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Impact of Estrogen Therapy on BRCA1-Associated Breast Cancer Progression in Transgender Women

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Abstract: *The combination of hormone treatment and genetic liabilities in transgender women leads to a complicated situation for breast cancer growth particularly linked to BRCA1 mutations. Gender-affirming treatment relies heavily on estrogen and causes intense cell growth and differentiation in breast tissue driven by estrogen receptor mechanisms. Mutations in BRCA1 lead to weak DNA repair processes which enhance an individual's vulnerability to cancerous changes. Rodestrogens enhance the functioning of proliferative pathways like PI3K/AKT and MAPK pathways in cells with dysfunctional BRCA1. This collaborative action elevates the threats posed by benign growths such as fibroadenomas leading to invasive breast cancer. By affecting the expression of vital regulatory proteins linked to cell proliferation estrogen further compromises the genomic integrity in cells harboring BRCA1 mutations. The hormone environment influenced by exogenous estrogen therapy can shape the tumor microenvironment for better cancer progression and metastasis. Comprehending the relationship between estrogen signaling and pathways related to BRCA1 is important for identifying the enhanced risk of cancer in transgender women using hormone therapy. This detailed study aligns recent discoveries regarding genetic vulnerability and hormonal impacts with cell mechanisms to reveal a detailed insight into breast cancer progression in these individuals. The study emphasizes the necessity for custom-designed cancer screening methods and targeted treatments to help mitigate risks and support transgender care. Understanding these pathways greatly enriches our knowledge of hormone-induced carcinogenesis among those who carry certain genetic markers while also guiding the creation of personalized care for transgender women at enhanced risk of breast cancer.*

Keywords: *Estrogen Therapy, BRCA1 Mutation, Transgender Women, Cell Cycle Dysregulation*

1. INTRODUCTION

Individuals who identify as women were formerly identified as men at birth. This gender identity differs from sexual orientation and originates from a deep sense of self. Transgender people exist in different numbers around the world due to cultural social and legal circumstances. Surveys reveal an estimated 0.6% of individuals over 18 in America are transgender with comparable or slightly varying figures in many other countries (Turban et al., 2022). For many transgender women seeking medical transition guidance gender-affirming hormonal therapy plays a key role by creating changes aligned with their gender identity. In GAHT applications estrogen and anti-androgen medications usually play a key role in lowering testosterone outputs and helping feminize individuals through estrogen treatment (Glintborg et al., 2021).

The breast tissue serves as the foundation of breast cancer; it leads to rare lesions mostly involving the lobules or the ducts in the breast. Breast cell proliferation is unchecked and can

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lead to encroachment on surrounding tissues followed by spread to distant organs. Cancer in the breast has several categories determined by factors such as where it started and how it looks under a microscope (Kothari et al., 2020)

Breast cancer ranks as the top diagnosed cancer and causes the highest number of deaths from cancer in women globally. In 2020 globally about 2.3 million new instances of breast cancer were recorded by the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), making up approximately 11.7% of all new cancers. Breast cancer diagnoses are on the rise because of factors like changing lifestyles and increasing diagnostic tools (Chou et al., 2024).

In areas such as North America and Europe rates of incidence tend to rise due to superior healthcare infrastructure and higher risks associated with reproductive activities. In contrast to developed areas rates of illness in emerging nations are lower; nonetheless death rates stay elevated because of inadequate access to screenings and healthcare. Women aged 50 and above are most at risk for breast cancer due to a higher risk as they get older (Monticciolo et al., 2021). Although young women in their 30s and 40s can get breast cancer too. Outcomes for survival change notably according to the diagnosis stage and type as well as treatment access. Early-stage diagnoses possess better outcomes and result in an 5-year survival rate over 90%. Survival rates for metastatic breast cancer are much lower than those with early detection and strong treatment approaches (Giaquinto et al., 2022).

About 5 to 10% of all cases stem from a genetic predisposition that importantly contributes to the cause of breast cancer. Breast cancers connected with heredity often result from mutations in certain genes responsible for cell growth control and DNA repair. In terms of genetic risk factors BRCA1 and BRCA2 hold considerable importance (Li, Silvestri, et al., 2022).

The tumor suppressing genes BRCA1 and BRCA2 engage in the repair of double-stranded DNA breaks with homologous recombination. The presence of BRCA1/2 gene mutations raises the chance of breast and ovarian cancer greatly. Mutations in BRCA1 usually lead to an increased chance of triple-negative breast cancer that has fewer treatment options and a worse outcome (Pogoda et al., 2020). The gene TP53 expresses the p53 protein which plays a vital role in controlling the cell cycle and inducing apoptosis. TP53 mutations cause Li-Fraumeni syndrome that increases the chance of various cancers among people including breast cancer. In repairing DNA, PALB2 generally works with BRCA2. Breast cancer risk rises with PALB2 mutations yet is not as pronounced as for BRCA1/2 mutations. Understanding these

genetic factors greatly influences the evaluation of risk and develops tailored preventive and treatment plans. Identifying BRCA1/2 variations permits high-risk people to engage in preventative actions including more frequent monitoring and treatment options (Foo & Xia, 2022).

