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ORAL CONTRACEPTIVE USE IN BREAST CANCER

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ABSTRACT

Most malignant neoplasms in women, including breast cancer (BrCa), begin in the mammary gland's epithelial tissue. Worldwide, 2,261,419 new cases were anticipated in 2020, making up 11.7% of all cancer cases and resulting in 684,996 fatalities. The mortality rates from BrCa were much greater in industrialized nations than in poorer ones (15.0 vs. 12.8 per 100,000). The majority of instances of breast cancer occur randomly, but around 5–10% are at increased risk due to a genetic predisposition. There is a high death rate and a lack of effective treatments for triple negative breast carcinoma (TNBC), a subtype of breast cancer. Based on clinical data, it may be inferred that areas with high rates of Oral Contraceptive Pill (OCP) use also have high rates of Estrogen Receptor+ (ER+) breast cancer and low rates of TNBC. Based on these findings, we postulate that OCP usage increases the likelihood of ER+ breast cancer while lowering the likelihood of TNBC. Since EGFR is often expressed by TNBC, we sought to distinguish between the effects of estrogen on the formation of ER+ and triple negative breast cancer tumors in our in-vitro investigation by examining the effects on the respective cancer cell lines. It is well-established that in several models, tumor suppression is the outcome of efficient EGFR degradation. The 155 patients hospitalized with primary invasive breast cancer over the course of three years made up this hospital-based observational human research. Information was gathered on ER, PR, HER2 status, clinical categorization, demographics, reproductive history, and OCP use. Two groups were formed from them. Group 1 consisted of 48 individuals who had previously used OCP, whereas group 2 consisted of 107 patients who had never used OCP. The invitro research used 17β-estradiol (E2) to treat MDA-MB-231 cells, and EGFR expression was assessed at various intervals using Cycloheximide chase and western blotting. We used MG-132 to assess the ubiquitination mechanism of EGFR degradation in the MDA-MB-231 cell line. Data was examined with the help of SPSS-20.

KEYWORDS: Breast cancer, estradiol ,cycloheximide, breast tumors, etiology

INTRODUCTION

Most malignant neoplasms in women, including breast cancer (BrCa), begin in the mammary gland's epithelial tissue. Worldwide, 2,261,419 new cases were anticipated in 2020, making up 11.7% of all cancer cases and resulting in 684,996 fatalities. The mortality rates from BrCa were much greater in industrialized nations than in poorer ones (15.0 vs. 12.8 per 100,000). The majority of instances of breast cancer occur randomly, but around 5–10% are at increased risk due to a genetic predisposition. This predisposition may manifest in several ways, including a personal or family history of cancer or inherited mutations. The presence or absence of molecular tumor markers such as estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor 2 (HER2, ERBB2), and a proliferation index (Ki67), in addition to tumor size, tumor grade, and nodal status, can show that BrCa is a diverse disease

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with various intrinsic tumor subtypes. A poorer prognosis and treatment responsiveness are linked to subtype differences in genomic and immunohistochemical markers, unique racial/ethnic occurrence patterns, and aggression levels. The majority of breast cancers are ER-positive (ER+). Luminal A and luminal B are subgroups that make up this category; they are present in around 60% of all malignancies. The subtype known as luminal A (ER+/PgR+/HER2− with low Ki67) accounts for about 40% of all cases. This subtype is marked by a sluggish growth rate, a lack of aggressiveness, a good survival rate, and the best response to hormone treatment. By contrast, the subtype known as luminal B, which may be defined as ER+/PgR+/HER2+ or HER2− with high Ki67, accounts for 10-20% of all cancer cases. This subtype is characterized by a greater relapse rate, histological grade, proliferative index, and a worse relapse survival rate.

Different subtypes of breast cancer may be identified by analyzing gene expression patterns or tumor marker staining. This allows for a more precise classification of this diverse illness. It is probable that these variations in etiology are reflected in the substantial clinical variations brought about by biological heterogeneity. There is growing recognition of triple-negative breast cancer as a category of tumors with important implications for public and clinical health. A basal-like pattern of gene expression is characteristic of triple-negative breast tumors, which comprise 10%-25% of invasive breast cancers. These malignancies are defined by a lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Presently, no targeted medicines exist for the treatment of triple-negative breast cancer, despite the fact that this subtype is linked to more aggressive pathology and a worse prognosis than the more common ER-positive (ER+) subtype. There should be different risk factors for triple-negative and ER+ breast cancers if the molecular profiles of the tumors are known from the start. The origin and profile of risk factors for triple-negative tumors are not well known, despite the fact that several research have detailed risk factors for ER+ breast cancer.

