SCHOLARLY REVIEW

A review of the role of TP53 in hereditary breast cancer

By Victoria Zhang

Author Biography

Victoria Zhang is a junior high school student at High Technology High School in New Jersey. She is passionate about biology, especially cancer and its causes through gene mutations and current, emerging treatments. Victoria first discovered her interest in cancer biology during her freshman-year biology class, and she continues to learn more about biology through research and her school's science club and biomedical engineering class. Outside STEM-related activities, she enjoys reading books, listening to music, and playing with her soccer team. In the future, Victoria hopes to potentially enter the medical field or pursue a career in cancer biology to help others around her.

Abstract

Breast cancer is the most prevalent cancer type affecting people worldwide. Although it is not transmittable, certain mutated genes can be inherited. Despite accounting for less than 1% of the population, hereditary breast cancer can be detrimental as it carries an inherited risk that elevates the lifetime risk of developing breast cancer and causes earlier onset of cancer. The p53 protein, produced by the TP53 gene, prevents cancer from developing by regulating the cell cycle and initiating apoptosis. Thus, when TP53 mutations occur, tumor suppression function is lost, cancer risk increases and gene activity becomes abnormal. This paper aims to review the role of TP53 mutations in hereditary breast cancer and explore the current treatments through a systematic search and analysis of peer-reviewed research articles on ScienceDirect. Results found numerous cases of TP53 mutations correlated with hereditary breast cancer, as well as many patients with LFS, which increases the risk for breast cancer. Current treatments advised include mastectomies and breast MRIs for diagnosis, while radiation therapies were generally not recommended. Early screenings and being informed about hereditary breast cancer are crucial for possible patients.

Keywords: p53, TP53, gene, mutations, hereditary breast cancer, LFS, treatment

Introduction

Cancer is one of the leading causes of death worldwide, causing nearly 10 million deaths in 2022 (World Health Organization, 2022). Not transmittable and caused by abnormal cell division, cancer has over 200 variants and continues to be a commonly studied topic as a significant amount of information remains unknown about cancer. Breast cancer (BC) is the most common type of cancer affecting women worldwide (Wahab et al., 2024) and it may carry a hereditary component caused by inherited mutations in genes, most commonly BRCA1 and BRCA2 (CDC, 2024). Because these mutations are inherited and passed down through families, they are present in all body cells. Although hereditary breast cancer affects less than 1% of the population, it is linked to 5 to 10% of BC in women, as well as many other types of cancer (Yale Medicine, 2024).

Even though mutations in the BRCA1 and BRCA2 genes are the most common causes of hereditary breast cancer, accounting for around 35% of hereditary breast cancers (Casaubon et al., 2023), mutations in other genes can also increase the risk of breast cancer; this includes PALB2, TP53, PTEN, CDH1, STK11. These genes are associated with syndromes that cause a risk of breast cancer with relatively high penetrance. For example, PTEN is associated with PTEN hamartoma tumor syndromes like Cowden syndrome, CDH1 is involved with lobular breast cancer syndrome, and TP53 is associated with Li-Fraumeni syndrome (LFS) (National Cancer Institute, 2024).

The gene TP53 is present on chromosome 17 and induces the production of the protein p53, a tumor suppressor that protects the genome by repairing or killing damaged DNA (Wahab et al., 2024). DNA damage sensor proteins sense damaged DNA and the p53 gene allows the cell to respond and repair DNA damage after cellular stress, which triggers multiple downstream repair pathways (Trombetta et al., 2020). These repair pathways can repair DNA lesions like single or double-strand breaks, induce apoptosis, also known as programmed cell death, or cause senescence, where the cell remains alive but permanently stops dividing (Maynard et al., 2013). Thus, p53 can prevent cancer from developing and play an important role in cell cycle control and apoptosis, by regulating cells from growing or dividing too fast. More specifically, domains or parts of p53 structured to recognize DNA allow the protein to bind directly to DNA, which is located in the nucleus of cells throughout the body. When DNA becomes damaged by agents like radiation or ultraviolet (UV) rays from the sun, p53 determines if the DNA will be repaired or self-destruct (Medline Plus, 2020). If the DNA is going to be repaired, p53 activates other genes to fix the damage. If the DNA cannot be repaired, the protein signals for the cell to undergo apoptosis, thus preventing the development of tumors. The TP53 gene is so crucial that it has been called the “guardian of the genome” (Petry et al., 2023).