Importance of Fibroadenoma

Though this is the most common benign breast tumor, fibroadenoma accounts for only about 10% of all the clinically palpable tumors seen in women, but there may be many cases unrecognized as well. Fibroadenomas are predominantly a disease of young women from age 15 through to 35 (Lee, 2021). It presents as a single, distinct, well-circumscribed, and mobile mass in the breast tissue and is usually painless. These fibers combine with glandular tissues making the tumor more grainy on the inside and nodulated when seen grossly. They are subclassified into histological types of fibroadenomas. One notable category, the simple fibroadenoma, has a standardized stromal and epithelial element with no cellular atypia. In comparison, complex fibroadenomas exhibit one or more of the following characteristics: cysts, sclerosing adenosis or papillary apocrine changes and have a slightly higher potential to increase your risk of developing breast cancer down the line. Juvenile Fibroadenoma – Similar to the previous variant, this particularly affects adolescents and is highlighted by a faster rate of growth. Based on the proliferative rate and overgrowth, these masses are highly cellular and collagenous in comparison with other types (Eleftheriades et al., 2023).

Fibroadenomas, though benign, have been the focus of numerous studies exploring their possible link to an increased risk of breast cancer. The relationship between fibroadenomas and breast cancer is complex, influenced by various factors such as the specific type of fibroadenoma, pathological features, genetic predispositions, and patient management strategies (Humphries et al., 2022).

Table 1. Comparison between Fibroadenoma and BRCA1-Associated Breast Cancer

Aspect	Fibroadenoma	BRCA1-Associated Breast Cancer
Definition	Benign breast tumors composed of glandular and fibrous tissue	Malignant breast cancer linked to BRCA1 gene mutations
Relation to BRCA1	Generally unrelated to BRCA1 mutations	Directly associated with inherited BRCA1 mutations
Impact of Estrogen Therapy	- Minimal influence on fibroadenoma growth - Estrogen therapy	- Estrogen can potentially stimulate cancer cell proliferation

	typically does not increase malignancy risk	- May accelerate tumor progression in BRCA1 mutation carriers - Requires careful hormone level management and regular monitoring
Risk Factors	- Younger age - Hormonal fluctuations	- BRCA1 mutation - Family history of breast cancer - Prolonged hormone exposure

Broadly speaking, fibroadenomas do not greatly increase the risk of developing breast cancer. But this relationship is further complicated by the genetics piece. Especially among patients with a BRCA1 mutation, the association between fibroadenomas and breast cancer risk is magnified. Furthermore hormonal factors, as estrogen therapy quite widely used in transgender women, may also play a role in the malignant transformation of these benign lesions, at least in those with predisposing genetics. Therefore, a better insight to how fibroadenomas could lead to the progression of breast cancer can guide polymorphous personalized prevention strategies such as targeted screening. And since people at high genetic risk are more likely to develop early onset disease, it is especially crucial for this population (Chung et al., 2020).

Breast Disease and BRCA Gene Corelation

BRCA1 is a critical tumor suppressor gene located on chromosome 17q21 and encodes breast cancer type 1 susceptibility protein, BRCA1. The protein encoded by this gene is a huge, multifunctional protein with a crucial role in many cellular processes (selected DNA repair, cell cycle regulation and maintenance of genomic stability). BRCA1 plays a crucial role in the homologous recombination repair (HRR) signaling pathway, which is also known as double-strand break repair. This pathway is an error-free mechanism required to repair double strand DNA breaks, a type of break that can be catastrophic if left unrepaired since they promote the acquisition of mutations that can eventually lead to cancer formation (Chahat et al., 2024).

The influence of mutations in the BRCA1 gene on one's risks for breast and ovarian cancers is well documented. Lifetime risks of breast cancer in women with BRCA1 mutations are between 55% and 65%, compared to approximately 12-13% for the general population. Additionally, these mutations are not only linked to a greater overall chance of developing breast cancer but also appear to lead to earlier-onset disease (Sabiani et al., 2020). More problematically, BRCA1-associated breast cancer frequently results in triple-negative breast

cancer. This subtype is particularly aggressive without any potential targeted treatments, with considerable challenges in management and prognosis. The importance of genetic screening, and controlled antiestrogenic intervention procedures in high-risk populations is emphasized by BRCA1 involvement in breast cancer (Song et al., 2020).

Overview of Genetic Pathways Involving BRCA1

BRCA1 is a central player in several pathways that work to suppress cancer. Among its functions, it plays a critical role in the DNA damage response and repair, cell cycle regulation, chromatin remodeling and protein degradation. All of these roles promote the preservation of genomic integrity, underscoring the critical nature of this gene for preventing cancer (Awaji et al., 2024).

One of the main roles of BRCA1 is in DNA damage response and repair, notably via homologous recombination repair (HRR). HRR, the high-fidelity pathway for repair of double-strand DNA breaks and a BRCA1-dependent process. It cooperates with RAD51 to promote strand invasion, and exchange between homologous chromosomes or sister chromatids, thereby ensuring an error-free repair of the lesions in damaged DNA which contributes to maintain the genomic integrity. As well as playing a role in HRR, BRCA1 also impacts on another type of DNA repair process called non-homologous end joining (NHEJ). BRCA1 modulates repair of double-strand breaks by choosing between non-homologous end-joining (NHEJ), which is erroneous, and homologous recombination repair (HRR), which can be completely error-free (VOUTSADAKIS & STRAVODIMOU, 2023).