LITREATURE REVIEW

Banday (2024) Purpose: There is a lack of information on how different molecular and receptor subtypes affect breast cancer (BC) in settings with low resources. In this retrospective research involving a single location in northern India, we examine the results of several molecular subtypes of BC. Procedures and Materials: All women who had treatment for BC at our State Cancer Institute between 2014 and 2018 were included. Clinicopathological characteristics and details of the follow-up were analyzed in the data. The four subtypes of malignancies used for data analysis were HR+HER2-, HR+HER2+, HR-HER2+, and HR-HER2-. Findings: Out of 944 patients analyzed, HR+HER2- was the most prevalent subtype at 49.1%, while HR+HER2+ was the least common at 13.1%. The subtype of receptor had a substantial effect on overall survival (OS). Three-year overall survival rates of 94.3% and 69.1%, respectively, were recorded for HR+HER2- and HRHER2-negative tumors. For patients with tumor grades II and III, disease stages II and III, and age groups of less than 40 and 40-60 years, respectively, the molecular subtype remained a significant factor in overall survival (OS). In each grouping, HR-HER2-cancers had the lowest cumulative survival rate. The prognosis for patients with metastatic BC was bleak regardless of molecular subtype, with the exception of HR+HER2. Conclusions:

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Triple negative BC patients fared the worst in terms of overall and subgroup outcomes. The immediate requirement to enhance long-term results for these patients is to guarantee optimum treatment usage, which includes affordable access to customized, individual therapy.

Min (2024) For many years, the mainstay of treatment for estrogen receptorexpressing breast cancer patients has been endocrine therapy, which inhibits estrogen receptor signaling. The problem of medication resistance, however, is a major obstacle in clinical practice. Hence, developing novel therapeutic drugs capable of inhibiting ERα activity is of utmost importance, especially in instances where ESR1 mutations are present. Next generation ER-targeted agents, such as oral selective ER degraders and proteolysis-targeting chimera ER degraders, as well as other novel molecules like selective estrogen receptor covalent antagonists and complete estrogen receptor antagonists, are highlighted in this review of recent drug development efforts. Each chemical's medicinal design, effectiveness, and clinical trials are described in depth here.

Ogayo (2024) Review Objectives Black women had a greater death rate from hormone receptor-positive, HER2-negative (HR + HER2-) breast cancer, despite a lower prevalence of the disease overall. Risk factors, tumor biology, therapy, and socioeconomic determinants of health are the four domains covered by the existing data in HR + HER2- breast cancer that exhibit inequalities. New Discoveries Even after controlling for potential confounders, racial differences are still present in a number of breast cancer- related outcomes for women who have HR + breast cancer. This highlights the many causes of differences in breast cancer outcomes.

Yip (2014) Among female cancers, breast cancer is by far the most prevalent. Overexpression of estrogen receptors (ERs) and progesterone receptors (PRs) is seen in most breast tumors. Tamoxifen and other hormone receptortargeting medications have greatly improved survival rates for women whose breast tumors tested positive for these receptors. Accurate testing is crucial for patient treatment, which is why quality assurance is essential for ER and PR data. Recent recommendations suggest that cells staining positive for ER and PR should be considered positively stained if their percentage is one percent or above. For prognostic and treatment purposes, semiquantitative evaluation of ER and PR is crucial. The most important prognostic and predictive biomarker is still hormone receptor status, even if genetic assays have been developed.

Mohapatra (2018) Although exceedingly uncommon in men, breast cancer is a prevalent malignancy in females. Breast cancer occurs when the cells in the breast begin to multiply uncontrolled. One out of every eight women will be diagnosed with breast cancer at some point in their life. This invasive malignancy is second only in cancer-related deaths to lung cancer. There are a number of risk factors that may lead to the development of breast cancer from breast tissue. Breast cancer risk factors include being overweight, using birth control pills, consuming alcohol, being childless or a late mother, and having thick breasts. It is crucial for the therapy of breast cancer to investigate the many kinds of receptors linked to the disease's etiology. With an emphasis on triple-negative breast cancer (TNBC), this research reviews the results about the role of several receptors in breast cancer. Alsaiari (2024) The most common