However, if the TP53 gene is mutated through inheritance or other factors such as radiation exposure or random errors during DNA replication, there would be an abnormal function of the gene and the p53 protein. Most importantly, p53 would lose its function as a tumor suppressor and be unable to detect DNA damage and stop cell division. Uncontrolled replication of mutated cells can lead to the start and progression of cancer (Medline Plus, 2020). Also, such mutations would impact p53’s ability to control apoptosis, damaging cells and limiting DNA repair. In general, TP53 mutations would increase cancer risk and those who inherit a TP53 mutation would likely develop Li-Fraumeni syndrome (LFS), which greatly increases the risk of developing cancer, especially breast cancer (Olivier et al., 2010). TP53 mutations may also cause poor prognosis and resistance to certain treatments like chemotherapy. Therefore, it is important to understand the relationship between TP53 mutations and hereditary breast cancer as well as current treatments to inform patients or those at risk better. Thus, this paper aims to review the role of TP53 mutations in hereditary breast cancer and explore the current treatments and medications advised.

Methodology

A systematic analysis of published literature was conducted using the ScienceDirect database search. First, a comprehensive search on ScienceDirect was completed using the keywords “tp53 ‘hereditary breast cancer’”. The inclusion criteria were only research articles in English from 2014 to 2024. The search resulted in 112 research articles that were reviewed for relevance. Research articles with no

significant mention of p53, TP53, or anything related to hereditary breast cancer were omitted. The last date research was done was July 18, 2024, and any articles published after that date and followed the same search criteria were not included in the review.

Results

After analyzing all research articles, 19 peer-reviewed studies were included in this review. These papers were divided into two informative sections: TP53 Relation to Breast Cancer and Current Treatment. TP53 Relation to Breast Cancer explains how mutations or variants in TP53 are related to or cause breast cancer. The Current Treatment section describes clinical treatments, their effectiveness, and what breast cancer patients, medical providers, and more can do to improve outcomes.

TP53 and Hereditary Breast Cancer

The TP53 gene is critical in cell cycle regulation, DNA repair, and apoptosis. Mutations in this gene can contribute to the development of various cancers, including hereditary breast cancer. Many different types of TP53 mutations can lead to this disease, but not all TP53 mutations carry the same risk. The types of TP53 mutations associated with hereditary breast cancer typically involve germline mutations (inherited mutations present in all cells). These mutations generally result in a loss of function of the p53 protein, compromising its role as a tumor suppressor

Breast cancer is a major global health issue, and early detection can be crucial to patient health (Wahab et al., 2024). Early detection through circulating tumor DNA (ctDNA) can be crucial to patient health since ctDNA can help detect cancer and evaluate the success of treatments. ctDNA is a biomarker of small pieces of DNA released into the bloodstream of tumor cells and measured to help diagnose patients and aid treatment planning. Wahab et al. (2024) analyzed nucleotide sequences for 10 cancer genes in 50 female patients identifying deleterious mutations and amino acid changes; from the variants observed, six were of TP53. Thus, according to the sequencing data, hereditary breast cancer was associated with mutations in TP53. This data confirms the findings of Himes and Shuman (2020) that approximately 1% of all hereditary breast cancer cases are the result of a TP53 gene mutation.