BRCA1 is not just important for DNA repair but also helps in controlling the cell cycle. It is a key participant in the G2/M checkpoint, which blocks mitosis until DNA damage is repaired. BRCA1 blocks cell cycle progression by interacting with Chk2 and p53, which actually allows the repair of DNA to take place before the cell cycle can be resumed at a later stage of division. The function of BRCA1 is further complicated by the fact that it also serves as a transcriptional co-regulator which can affect expression of genes, such as those involved in cell proliferation, apoptosis, differentiation. This regulatory role is crucial for keeping cellular homeostasis, and preventing cells from proliferating uncontrollably (Li, Wang, et al., 2022).

In addition, BRCA1 plays a role in chromatin remodeling, which involves changes to the structure of chromatin that allow DNA itself to be accessed during repair or transcription. As part of chromatin remodelling complexes, BRCA1 facilitates the execution of DNA repair mechanisms. Additionally, BRCA1 has been shown to have E3 ubiquitin ligase activity that leads to the degradation of certain proteins. The function for this mechanism is significant in

clearing bunk polypeptides which generated under the reason of defects to contributing reduce cellular stress so as abate apoptosis, too (Banerjee & Roy, 2021).

The various and intricate activities of BRCA1 in maintaining genome stableness spot it because important player for most tumor protection. Disruption of these pathways occurs when BRCA1 is functionless because the cells lost their natural protection, following gene mutations that create characteristic breast cancer subtypes. This disruption results in the loss of genomic stability and permits mutations to accumulate which can cause tumorigenesis. Exploring the various roles of BRCA1 in these genetic pathways will hopefully help us better understand the ways in which it can go wrong and thereby allow cancer to develop (Miklikova et al., 2021).

Table 2. Comparison of BRCA1 and BRCA2 Mutations with the Implications for Estrogen Therapy

Feature	BRCA1	BRCA2	Similarities
Gene Location	Chromosome 17q21	Chromosome 13q13.1	Both are tumor suppressor genes involved in DNA repair.
Cancer Risks	Increased risk of breast, ovarian, fallopian tube, and peritoneal cancers. Also associated with increased risk of prostate and pancreatic cancers.	Increased risk of breast, ovarian, and pancreatic cancers, and possibly prostate cancer.	Mutations in both genes significantly elevate the risk of breast and ovarian cancers.
Mutation Impact	Mutations lead to impaired DNA repair, genomic instability, and increased cancer susceptibility.	Mutations disrupt RAD51-mediated DNA repair, leading to similar outcomes in genomic instability and cancer risk.	Both mutations result in deficient homologous recombination repair, leading to elevated cancer risk.

Structure & Pathway of BRCA1 Gene

The BRCA1 gene is a large gene which has 24 parts that make a protein important for DNA fixing and tumor prevention. Each of these areas, or domains are part of what functions for this protein. At one end of the protein is its RING domain, which allows it to bind to another protein related to breast cancer called BARD1. This complex together helps in tagging the proteins which might be damaged and then removed from the cell to maintain its health. Other

regions of the protein are involved in phosphorylation, which changes BRCA1 activity in response to DNA damage (Tarsounas & Sung, 2020).

At one end of the protein are the BRCT domains which allow the protein to attach to other proteins that participate in DNA repair. This result, called the capability to specifically bind to proteins that search for and repair DNA damage before it can be passed on, is vital for brushing up torn DNA breaks and conserving genome stability. In short, this structure positions the BRCA1 protein to play multiple roles in DNA repair. Destroying this structure disables the gene from protecting against cancer (Peña-Guerrero et al., 2023).