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types of cancer include breast, lung, colonrectum, and prostate cancers. Of these, 2.26 million cases and about 685,000 deaths will be caused by breast cancer in 2020. The disease usually starts in the milk ducts or lobules, which are responsible for producing and transporting milk during lactation. Treatment is becoming more difficult as tissues develop resistance, prompting the urgent need for new multitargeted drugs. Fortunately, there is an improved solution: multitargeted drug design. By concurrently targeting many routes, this design ensures that the medicine will still be effective for other pathways, even if it resists one. In this study, we included four crucial proteins that perform signalling, receptor, and regulatory action, namely- NUDIX Hydrolases, Dihydrofolate Reductase, HER2/neu Kinase and EGFR and performed multitargeted molecular docking studies against human-approved drugs using HTVS, SP and extra precise algorithms and filtered the poses with MM\GBSA, suggested a benzodiazepine derivative chlordiazepoxide, used as an anxiolytic agent, can be a multitargeted inhibitor with docking and MM\GBSA score ranging from − 4.628 to − 7.877 and − 18.59 to − 135.86 kcal/mol, respectively, and the most interacted residues were 6ARG, 6GLU, 3TRP, and 3VAL. Chlordiazepoxide has the potential to be a multitargeted inhibitor of breast cancer, according to QikProp-based ADMET and DFT calculations that demonstrated the drug candidate's suitability and stability. Subsequently, 100 ns MD simulations in water and MMGBSA on trajectories confirmed the candidate's stability and performance, and numerous intermolecular interactions strengthened the complexes. Nevertheless, prior to its use, experimental validation is necessary.

Curigliano (2024) Around 60% of breast tumors that do not express human epidermal growth factor receptor 2 (HER2) (HER2-low) when diagnosed with immunohistochemistry (IHC) 1þ or IHC 2þ/in situ hybridization (ISH) are considered to have this characteristic. Many breast tumors, including those that are hormone receptor-positive (up to 85%) or triple-negative (up to 63%), fall into the category of HER2-low. After the DESTINY-Breast04 study shown that tumors with low HER2 expression may be targeted, trastuzumab deruxtecan (T-DXd) was approved as the first HER2-directed medication for the treatment of HER2-low breast cancer in Europe and the US. Concerns around HER2 evaluation and patient identification are just two of many that have arisen as a consequence of this shift in the therapeutic environment.in order to determine whether patients are suitable for T-DXd, it is necessary to thoroughly evaluate their HER2 expression. Regarding sample kinds, scoring and reporting HER2 status, testing methodologies and assays, and the identification of individuals with HER2-low breast cancer, this review offers background. Management of significant adverse events associated to T-DXd is also covered. The current data suggests that T-DXd is effective for patients who have a history of IHC 1þ or IHC 2þ/ISH scores. However, more study might narrow down the target group for T-DXd or other HER2-directed treatments and find new ways to identify individuals. Due to the fact that HER2 expression might alter as the illness advances or as a result of therapy, and that there is some variation in the scoring and interpretation of HER2 status, it may be necessary to reevaluate certain situations in order to find additional individuals who could benefit from T-DXd.

Khan (2022) Both sexes rely on estrogen to regulate a wide range of physiological and pathological processes. In both premenopausal and postmenopausal women, several health issues may be attributed to 17βestradiol, an endogenous estrogen.

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Endogenous estrogen is primarily controlled by nuclear estrogen receptors (ERs) ERα and ERβ, however cell proliferation and death are also regulated by non-genomic cytoplasmic mechanisms. When it comes to the development and advancement of breast cancer, estrogen played a crucial part. A comprehensive and extensive examination of estrogen receptors is offered in this review, which hyphenates several papers pertaining to ERs. This study covers several facets of estrogens, including receptor types, structures, isoforms, signaling pathways, crystal structures, pathogenic functions, ER ligands, and therapeutic techniques to overcome resistance. It also discusses ERα, ERβ, and GPER.

METHEDOLOGY

TYPE OF STUDY: Future research

STUDY DESIGN: Investigation based on observation

DURATION OF COLLECTION OF DATA: Observational research from August 2022 to November 2024

PLACE OF CONDUCT OF RESEARCH: Research involving humans: SDM university of health sciences and hospital, Dharwad.

STUDY POPULATION:

The sample was selected from our institution's outpatient and inpatient departments. The research included 155 people with breast cancer. Two groups were formed from the total number of breast cancer patients recruited. Forty-eight women with breast cancer who had been on the pill for at least six months and had a certain molecular subtype made up Group 1. For Group 2, we included 107 age-matched controls who had never used an oral contraceptive pill and had breast cancer of various molecular subtypes.