There are numerous genetic variations of different cancer-causing genes. Using targeted sequencing of selected genes from breast cancer patients, Alanazi et al. (2020) identified 37 potential mutations in 25 breast cancer risk-associated genes. Seven mutations in TP53 were observed with base changes in amino acids, also known as single nucleotide polymorphism (SNP). SNPs may disrupt protein coding or cause deletions in the sequence and stop gains, which are premature stopping codons that truncate proteins. Hereditary mutations in TP53 are also associated with Li-Fraumeni syndrome (LFS), which increases the risk of youth cancer and challenging prognosis (Wahab et al., 2024). Kwong et al. (2016) in a study detecting hereditary mutations in breast/ovarian cancer with next-generation sequencing found amongst 948 patients two cases associated with LFS and five cases of TP53 mutations, all of which were amino acid changes. Such changes negatively affect TP53 structure and function, sometimes inactivating the TP53 gene. These variants may affect gene functions; therefore, increasing the importance of research on the role of SNPs in carcinogenesis.

Similarly, Vieira et al. (2024) stated that mutated TP53 can lose its tumor-suppressive function and gain new oncogenic, or cancerous, properties. These hereditary pathogenic TP53 variants can cause LFS, which can result in breast cancer. Additionally, such variants can cause amino acid changes in exons 5-8, which affects a region of the genome associated with messenger RNA (mRNA) molecules. MicroRNA (miRNA) is a kind of non-coding RNA that helps cells control gene expression by preventing mRNA from making proteins. Some miRNAs are direct or indirect regulators of genes involved in the p53 network. More specifically they may belong to the miR-34 family, which positively regulates p53 expression and activity. Thus, the study focused on the effects of two miRNA-related SNPs in a group of 273 LFS patients by doing SNP genotyping and Sanger sequencing. Results found that the two SNPs had genotype frequency and association with clinical features of the LFS group, highlighting the importance of studying miRNA genes that indirectly regulate p53 expression.

Breast cancer is estimated to be hereditary in 10% of patients (Salmaz et al., 2021). Carriers of pathogenic variants (PVs) of hereditary TP53 usually develop cancer during childhood or young adulthood and have very high lifetime risks of malignancies. Rosenthal et al. (2017) screened 9,641 women for high-risk breast cancer through expanded genetic testing finding 205 PVs in TP53 for 199 women. Out of those patients, based on family history, 19.6% had an estimated lifetime risk greater than 20%, and 25.4% had daughters with an estimated risk greater than 20%. Petry et al. (2023) determined a specific hereditary TP53 PV at codon R337H that is highly prevalent in southern regions. The study evaluated 138 LFS patients with breast cancer by using blood DNA collections and analyzing the p. R337H mutation by polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP). Among the patients, 93 were diagnosed with TP53 PVs, and 81 were carriers of TP53 p. R337H. Patient characteristics, treatments, responses, cancer recurrences, and deaths were also accounted for. In conclusion, patients with LFS and breast cancer had a higher rate of second malignancies, but when compared with breast cancer patients without a hereditary PV, no differences were seen. Breast cancer in LFS was also frequently estrogen receptor-positive, meaning cancer cells need to bind to the hormone estrogen to grow, which means cancer cells have too much human epidermal growth factor receptor 2 protein (HER2) and therefore grow and spread faster.

Similar to the findings of Petry et al. (2023), other recent studies have found numerous tumors of LFS breast cancer patients, caused by hereditary TP53 mutations, to be estrogen receptor positive with frequent HER2 co-expression. However, the aspects of these tumors are not well known. Kuba et al. (2021) evaluated the features of 27 invasive and in situ carcinomas, abnormal cells found only where they first formed in the body, from LFS patients with known hereditary TP53 mutations. Histologic analysis was done to classify carcinoma types and growth patterns, as well as immunohistochemical studies and scoring to detect and evaluate antibodies. Most noticeably, 60% of cases were HER2 positive, and 44% co-expressed estrogen receptors, stressing the importance of testing hereditary TP53 carriers. Results also suggest that TP53 inactivation occurs in lesions before tumors, so understanding the early steps in LFS-associated breast cancer would be crucial for information and designing treatment trials.