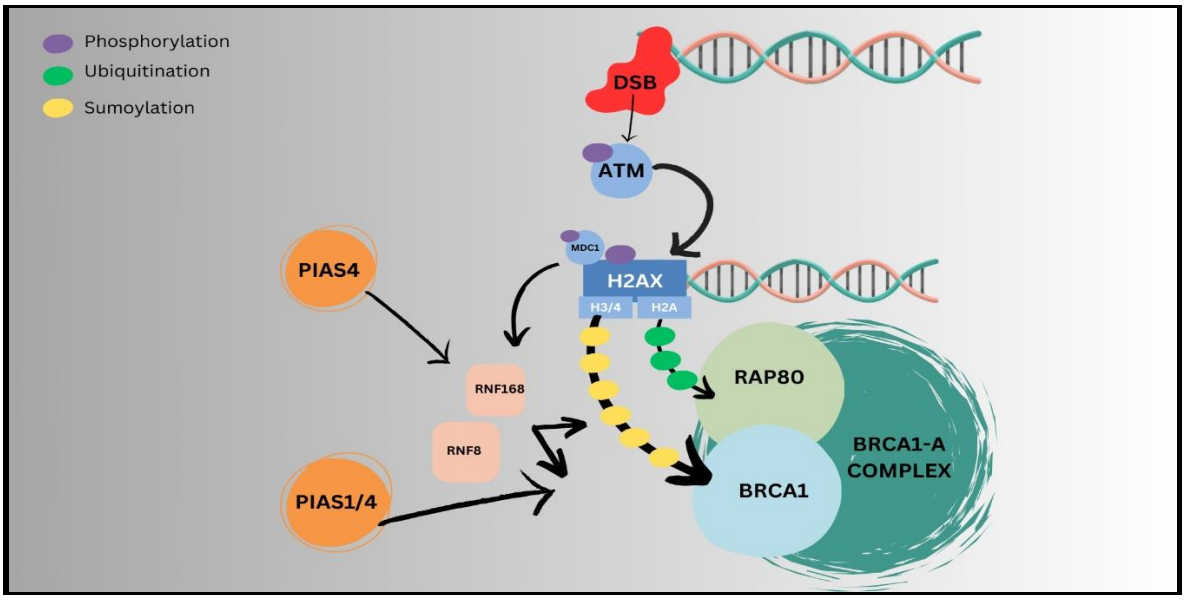

Figure 1. BRCA1-Mediated DNA Damage Response Pathway in Double-Strand Break Repair

Figure 1. illustrates the "BRCA1-Mediated DNA Damage Response Pathway in Double-Strand Break Repair." This figure was custom-designed by the authors using Canva, and further details can be found at this link. https://s.id/BRCA1Pathway

BRCA1 plays a critical role in several interconnected pathways that maintain genomic stability by facilitating accurate DNA repair and ensuring an appropriate cellular response to DNA damage. These pathways include DNA repair mechanisms. Any disruption to this pathway, often due to mutations in BRCA1, can lead to genomic instability and an increased risk of cancer (Raimundo et al., 2021).

In the pathway, Double-strand breaks (DSBs) in DNA, which is a serious type of genetic damage. When such breaks occur, the cell must respond quickly to prevent further issues like

mutations (Zeng et al., 2022). The process starts when a DSB, indicated by the red burst at the top of **Figure 1.**, is detected. These breaks can result from various factors such as radiation, chemical exposure, or even errors during DNA replication. This detection of DNA damage triggers a cellular response to repair the break and maintain genetic stability (Turan & Oktay, 2020).

The first responder to this break is the protein called ATM (Ataxia-Telangiectasia Mutated), shown in the blue oval in the figure. Once activated, ATM starts the repair process by phosphorylating (adding a phosphate group) other proteins involved in DNA repair, marked by the purple circles in the figure. One of the proteins phosphorylated by ATM is H2AX, a variant of the histone protein found in chromatin (Huang & Zhou, 2020). The phosphorylated form of H2AX, known as γH2AX, serves as a beacon to recruit additional proteins to the site of the DNA break. This is shown in the image where the phosphorylated H2AX attracts MDC1, facilitating the assembly of the DNA repair complex.

Following this, other proteins such as RNF8 and RNF168 (depicted in pink rectangles in **Figure 1.**) come into play. These proteins are responsible for ubiquitinating H2AX, which is represented by the green circles in the figure. Ubiquitination is a process where proteins are tagged to signal different cellular functions, in this case, recruiting more repair proteins to the damage site. BRCA1, a key protein in the repair process, is part of a larger complex shown in the image as the "BRCA1-A Complex," along with RAP80 and other components. This complex is essential for initiating homologous recombination repair (HRR), a precise and error-free DNA repair process. BRCA1 helps facilitate the resection of the DNA ends, generating single-stranded DNA necessary for repair. This step ensures that the genetic material is correctly restored without introducing mutations (Kloeber & Lou, 2022).

Additionally, the figure highlights the involvement of proteins like PIAS4 and PIAS1/4 (depicted as orange shapes). These proteins regulate sumoylation (marked by yellow circles) at the DNA damage site, further influencing the recruitment and activity of the BRCA1 complex. In summary, **Figure 1.** demonstrates the coordinated effort of multiple proteins, led by BRCA1, to repair DNA damage accurately and maintain genomic integrity (Han et al., 2022).

How Damage Occurs and Leads to Cancer:

When the BRCA1 gene is functioning correctly, as outlined in **Figure 1.**, it plays a critical role in ensuring that DSBs are repaired through homologous recombination, preserving the accuracy of the genetic code. However, mutations in the BRCA1 gene can disrupt this entire pathway. For instance, if BRCA1's domains—such as the RING domain or BRCT domains—

are mutated, the protein loses its ability to bind to other key repair proteins or regulate the processes depicted in the figure, like ubiquitination and sumoylation. This loss of function results in an impaired DNA repair process (Rabellino & Khanna, 2020).

Without effective BRCA1-mediated repair, DSBs are either left unrepaired or are repaired through more error-prone methods, such as non-homologous end joining (NHEJ). These error-prone repairs can introduce mutations or chromosomal abnormalities into the DNA, leading to genomic instability. Over time, this accumulation of genetic errors can disrupt normal cell growth and division controls, setting the stage for tumorigenesis. As BRCA1 is also involved in regulating cell cycle checkpoints (not explicitly shown in **Figure 1.**), its mutation allows cells with damaged DNA to continue dividing. This unchecked division of genetically unstable cells significantly increases the risk of developing cancers, particularly breast and ovarian cancers.

