impairs normal responses and exacerbates the susceptibility to disease in organ targets. This theory also fits data for several tumor suppressors beyond BRCA1 or BRCA2 genes. A major advantage of this model is that it suggests there may be some options in addition to prophylactic surgery.[56]

Low expression of BRCA1 in breast and ovarian cancers:

BRCA1 expression is reduced or undetectable in the majority of high grade, ductal breast cancers.[57] It has long been noted that loss of BRCA1 activity, either by germ-line mutations or by down-regulation of gene expression, leads to tumor formation in specific target tissues. In particular, decreased BRCA1 expression contributes to both sporadic and inherited breast tumor progression.[58] Reduced expression of BRCA1 is tumorigenic because it plays an important role in the repair of DNA damages, especially double-strand breaks, by the potentially error-free pathway of homologous recombination. Since cells that lack the BRCA1 protein tend to repair DNA damages by alternative more error-prone mechanisms, the reduction or silencing of this protein generates mutations and gross chromosomal rearrangements that can lead to progression to breast cancer.[59]

Similarly BRCA1 gene expression is low in the majority (55%) of sporadic epithelial ovarian cancers (EOCs) wherever EOCs are the common ovarian type of cancer, representing approximately 90% of ovarian cancers.[60] In serous ovarian carcinomas, a sub-category constituting about 2/3 of EOCs, low BRCA1 expression occurs in more than 50% of cases.[61]

Mutation of BRCA1 in breast and ovarian cancer:

Only about 3%–8% of all women with breast cancer carry a mutation in BRCA1 or BRCA2.[62] Similarly, BRCA1 mutations are only seen in about 18% of ovarian cancers (13% germline mutations and 5% somatic mutations).[63]Thus, while BRCA1 expression is low in the majority of these cancers, BRCA1 mutation is not a major cause of reduced expression.

BRCA1 promoter hypermethylation in breast and ovarian cancer:

BRCA1 promoter hypermethylation was present in only 13% of unselected primary breast carcinomas.[64] Similarly, BRCA1 promoter hypermethylation was present in only 5% to 15% of EOC cases.[60] Thus, while BRCA1 expression is low in these cancers, BRCA1 promoter methylation is only a minor cause of reduced expression.

BRCA2:

BRCA2 are a human gene, it is made up of proteins, respectively. The official symbol (BRCA2, italic for the gene, non-italic for the protein) and the official name (originally breast cancer 2; currently BRCA2, DNA repair associated) are maintained by the HUGO Gene Nomenclature Committee (HGNC). One alternative symbol, FANCD1, recognizes its association with the FANC protein complex. Orthologs, styled BRCA2 gene and BRCA2 gene are common in other mammalian species.[65]BRCA2 gene covers about 70kb of genomic sequence in 13q12, encoding a protein of 3418 amino acids. The coding region of BRCA2 is composed of 27 exons with a non-translating exon. However, the gene sequence of BRCA2 bears no obvious homology to any known gene including BRCA1, and the protein contains no defined functional domains.[66]BRCA2 can bind with BRCA1, participating in DNA damage response pathway associated with the activation of homologous recombination and double-strand break repair.[67]BRCA2 associated breast carcinomas are rarely that "basal-like" phenotype, but a subtype that has higher grade (usually Grade 2/3) than sporadic cage-matched controls (Breast Cancer Linkage Consortium,1997), and tend to be ER and progesterone receptor (PR) positive.[68]

Gene location:

The BRCA2 gene is located on the long (q) arm of chromosome 13 at position 12.3 (13q12.3).[69]