Moreover, according to Eccles et al. (2016), patients with a hereditary mutation in the TP53 gene predominantly develop HER2-positive breast cancer. The study explored breast cancer susceptibility genes testing on patients with HER2+ breast cancer by selecting a cohort of 591 HER2+ patients younger than or equal to 40 years old, panel testing them, which was followed by next-generation sequencing. Although BRCA1 and BRCA2 were the study's focus, a subset was tested for TP53 mutations, and out of 304 patients, nine had pathogenic, deleterious TP53 mutations. The study found that a large number of TP53 hereditary mutations were in those with only breast cancer family histories. Additionally, these mutations were more likely to be truncating mutations rather than those from amino acid changes (missense mutations) when the family history was not LFS-like.

Mutations in TP53 are generally discovered in patients with very severe hereditary cancer disorders, like LFS. Recent studies have found that inborn TP53 defects may be limited in certain women by breast cancer development. Sokolenko et al. (2015), performed gene analysis on 95 high-risk Russian breast cancer patients for hereditary defects in DNA repair genes. The TP53 analysis revealed one patient carrying the R282W allele mutant, which is associated with TP53 function loss. This breast cancer patient suffered from ER+ and HER2+ disease and reported breast cancer in the mother. After analyzing 108 breast cancer patients, the study found an additional patient with TP53 inherited defect, who suffered from bilateral cancer (in both breasts) and had ER+ but HER2- receptor phenotypes. Overall, the study confirmed the non-random occurrence of TP53 hereditary mutations in breast cancer patients with clinical features of familial disease predisposition. However, it should be further studied why some TP53 mutation carriers experience multiple abnormal masses of tissue (neoplasms) starting from adolescence while others remain cancer-free until around midlife and develop single-site breast cancer diseases.

Racial differences can also cause varying amounts of mutations in triple-negative breast cancer (TNBC), breast cancer that either lacks or shows low levels of ER, progesterone receptor (PR), HER2 overexpression, or gene amplification (American Cancer Society, 2023). A study by Chang et al. (2019) conducted a genomic analysis of TNBC between African Americans (AA) and women of European

descent (CA). Results found the TP53 gene to be the third most frequently mutated gene (61% AA, 77% CA). Although the percentage of TP53 mutations in AA samples was smaller, the actual number of members with the mutation was higher in the AA samples. Despite these varying numbers, mutations of TP53 affected both races similarly by causing a loss of TP53 function and having both increased and decreased gene expression levels. These mutations were caused by frameshifts in the DNA, improper stop codons, and inframe deletions. Overall, the majority of variants occurred in the DNA-binding domain of the TP53 gene and the variants did not differ between races, but these mutations were associated with a higher rate of disease relapse.

Yet despite the malignancy of TP53 mutations, Jia et al. (2022) studying 386,000 Asian and European-ancestry women, with combined data of 165,000 breast cancer individuals, found little relation to TP53. 222 genetic risk loci and 137 genes associated with breast cancer were found, and the signaling pathway for p53 was significantly associated with breast cancer, however, TP53 mutations were detected in only less than 1% of individuals. Likewise, another study about breast cancer genetics in the United Arab Emirates by Altinoz et al. (2020) found 130 patients with positive breast cancer susceptibility genes, of which only 3 cases were associated with TP53. Yet, Jia et al. (2022) detected 15 genes involved in the p53 signaling pathway, showing that TP53 pathways may play a more significant role in the cause of breast cancer than what is currently recognized.

Furthermore, a study by Meiss et al. (2018) found that out of 612 female breast cancer patients who underwent germline testing, only 16 (2.6%) women had mutations in non-BRCA genes. And out of those 16, only four patients had TP53 mutations. Despite small numbers, this study aimed to characterize breast carcinomas in non-BRCA hereditary mutations. Regarding TP53, they found three of the TP53 cases to be associated with LFS and 1 case to be a lobular carcinoma, breast cancer starting from the milk glands (lobules) of the breast. One TP53 case was one of two high-grade or poorly differentiated mutations, carcinomas, and HER2-positive, while three of the four cases were ER-positive. Ultimately, the study's characterization reinforced previous conclusions regarding TP53 mutations.