In conclusion, **Figure 1.** illustrates the normal functioning of the DNA damage response pathway involving BRCA1. However, when mutations in the BRCA1 gene compromise its ability to facilitate accurate repair and regulate cell cycle checkpoints, the pathway breaks down. This leads to the accumulation of mutations, genomic instability, and an increased risk of cancer development, highlighting the essential role of BRCA1 in maintaining cellular health (Rabellino & Khanna, 2020).

Significance of BRCA1 in Breast Cancer Progression

BRCA1 is a key gene that suppresses the development of breast cancer by repairing DNA damage, controlling cell cycle and maintaining genomic stability. The loss of a fully functional BRCA1 protein is likely to seriously impair DNA repair in those with BRCA1 mutations, leading to an increase in unrepaired genetic damage and genomic instability. This instability favors the onset of malignant transformation and tumor formation (Jin et al., 2022).

DNA repair and genomic integrity are one of the most important consequences of BRCA1 mutations. BRCA1 is an important member of the homologous recombination repair (HRR) pathway and ensures error-free double-strand DNA break repair. Mutations that disrupt the function of BRCA1 interfere with this repair process. As a consequence DNA Injury however lingers and The end result is chromosomal aberrations (that can cause birth problems as well as worse Cancer!) and increased mutation rates. Inability to repair DNA damage the right way compromises cellular integrity, leading to accrual of oncogenic mutations, which fuel cancer initiation and progression (Cortesi et al., 2021).

BRCA1 is also key in controlling the cell cycle checkpoints, especially those occurring at G2/M. This checkpoint checks that cells with damaged DNA do not enter mitosis, which is

known to ensure that cell division occurs only in the case of an intact genetic material. The thing is, we need this control mechanism to keep cells with too much un-repaired DNA damage from continuing to proliferate — and in cells that have no functional BRCA1, it fails. Such unsupervised cycle progression leads to the unlimited clonal expansion genetically unstable cell populations and thus significantly accelerates transformation and promotes metastasis (Hauge et al., 2023).

BRCA1 not only plays a role in DNA repair and cell cycle control but also interacts with hormonal pathways that can add even more layers of complexity to cancer risk. For instance, estrogen therapy can increase the risk of breast cancer in women with BRCA1 mutations. In breast tissue, this estrogen that binds to the receptors induces cellular proliferation and differentiation. With BRCA1 mutations this increased risk is augmented by estrogen-mediated proliferation and deficient DNA repair concomitantly. Degree of susceptibility to hormone-related cancers in those with BRCA1 mutations, be partially rooted by the interplay between hormonal influences and genetic predisposition (Rajan et al., 2021).

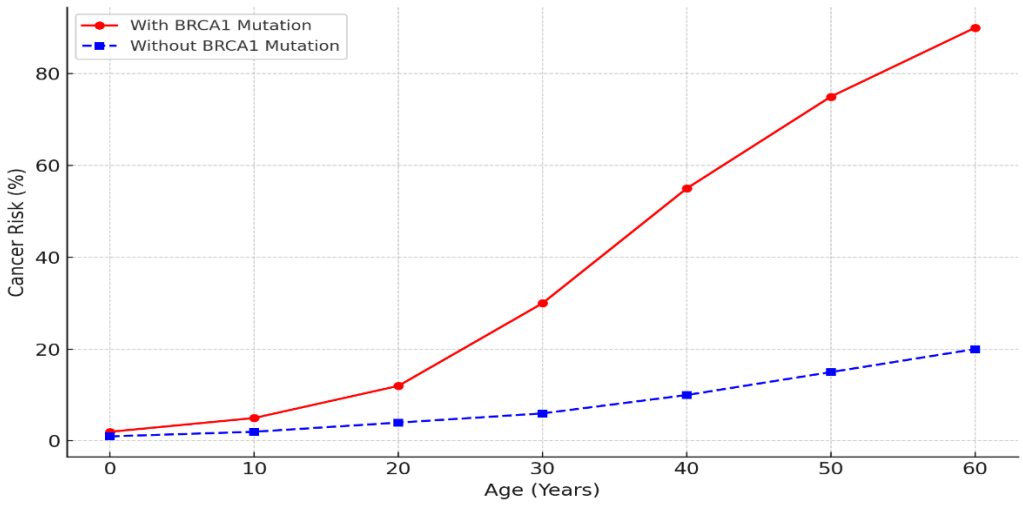

Figure 2.: Age-Related Breast Cancer Risk in Individuals With and Without BRCA1 Mutations (Hu et al., 2020a)

Figure 2. presents a graph depicting the age-related breast cancer risk in individuals with and without BRCA1 mutations. The data and analysis for this graph are based on the article: *Hu, C., Polley, E. C., Yadav, S., Lilyquist, J., Shimelis, H., Na, J., Hart, S. N., Goldgar, D. E., Shah, S., Pesaran, T., Dolinsky, J. S., LaDuca, H., & Couch, F. J. (2020). The contribution of germline predisposition gene mutations to clinical subtypes of invasive breast cancer from a clinical genetic testing cohort. JNCI: Journal of the National Cancer Institute, 112(12), 1231–1241.* https://doi.org/10.1093/jnci/djaa023

Breast cancer risk over time based on whether individuals have a BRCA1 mutation It demonstrates that at 61 years, the risk for people with BRCA1 mutation (red line) is much increased and this elevates more quickly as those persons get older, mostly after they are in their 30s. By comparison, people who do not have the mutation (blue dashed line) experience a much more moderate and continuous increase in risk of cancer. This underscores the significant risk for breast cancer associated with BRCA1 mutations and the need for programs that provide mutation carriers early detection and prevention strategies (Hu et al., 2020b).