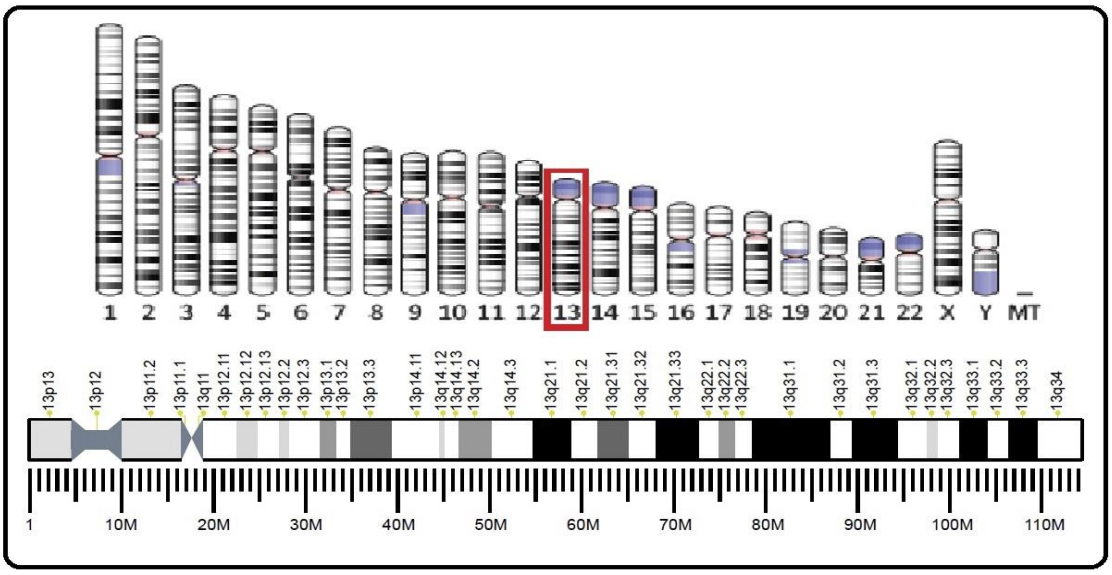

Fig. 4: BRCA2 Gene location (Human)

Function:

Although the structures of the BRCA1 and BRCA2 genes are very different, at least some functions are interconnected. The proteins made by both genes are essential for repairing damaged DNA (see Fig. 5 of recombinational repair steps). BRCA2 binds the single strand DNA and directly interacts with the recombinase RAD51 to stimulate strand invasion, a vital step of homologous recombination. The localization of RAD51 to the DNA double-strand break needs to the formation of the BRCA1-PALB2-BRCA2 complex. Function of PALB2 (Partner and localizer of BRCA2)[70] can synergistically with a BRCA2 chimera (termed piccolo, or piBRCA2) to further promote strand invasion.[71] These breaks can be caused by natural and medical radiation or any other environmental exposures, but also occur when chromosomes exchange genetic material during a special type of cell division that creates sperm and eggs (meiosis). Double strand breaks are also generated during repair of deoxyribonucleic acid (DNA) cross links. By repairing DNA, these proteins play a role in maintaining the stability of the human genome and prevent dangerous gene rearrangements that can lead to hematologic and other cancers. BRCA2 has been shown to possess a crucial role in protection from the MRE11-dependent nucleolytic degradation of the reversed forks that are forming during DNA replication fork stalling (caused by obstacles such as mutations, intercalating agents etc.).[72]

BRCA2 expression in cancer:

In eukaryotes, BRCA2 protein has a very important role in homologous recombinational repair. In humans and mice, BRCA2 genes are primarily mediates orderly assembly of RAD51 on single-stranded DNA, the form that is active for homologous pairing and strand invasion. BRCA2 also redirects RAD51 from double-stranded DNA and prevents dissociation from single-stranded DNA.[73]

In addition, the four paralogs of RAD51, consisting of RAD51B (RAD51L1), RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2form a complex called the BCDX2 complex (see Figure 5: Recombinational repair of DNA). This complex participates in RAD51 recruitment or stabilization at damage sites.[74]