Current Treatment: What is and can be done?

According to Wahab et al. (2024), LFS is autosomal dominant, making it more likely to be inherited, so patients with TP53 mutations must be screened early and determine if they're carriers. Furthermore, when identifying patients for LFS testing, two sets of criteria should be used: classic LFS criteria and Chompret criteria. A study by Himes & Shuman (2020) aimed to understand hereditary cancer beyond BRCA and found that the use of both criteria increased the detection sensitivity from 40% to 95%. LFS testing should also be considered for patients who do not meet the criteria since TP53 hereditary mutations are often found in women with early-onset breast cancer. Additionally, anyone with a first-degree blood relative with a known TP53 mutation should be tested.

Regarding families, findings of TP53 mutations are difficult due to implications for potential childhood malignancies and for young children families may already have (Eccles et al., 2016). Thus, those families need to know about options for prenatal and preimplantation diagnosis if they are planning to have children in the future. Furthermore, when counseling patients, it is important to consider that younger patients have a higher proportion of truncating mutations rather than missense mutations. This is because repeated exposure to imaging using X-irradiation, like mammograms and PT scanning, can present hazards and challenges for long-term surveillance of at-risk family members.

For breast cancer patients with hereditary mutations, the use of radiation therapy (RT) to treat patients is not well understood. Furthermore, the genetic test multigene panel testing analyzes multiple genes at once to identify mutations, which has improved time and cost-effectiveness. Hence, Chapman et al. (2022) analyzed oncologic outcomes and toxicity after RT in a cohort of breast cancer patients with or without hereditary mutations on multigene panel testing. The study reviewed the records of 286 women who underwent RT and then evaluated rates of overall survival, recurrence, disease-specific death, and radiation-related toxicities. Similar results were found after RT in women with PV hereditary mutations and those in patients without detectable mutations, which supports the use of RT.

Breast RT is a beneficial therapy with minor long-term adverse effects; however, it should be considered with caution for patients with certain PVs.

In contrast, a study by Trombetta et al. (2020) advised against RT for patients with hereditary TP53 mutations. The American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO) conducted a systematic literature review and randomized controlled trials to develop an expert panel regarding locoregional therapy recommendations. Because the p53 gene is a tumor suppressor gene that prevents cancer development, carriers of TP53 mutations would be expected to be unable to repair DNA damage from RT and at risk for RT-associated damage. Thus, the study concluded that RT be avoided for patients with hereditary TP53 mutations and advised mastectomies instead. Specifically, patients should consider risk-reducing mastectomies (RRMs) and breast MRIs (Rosenthal et al., 2017).

Additionally, there are many side effects of cancer therapies, like inducing signaling pathways. A study by McCubrey et al. (2014) focused on targeting breast cancer-initiating cells and current advances in breast cancer research and therapy. Chemo- and radiotherapy can sometimes produce reactive oxygen species (ROS), activating multiple signaling pathways. For example, radiation activates the EGFR1 pathway and the chemotherapeutic drug doxorubicin induces the TP53 pathway. The activation of these signaling pathways can induce transcription genes involved in drug resistance and therefore cause therapeutic resistance. Despite this, numerous other drugs and breast cancer therapies can be used in place. For instance, the anti-diabetes drug metformin has shown some success in treating breast cancer. Metformin acts as a weak mitochondrial poison and prevents oxidative mitochondrial metabolism, which is usually essential for tumor growth. Natural products also exist and can induce autophagy, or self-eating when cells naturally break down old, damaged, or abnormal parts, suppressing malignant transformation but also have the risk of promoting tumor growth. Some examples include ginseng, a medicinal herb that induces cell death, and rottlerin, a plant-derived chemopreventive agent that induces autophagy in breast cancer-inducing cells.