These findings have broad therapeutic implications in breast cancer treatment that hinge on the concept of BRCA1 acting as a gatekeeper to tumor progression. A promising strategy focuses on agents targeting PARP (poly ADP-ribose polymerase). Because of the principle of synthetic lethality, these drugs target other DNA-repair systems in BRCA1 -deficient cells and kill them. Moreover, personalized medicine approaches have allowed us to individualize treatment strategies according to BRCA1 mutational status in the form of an improved response while reducing adverse effects (Jurkovicova et al., 2022).

In conclusion, we showed that the versatile features of BRCA1 in DNA repair, cell-cycle control and genomic stability form a basis for keeping breast cancer in check. However, if mutations sabotages BRCA1 function, the subsequent genomic instability will make another drastic increase in cancer susceptibility. This conclusion highlights the necessity of providing adjusted therapeutic plans based on a personalized medicine approach regarding individuals with BRCA1 mutations.

Impact of Estrogen Therapy on BRCA1-Associated Breast Cancer Progression

The BRCA1 gene is an important guardian of genomic stability because it participates in DNA repair, specifically the homologous recombination repair (HRR) pathway. A fundamental hormone required to stimulate breast tissue development is estrogen and this procured through binding of the sex steroid hormone estrogen not only activates specific signaling pathways in breast epithelial cells (via ERα and/or ERβ), but it also stimulates cellular proliferation and survival (Mekonnen et al., 2022).

In those with functional BRCA1, a fine balance between the ability of estrogen to induce proliferation is tightly controlled. Furthermore, BRCA1 modulates ERα signaling through its interaction with the receptor as a co-repressor to suppress aberrant estrogen signaling. This interaction prevents the phenomenon of uncontrolled cell growth and ensures genome integrity by not allowing estrogen-driven cellular divisions to amplify the number DNA replication errors (Yedidia-Aryeh & Goldberg, 2022).

However, the presence of BRCA1 mutations disrupts this regulatory mechanism. In contrast, the mutant BRCA1 proteins are much less efficient in repressing ERα activity and the consequence is an increased estrogen receptor pathway. The lack of these checks, due to the ongoing unrestrained estrogen activity, further activates proliferation and enhances tumorigenesis without the control normally provided by an effective DNA repair mechanism. Therefore, in the context of high estrogen signalling and DNA repair dysfunction, genetic mutations may be more easily acquired creating a background that is prone to malignant transformation (Miziak et al., 2023).

Synergistic Effects of Estrogen Therapy and BRCA1 Mutations

Estrogen therapy, commonly used in transgender women for gender affirmation, introduces exogenous estrogen into the body, amplifying the natural estrogen signaling pathways in breast tissue. When combined with BRCA1 mutations, estrogen therapy can have synergistic effects that significantly elevate breast cancer risk through the following mechanisms:

- **Enhanced Cellular Proliferation:** Exogenous estrogen therapy causes proliferation of breast epithelial cells Since the HRR pathway is insufficient/inactive in BRCA1-mutated cells, DNA replication errors induced by this rapid cell division are not correctly repaired. This induces the acquisition of genetic mutations, some of which may involve oncogenes and additional tumor suppressor genes, facilitating the transition from benign lesions to malignant tumors (Rajan et al., 2022).
- **Increased Genomic Instability:** ROS Induced by Estrogen Metabolism May Cause DNA Adducts and DNA Damage This deficiency in repairing such damage increases genomic instability in the BRCA1-mutated cells. This instability, in turn promotes chromosomal aberrations that can drive aggressive cancer phenotypes (Rajan et al., 2022).
- **Promotion of Survival Pathways:** these pathways such as PI3K/AKT and MAPK have been shown to be activated by estrogen leading to cell survival and proliferation. In cells with BRCA1 mutations, these pathways may act to oppose apoptotic signals, leading to a sub-population of genetically unstable cells that is maintained despite ongoing and extensive DNA damage. This additionally improves malignancy and metastasis (Xiang et al., 2021).
- **Altered Tumor Microenvironment:** Estrogen therapy also has an effect on the tumor microenvironment by inducing angiogenesis and changing the extracellular matrix. Together these changes foster a tumor promoting and metastatic microenvironment that

facilitates invasion of the surrounding stroma and distant organ colonization (Somasundaram et al., 2020).