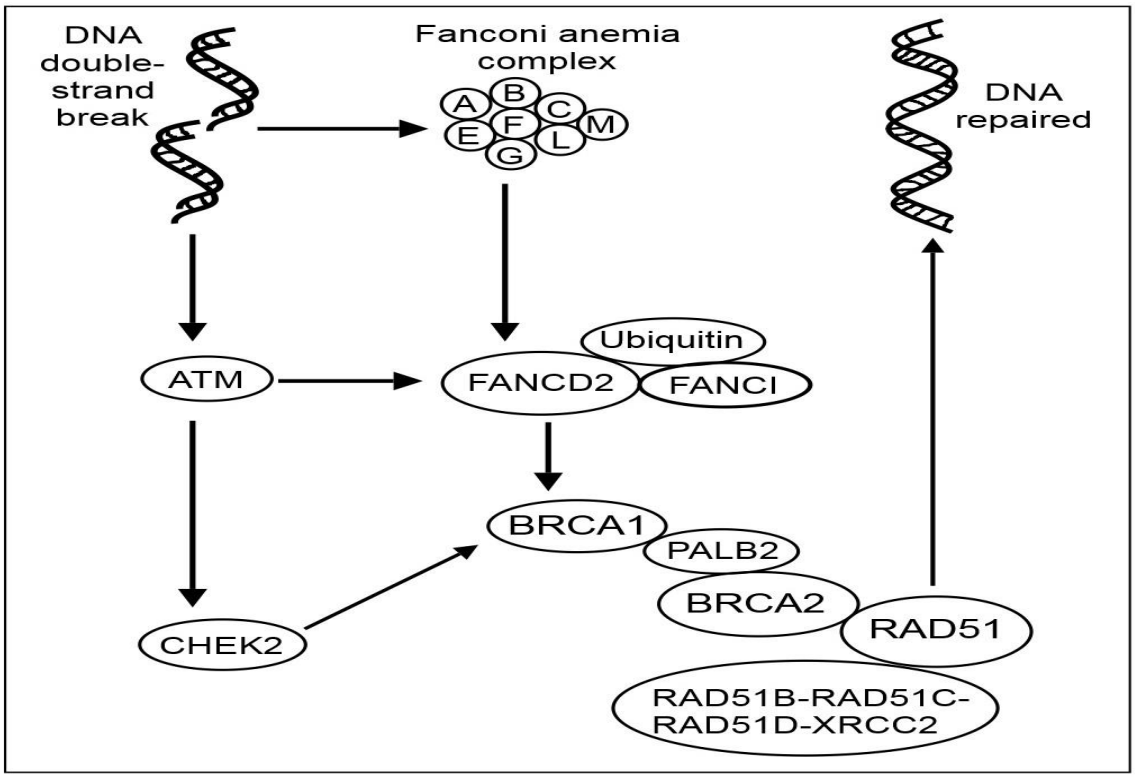

Fig. 5: Recombinational repair of DNA

The BCDX2 complex appears to act by facilitating the assembly or stability of the RAD51 nucleoprotein filament. RAD51 catalyses strand transfer between a broken sequence and its undamaged homologue to allow re-synthesis of the broken region.

Many cancers have epigenetic deficiencies in various DNA repair genes (see Frequencies of epimutations in DNA repair genes in cancers). These repair deficiencies likely cause raised unrepaired DNA damages. The over-expression of BRCA2 seen in many cancers may reflect compensatory BRCA2 over-expression and increased homologous recombinational repair to at least partially deal with such excess DNA damages.[75]

Table No. 1: Germline mutations and founder effect of BRCA1 and BRCA2[76,77]

Population or subgroup	BRCA1 mutations	BRCA1 mutations
African-Americans	943ins10, M1775R	-
Afrikaners	E881X	-
Ashkenazi Jewish	185delAG, 188del11, 5382insC	6174delT
Austrians	2795delA, C61G, 5382insC, Q1806stop	-
Belgians	2804delAA, IVS5+3A>G	-
Dutch	Exon 2 deletion, exon 13 deletion, 2804delAA	5579insA
Finns	3745delT, IVS11-2A>G	8555T>G, 999del5, IVS23-2A>G
French	3600del11, G1710X	-
French Canadians	C4446T	8765delAG, 3398delAAAAG
Germans	5382insC, 4184del4	-
Greeks	5382insC	-
Hungarians	300T>G, 5382insC, 185delAG	9326insA
Icelanders	-	999del5
Italians	5083del19	8765delAG
Japanese	L63X, Q934X	-
Native North Americans	1510insG, 1506A>G	-
Northern Irish	2800delAA	6503delTT
Norwegians	816delGT, 1135insA, 1675delA, 3347delAG	-
Pakistanis	2080insA, 3889delAG, 4184del4, 4284delAG, IVS14-1A>G	3337C>T
Polish	300T>G, 5382insC, C61G, 4153delA	-
Russians	5382insC, 4153delA	-
Scottish	2800delAA	6503delTT
Slovenians	-	IVS16-2A>G
Spanish	R71G	3034delAAAC(codon936), 9254del5
Swedish	Q563X, 3171ins5, 1201del11, 2594delC	4486delG

CONCLUSSION:

The review study presented in this article details about the breast cancer which accounts majorly for more than ~29-34%, of death cases amongst the women population. Mostly the gene mutation breast cancer is affected in women. BRCA1 gene mutation breast cancer is more affected than BRCA2. This BRCA2 gene mutation is not common but can be higher in specific populations.

AUTHOR'S CONTRIBUTION

Dr.B.Jayakar reporting preparation of review article, Prof.Dr.B.S.Venakateswarlu & Prof.Dr.R.Margret Chandira supervised the manuscript preparation and reviewed the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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