SAMPLE SIZE CALCULATION

Research will be able to assess the association between using the oral contraceptive pill (OCP) and the expression pattern of distinct molecular subtypes of breast cancer with a sample size of 151 patients, a 95% confidence level, and a margin of error of ±8%. The computation was carried out by use of the formula: n = z2p(1-p)/d2

where Z= z statistic at 5% level of significance d is margin of error The highest possible expected incidence of breast cancer is denoted by p.

RESULTS

Table 1 shows that there was no statistically significant difference in age between those who used OCP and those who did not. In comparison to non- users, OCP users had a mean age of 47.6.5 years. Those who used OCP and those who did not did not vary significantly in terms of height, weight, or body mass index. Breast cancer parity, age of menarche (AOM), menopausal status, breastfeeding status, and cancer stage at admission were not significantly different between OCP users and non-users. When

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comparing OCP users to non-users, there was no statistically significant difference in the stage of basallike (TNBC) patients. In Table 2, Cases tended to take OCP for an average of one year and three months. Vase Ki-67 levels did not differ significantly between OCP users (31.4±18.3) and non-users (33.4±21.3), with a p-value of just 0.480.

Table-1: Demographic characters, parity and Age of menarche (AOM) of breast cancer patients in OCP users and non-users

	OCP users	OCP non users	T value	P value
	(N=48)	(N=107)		
Age (yrs)	47.6±8.4	49.8±8.1	-1.482	0.139
Height (cm)	147±31	138.2±44	1.322	0.188
Weight (Kgs)	57.4±9.8	58.3±3	-0.515	0.607
BMI (Kg/M^2)	24.1±3.6	24.3±3.3	-1.972	0.051
Parity	2.59±0.9	2.98±1.8	-1.273	0.206
AOM (yr)	13.02±0.5	13.19±0.6	-1.434	0.154

* ($p < 0.05$); BMI: Body mass index; AOM: Age of menarche

Table-2: Reproductive history, family history of breast cancer (FHBC) and stage of breast cancer patients in OCP users and non-users.

	OCP users (N=48)	OCP non users (N=107)	Chi square value	p-value	Odds Ratio
FHBC	3 (6.6)/45	11 (10.2)/96	0.655	0.316	0.582 [0.155-2.188]
Nulliparity	7 (14.50/41	21 (19.6)/85	0.607	0.295	0.691 [0.272-1.757]

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Menopause	38 (79.1)/9	91 (85)/15	0.433	0.289	0.696[0.280-1.727]
HOBF	40 (83.3)/8	85 (79.4)/21	0.214	0.412	1.235 [0.504-3.029]
Stage 2	9 (18.7)	19 (17.7)	3.352	0.187	
3	28 (58.3)	48 (44.8)			
4	11 (22.9)	40 (37.3)			

* ($p<0.05$); FHBC: Family history of breast cancer; HOBF: History of breast feeding. (Values in the brackets are in percentage)

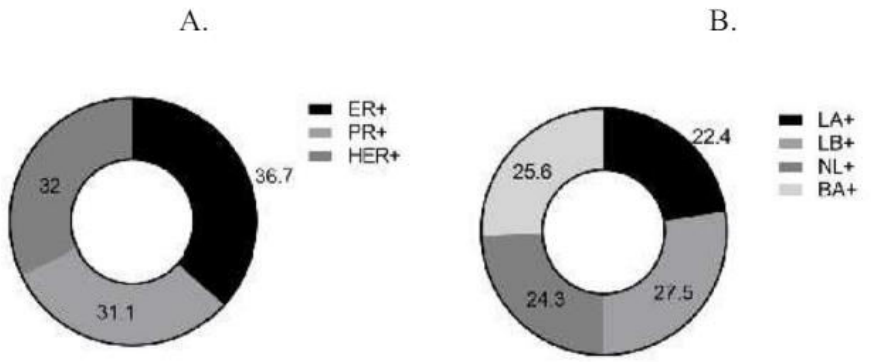

Figure1: (A) Distribution of Estrogen Receptor+ (ER+), Progesterone Receptor+ (PR+) and Human Epidermal Growth Factor Receptor 2+ (HER2+ in total number of cases. (B) Distribution of Luminal A (LA), Luminal B (LB), Non luminal (NL)/ HER2+ enriched and Basal like (BA)/TNBC in total number of cases. (Values are in percentage)