According to Coogan et al. (2023), which aimed to understand adherence to current screening practices and patient guidelines, 5-10% of breast cancer is attributed to hereditary mutations and TP53 is a high penetrance gene for hereditary breast cancer. By surveying patients and using data from manual chart reviews, percentages for adherence to certain treatments were found and generally older age tended to have improved adherence. Ultimately, the main factors influencing adherence to screening practices are education, family members' experience, and recognizing risks, but reliable protocols, responsible providers and patients, and genetic counselors are also crucial. Barriers like access and patient understanding should also be studied.

Overall, TP53 mutations play a critical role in hereditary breast cancer, which is often associated with Li-Fraumeni Syndrome (LFS) and affects the tumor-suppressing functions of the p53 protein. Numerous aspects of TP53 can be analyzed regarding hereditary breast cancer. ctDNA has the potential for early detection and treatment monitoring of hereditary breast cancer, while single nucleotide polymorphisms (SNPs) impact the functionality and structure of TP53 and often occur in hereditary breast cancer, which may affect gene functions and issues in protein sequences. miRNA genes may also indirectly affect p53 expression. Furthermore, estrogen receptor-positive (ER+) and HER2-positive breast cancer are often associated with TP53 mutation carriers, and different populations experience varying mutation frequencies. Ultimately, while the role of TP53 is well-researched, hereditary breast cancer caused by TP53 mutations is generally rare but more aggressive, and the protein's role is still relatively unknown.

Generally, early screening for TP53 mutations, particularly using classic and Chompret criteria, is essential for detecting carriers since these mutations increase the risk of early-onset breast cancer. The effects of radiation therapy (RT) for patients are not well known and are sometimes considered beneficial while other times advised against using due to the risk of damaging DNA. Instead, therapies like mastectomies, breast MRIs, and targeted drugs like metformin, have proven to be alternatives with less harmful side effects. Yet, education and reliable protocols, providers, and patients are also crucial when it comes to treatment.

Conclusion

TP53 plays a vital role in regulating the cell cycle, DNA repair, and apoptosis. Li-Fraumeni Syndrome (LFS) is a rare inherited disorder often caused by gene mutations or damaged DNA and increases the risk of cancers, especially hereditary breast cancer. Thus, TP53 mutations, which cause abnormal cell functions, are associated with LFS and play a key role in hereditary breast cancer. Furthermore, single nucleotide polymorphisms (SNPs) can impact TP53, causing hereditary breast cancer that is often estrogen receptor-positive (ER+) and HER2-positive. Currently, there is no direct treatment for breast cancer, however, mastectomies, breast MRIs, and targeted drugs are recommended while radiotherapy (RT) is advised with caution.

Although countless accounts of research have been done on the role of TP53 mutations in hereditary breast cancer, more research is vital for better understanding since there are still many unknowns about this topic. The specific mechanisms that lead TP53 mutations to cause breast cancer rather than other types of tumorigenesis are still unknown, as well as the reason why some individuals with TP53 mutations develop cancer earlier than others and have different outcomes in terms of risk. Furthermore, it is still inconclusive as to how TP53 mutations affect breast cancer prognosis, treatment outcomes, and whether certain treatments are favorable over others. Population disparities of TP53 mutations also occur, thus increasing the importance of further research regarding TP53 mutations in correlation to hereditary breast cancer. Better knowledge and understanding could improve patient outcomes, ensure more tailored treatments, and reduce cancer mortality.