Table 3.: Synergistic Effects of Estrogen Therapy and BRCA1 Mutations

Effect	Estrogen Therapy	BRCA1 Mutation	Combined Synergistic Effect
Cellular Proliferation	Increases breast epithelial cell division	Impaired DNA repair leads to accumulation of mutations	Unchecked proliferation with higher mutation rates
Genomic Stability	Generates reactive oxygen species (ROS)	Deficient homologous recombination repair (HRR)	Elevated genomic instability and chromosomal aberrations
Apoptotic Regulation	Activates survival pathways (PI3K/AKT, MAPK)	Reduced p53-mediated apoptosis	Enhanced survival of genetically unstable cells
Tumor Microenvironment	Promotes angiogenesis and extracellular matrix changes	N/A	Supports tumor growth and metastasis

Cycle of Estrogen Therapy Impact on BRCA1 Progression

Estrogen therapy is a cornerstone of the gender-affirming care for many transgender women, but may be associated with a marked increase risk of breast cancer in transgender individuals who also carry BRCA1 mutations. This susceptibility is the result of a network of interacting pathways that converge to establish an autoreinforcing loop driving tumor development.

One cycle starts by administering estrogen treatment. Transgender women take exogenous estrogen high levels of it, and that requires the support of testosterone for certain body functions. Estrogen receptors (ERα and ERβ) on breast epithelial cells are activated by this increase in estrogen. When this binds to these receptors, it activates signaling pathways that encourages cell proliferation. Thes signal cascades involve the activation of ostensibly cell cycle promotional genes, which a allow an increase in cell division rates. This proliferation is a normal step in the healing of damaged lung tissue by estrogen-reactivating signaling pathways; however, this increase will create health risks when BRCA1 mutations are treated hormone therapy (Santen et al., 2020).

Cell cycle progression is driven by estrogen receptors and causes increased cellular proliferation and DNA replication. Lots of cellular proliferation, with the DNA replication machinery takes a lot of punishment. As a function of this sped up replication, DNA copying mistakes are more probable, particularly the development of double-strand DNA breaks. These breaks are usually mended by cellular processes that serve to keep the genome in good repair, but when restorative processes fail or falter — as they tend to do with BRCA1 mutations — trouble ensues (Loizzi et al., 2023).

In a cycle, impaired DNA repair in BRCA1-mutated cells becomes essential. BRCA1 is an integral component of the homologous recombination repair (HRR) pathway, a high fidelity double-strand break repair mechanism. HRR is invoked for repair of the vast majority of DSBs, and loss of susceptibility to HRR leads to the need by cells to utilize other DNA repair mechanisms, such as non-homologous end joining (NHEJ), which is error-prone. This mechanism often results in additional genetic mistakes made during the repair, thus mutations pile up. These mutations can accumulate over time, activating oncogenes (cancer-promoting genes) or inactivating tumor suppressor genes, respectively pushing the cells closer to becoming malignant (Zhou et al., 2020).

The route continues with genomic instability and mutation accumulation. The ongoing DNA damage and use of error-prone repair pathways in cells that have mutated forms of BRCA1 allow mutations to build up over time.Writer Such genomic instability allows the transition of normal breast epithelial cells to a malignant state and provides an environment supportive of cancer growth and evolution. Collectively, these mutations disrupt cellular regulation and promote the hyperproliferation typical of fully transformed tumours from previously benign lesions.

The tumor growth and microenvironment modification act as the competitive selection drivers after malignant transformation. Estrogen stimulates the production of growth factors like vascular endothelial growth factor (VEGF) pushes to produce new blood vessels (angiogenesis). This increases the nascent tumor's access to oxygen and nutrients, permitting solid growth. Estrogen can also alter the tumor microenvironment in ways that suppress immune cell function, inhibiting the body's ability to sense and eradicate early cancerous cells. This immune evasion enables cancer cells to multiply that in turn reinforce the growth of tumor (Brogowska et al., 2023).

One critical feature of this cycle is feedback amplification produced by estrogen therapy. Such genetic lesions and resultant activation of oncogenic pathways collectively increase signaling through the estrogen receptor and other proliferative signals. This sets up a positive

feedback loop where increased estrogen signaling fuels additional cell proliferation and mutation accumulation to promote cancer progression. Furthermore, estrogen induces processes such as epithelial-to-mesenchymal transitions (EMT) which are responsible for the migratory and invasive properties that are so critical for metastatic disease. This, in turn, makes the cell cycle upregulated not just more aggressive of a tumour, but also more capable of breaking down tissues around it into new vessels to invade new areas of the body (Cao et al., 2020).

In summary, the effect of estrogen therapy on progression of BRCA1-associated breast cancer is a circle involving hormonal signaling, genetic instability, and alterations in tumor microenvironment. This cycle emphasizes the need for rigorous risk assessment and monitoring in transgender women undergoing estrogen therapy, especially those who may have a genetic predisposition to breast cancer such as BRCA1.

Potential Feedback Mechanisms and Amplification of Cancer Risk

A number of feedback mechanisms add to the worsening effect of estrogen therapy on BRCA1-related breast cancer. These systems heighten cancer risk and establish a relentless mechanism that encourages the emergence of more severe and difficult-to-treat tumors. Grasping these feedback mechanisms is essential for creating beneficial strategies for transgender women on estrogen treatment and especially for women with BRCA1 mutations.