CONCLUSION

Molecular subtypes ER+, PR+, and Luminal B breast tumors were more common in OCP users compared to non-users, according to observations from human studies. When comparing OCP users to non-users, the age at admission for ER+ cancer was significantly lower in the former group (45.3 years) than in the latter (52.2 years). Alternatively, compared to non-users (45.4 years), patients with basal (TNBC) cancer who were OCP users were older at the time of admission (53.1 years). Logistic analysis showed that compared to nonusers, OCP users had an 18% greater risk of TNBC and an 8% lower risk of ER+, PR+, and Luminal B, respectively, with each additional year of age. The expression of EGFR was shown to be decreased in an in-vitro investigation using the MDA-MB-231 cell line treated with β-estradiol and a cycloheximide chase. It seems that estrogen destroys EGFR via the ubiquitination route, as EGFR expression did not decrease under treatment with MG-132 and E2. We found that ER+, PR+, and Luminal B breast cancer rates may rise in association with OCP usage. In fact, there is some evidence that OCP usage is associated with a

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slowed advancement of TNBC. Results from an in vitro experiment showed that estrogen ubiquitinates EGFR in MDA-MB-231 cells, destroying the protein.

REFERENCE

1. Khan, Muhammad & Uzair, Muhammad & Nazli, Adila & Chen, JianZhong. (2022). An overview on Estrogen receptors signaling and its ligands in breast cancer. European Journal of Medicinal Chemistry. 241. 114658. 10.1016/j.ejmech.2022.114658.

2. Curigliano, G. & Dent, R. & Earle, H. & Modi, S. & Tarantino, P. & Viale, G. & Tolaney, S.M. (2024). Open questions, current challenges, and future perspectives in targeting human epidermal growth factor receptor 2-low breast cancer. ESMO Open. 9. 102989. 10.1016/j.esmoop.2024.102989.

3. Shaikhali Barodawala (2024). Immunohistochemical Characterization of Breast Carcinoma: Clinical Correlations, Molecular Subtypes, and Therapeutic Implications. Archives of Breast Cancer. 11. 108-117. 10.32768/abc.2024112116-117.

4. Alsaiari, Ahad & Gharib, Amal & Bakhuraysah, Maha & Alrehaili, Amani & Algethami, Shatha & Alsaif, Hayfa & Harthi, Norah & Hakami, Mohammed. (2024). Chlordiazepoxide against signalling, receptor and regulatory proteins of breast cancer: a structure-based in-silico approach. Medical Oncology. 41. 10.1007/s12032-024-02366-w.

5. Mohapatra, Shuvendu & Dash, Anshurekha & Jena, Manoj. (2018). Receptors associated with Pathogenesis of Breast Cancer: A MiniReview. 21. Yip, Cheng-Har & Rhodes, Anthony. (2014). Estrogen and progesterone receptors in breast cancer. Future oncology (London, England). 10. 2293- 301. 10.2217/fon.14.110.

6. Ogayo, Esther & Mittendorf, Elizabeth & Kantor, Olga. (2024). Disparities in Hormone Receptor-Positive Breast Cancer. Current Breast Cancer Reports. 16. 1-10. 10.1007/s12609-024-00529-2.

7. Min, Jian & Liu, Xin & Peng, Rouming & Chen, Chun-Chi & Wang, Wei & Guo, Rey-Ting. (2024). New generation estrogen receptor-targeted agents in breast cancer: present situation and future prospectives. Acta Materia Medica. 3. 10.15212/AMM-2024-0006.

8. Banday, Saquib & Ayub, Maniza & Ahmed, Z & Banday, Aaqib & Naveed, Shah & Guru, Faisal & Mir, Mohmad & Akhter, Shareefa & Bhat, Mudasir & Yaseen, Syed & Afroz, Fir & Bhat, Gull & Lone, Mohammad & Aziz, Shiekh. (2024). Receptor subtype and outcome of breast cancer -Single-center experience from north India. 10.4103/jcrt.jcrt_56_23. 25.

9. Malmgren, Judith & Atwood, Mary & Kaplan, Henry. (2012). Breast Cancer Detection Method Among 20- to 49-Year-Old Patients at a Community Based Cancer Center: 1990-2008. The breast journals. 18. 257-60. 10.1111/j.1524-4741.2012.01231. x.

ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 11, Issu 13, 2022

10. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)- negative, and HER2-negative invasive breast cancer, the so-called triple- negative phenotype: a population-based study from the California Cancer Registry. Cancer. 2007; 109:1721–1728. Doi: 10.1002/cncr.22618.

11. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst. 2011; 103:250–263. Doi: 10.1093/jnci/djq526.

12. Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell LL, Rosenberg L. Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. Cancer Epidemiol Biomarkers Prev. 2011; 20:1883–1891. Doi: 10.1158/1055-9965.EPI-11-

13. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev. 2004; 13:1558–1568.