References

Alanazi, M., Parine, N. R., Shaik, J. P., Naeem, A. A., & Aldhaian, S. (2020, October). Targeted Alanazi, M., Parine, N. R., Shaik, J. P., Naeem, A. A., & Aldhaian, S. (2020, October). Targeted sequencing of crucial cancer causing genes of breast cancer in Saudi patients. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1319562X20302278

Altinoz, A., Ameri, M. A., Qureshi, W., Boush, N., Nair, S. C., & Abdel-Aziz, A. (2020, October). Clinicopathological characteristics of gene-positive breast cancer in the United Arab Emirates. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0960977620301478

Casaubon, J. T., Kashyap, S., & Regan, J.-P. (2024). BRCA1 and BRCA2 Mutations. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470239/#:~:text=BRCA%201%20Mutation.%20Responsible%20for%20approximately%2035%

CDC. (2024, April 16). Hereditary Breast Cancer and BRCA Genes. Bring Your Brave Campaign. https://www.cdc.gov/bring-your-brave/hereditary-breast-cancer/index.html

Chang, C.-S., Kitamura, E., Johnson, J., Bollag, R., & Hawthorn, L. (2019, December). Genomic analysis of racial differences in triple negative breast cancer. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0888754318300454

Chapman, B., Liu, D., Shen, Y., Olamigoke, O. O., Lakomy, D. S., Barrera, A. M. G., Stecklein, S. R., Sawakuchi, G. O., Bright, S. J., Bedrosian, I., Litton, J. K., Smith, B. D., Woodward, W. A., Perkins, G. H., Hoffman, K. E., Stauder, M. C., Strom, E. A., Arun, B. K., & Shaitelman, S. F. (2022, February 1). Breast Radiation Therapy-Related Treatment Outcomes in Patients With or Without Germline Mutations on Multigene Panel Testing. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0360301621028303

Coogan, A., Lunt, L., & Zhang, Y. (2023, November). Screening Practices for Breast and Nonbreast Cancers in High-Risk Mutation Carriers. ScienceDirect. https://www.sciencedirect.com/science/article/abs/pii/S0022480423002445

Eccles, D. M., Li, N., Handwerker, R., Maishman, T., Copson, E. R., Durcan, L. T., Gerty, S. M., Jones, L., Evans, D. G., Haywood, L., & Campbell, I. (2016, March). Genetic testing in a cohort of young patients with HER2-amplified breast cancer. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0923753419355899

Himes, D., & Shuman, H. (2020, July). Hereditary Cancer Syndrome Recognition and Testing: Beyond BRCA. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1555415520301756

Jia, G., Ping, J., Shu, X., Yang, Y., Cai, Q., Kweon, S.-S., Choi, J.-Y., Kubo, M., Park, S. K., Bolla, M. K., Dennis, J., Wang, Q., Guo, X., Li, B, Tao, R., Aronson, K. J., Chan, T. L., Gao, Y.-T., Hartman, M.,…Zheng, W. (2022, December 1). Genome- and transcriptome-wide association studies of 386,000 Asian and European-ancestry women provide new insights into breast cancer genetics. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0002929722004591

Kuba, G., Lester, S. C., Bowman, T., Stokes, S. M., Taneja, K. L., Garber, J. E., & Dillon, D. A. (2021, March). Histopathologic features of breast cancer in Li–Fraumeni syndrome. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0893395222006548

Kwong, A., Shin, V. Y., Au, C. H., Law, F. B. F., Ip, B. K., Wong, A. T. C., Lau, S. S., To, R. M. Y., Choy, G., Ford, J. M., & Chan, T. L. (2016, July). Detection of Germline Mutation in Hereditary Breast and/or Ovarian Cancers by Next-Generation Sequencing on a Four-Gene Panel. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1525157816300277

Maynard, S., Fang, E. F., Scheibye-Knudsen, M., Croteau, D. L., & Bohr, V. A. (2015). DNA Damage, DNA Repair, Aging, and Neurodegeneration. Cold Spring Harbor Perspectives in Medicine, 5(10), a025130. https://doi.org/10.1101/cshperspect.a025130

McCubrey, J., Davis, N. M., Abrams, S. L., Montalto, G., Cervello, M., Libra, M., Nicoletti, F., D'Assoro, A. B., Cocco, L., Martelli, A. M., & Steelman, L. S. (2014, September). Targeting breast cancer initiating cells: Advances in breast cancer research and therapy. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S2212492614000098