A key feedback mechanism includes mutated genes from weakened DNA repair that boosts estrogen receptor activity. The damage to DNA by BRCA1 mutations allows more errors in the genetic code to build up. Alternative genetic changes might transform essential signaling factors within the cell to enhance estrogen receptor signaling. Larger amounts of estrogen activate cell reproduction and raise the probability of further genetic faults. This creates a situation in which instability and cell proliferation mutually enhance the cancer risk (Clusan et al., 2023).

Mutations found in this cycle can boost estrogen receptivity or the pathways involved downstream. Tissues with these genetic anomalies react more effusively to estrogen which boosts the mechanisms involved in cell expansion and survival. The rise in number of estrogen receptors raises the cell's estrogen sensitivity intensifying the influence of estrogen therapy. This results in increased cell division and prolongs the chances for added mutations that strengthen the growth of cancer.

Using estrogen could modify the surroundings of a tumor to promote its growth. Angiogenesis arises due to estrogen signaling as a key alteration. The result delivers a continuous supply of nutrients and oxygen to the tumor as it thrives rapidly and creates routes

for the spread of cancer cells. The tumor environment's immune responses can be affected by estrogen. It has the capacity to decrease immune cell activity that identifies and destroys cancer cells and thus allows the tumor to escape immune monitoring. Microenvironmental alterations enhance the expansion of the main tumor and promote metastasis (Dama et al., 2021).

Cancer cells produce growth factors that either act on their own cells or influence neighboring cells while boosting replication and lifespan. In an autocrine cycle established by cancer cells those cells produce growth factors that bind to their own receptors to enhance growth. In neighboring cells of the microenvironment they create conditions supporting tumor proliferation. This signal keeps the cancerous situation active by regularly stimulating processes that support cell reproduction and invasion (Bożyk et al., 2022).

Changes in gene expression result from estrogen therapy through epigenetic processes irrespective of modifications in the underlying DNA. Histones and DNA methylation alterations might continuously elevate oncogene expression while suppressing tumor suppressor genes. By altering the cell's epigenetic environment estrogen facilitates tumor advancement. Activating pathways that drive cell growth keeps the cancerous state intact over time and boosts tumor aggressiveness along with treatment resistance.

Together, these feedback mechanisms form a self-perpetuating cycle, where each stage of cancer progression reinforces the subsequent stages. The mutual intensification of genomic instability, enhanced estrogen responsiveness, microenvironmental changes, autocrine/paracrine signaling, and epigenetic alterations leads to the development of more aggressive tumors that are difficult to treat. Understanding these interactions is crucial for developing targeted interventions that can disrupt these feedback loops, thereby mitigating cancer risk and improving clinical outcomes for transgender women undergoing estrogen therapy with BRCA1 mutations.

2. CONCLUSION

In transgender women treating breast cancer caused by BRCA1 mutations heavily relies on the complex relationship between hormones and genetics. Gender-affirming treatment relies on estrogen therapy that brings about major changes in breast tissue. When BRCA1 mutations occur the proliferative signals work effectively in a flawed genomic context that encourages the buildup of genetic alterations and chromosomal anomalies.

Hormones and the BRCA1 pathway cooperate in elevating breast cancer risk due to estrogen therapy. As a key component in cancer suppression BRCA1 helps ensure DNA repair with homologous recombination and modulates estrogen receptors to limit excessive cell

division. Disruptions in BRCA1 alter these governing roles which increases estrogen receptor activity and maintains growth signals. Estrogen-regulated cellular division leads to instability in the genome while this disruption encourages the generation of oncogenic mutations transforming benign breast lesions into malignant tumors.

When estrogen therapy acts alongside BRCA1 mutations there is growth in cells along with more instability in the genome along with enhanced survival pathways which hasten cancer growth. In the absence of BRCA1 estrogen increases signaling through pathways responsible for survival and proliferation such as PI3K/AKT and MAPK resulting in the survival of unstable cells. As a result of estrogen on the microenvironment within tumors angiogenesis is increased and the extracellular matrix transforms to favor tumor expansion and metastasis.

The cycling relationship between estrogen therapy and BRCA1-associated pathways reveals a system where each cycle of estrogen-enhanced cell division and genomic instability fuels further oncogenic evolution. The interaction of estrogen injections and cell division creates a model that explains the increased breast cancer risk seen in transgender women carrying BRCA1 mutations.

BRCA1-associated breast cancer development in transgender women is significantly hastened by estrogen therapy; this occurs partly through genetic susceptibilities and hormone stimulation. The described pathways and cycles explain the fundamental reasons for this elevated risk and stress the important necessity for focused screening and individualized therapies to reduce the risk of breast cancer in this susceptible community. The extensive analysis finds that estrogen therapy is indispensable for transgender individuals to express their gender but has a key impact on BRCA1-linked cancers requiring an attentive approach in health management.

Ethical Statement

This review article does not involve any original research with human participants or animals. All data and information presented are derived from previously published studies and publicly available sources. Ethical approval was not required for this study.

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