Medline Plus. (2020, August 18). TP53 gene: MedlinePlus Genetics. Medlineplus.gov. https://medlineplus.gov/genetics/gene/tp53/

Meiss, A., Thomas, M., Modesitt, S. C., Ring, K. L., Atkins, K. A., & Mills, A. M. (2018, December). Clinicopathologic characterization of breast carcinomas in patients with non-BRCA germline mutations: results from a single institution's high-risk population. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0046817718302387

National Cancer Institute. (2023, March 10). Genetics of Breast and Gynecologic Cancers (PDQ®)–Health Professional Version - NCI. Www.cancer.gov. https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq#:~:text=Associated%20Genes%20and%20Syndromes

Olivier, M., Hollstein, M., & Hainaut, P. (2009). TP53 Mutations in Human Cancers: Origins, Consequences, and Clinical Use. Cold Spring Harbor Perspectives in Biology, 2(1), a001008–a001008. https://doi.org/10.1101/cshperspect.a001008

Petry, V., Bonadio, R. C., Testa, L., Cohn, D., Cagnacci, A., Campos, R. G., Fragoso, M. C. B., & Estevez-Diaz, M. P. (2023, April). A matched case-control study of the prognosis of early breast cancer in patients with Li-Fraumeni syndrome (BREAST TP53). ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0960977623000255

Rosenthal, E., Evans, B., Kidd, J., Brown, K., Gorringe, H., Orman, M., & Manley, S. (2017, April). Increased Identification of Candidates for High-Risk Breast Cancer Screening Through Expanded Genetic Testing. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1546144016310328

Sokolenko, A., Preobrazhenskaya, E. V., Aleksakhina, S. N., Iyevleva, A. G., Mitiushkina, N. V., Zaitseva, O. A., Yatsuk, O. S., Tiurin, V. I., Strelkova, T. N., & Imyantiov, E. N. (2015, April 10). Candidate gene analysis of BRCA1/2 mutation-negative high-risk Russian breast cancer patients. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0304383515000555

Solmaz, A., Yeniay, L., Gökmen, E., Zekioğlu, O., Haydaroğlu, A., Bilgen, I., Özkınay, F., & Onay, H. (2021, December). Clinical Contribution of Next-Generation Sequencing Multigene Panel Testing for BRCA Negative High-Risk Patients With Breast Cancer. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1526820921000707

Trombetta, M., Dragun, A., Mayr, N. A., & Pierce, L. J. (2020, July). ASTRO Radiation Therapy Summary of the ASCO-ASTRO-SSO Guideline on Management of Hereditary Breast Cancer. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S1879850020300990

Vieira, I., Pezzi, E., & Bandeira, I. (2024, March 10). Functional pri-miR-34b/c rs4938723 and KRAS 3′UTR rs61764370 SNPs: Novel phenotype modifiers in Li-Fraumeni Syndrome? ScienceDirect. https://www.sciencedirect.com/science/article/abs/pii/S0378111923009101

Wahab, M., Palaniyandi, T., & Thamada, S. (2024, July 15). Assessment of genome mutation analysis for tumor-informed detection of circulating tumor DNA in patients with breast cancer. ScienceDirect. https://www.sciencedirect.com/science/article/abs/pii/S0009898124020709

World Health Organization. (2024). Cancer Today. Iarc.fr. https://gco.iarc.fr/today/en/dataviz/tables?mode=population&group_populations=0&multiple_populations=1&types=1

Yale Medicine. (2024). Hereditary Breast and Ovarian Cancer Syndrome (HBOC). Yale Medicine. https://www.yalemedicine.org/conditions/hereditary-breast-and-ovarian-cancer-syndrome-hboc

Altinoz, A., Ameri, M. A., Qureshi, W., Boush, N., Nair, S. C., & Abdel-Aziz, A. (2020, October). Clinicopathological characteristics of gene-positive breast cancer in the United Arab Emirates. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0960977620301478