International Journal of Multidisciplinary Research and Growth Evaluation.

The Relationship between oral Contraceptive Use, Mammographic Breast Density, and Breast Cancer Risk

Kayode Ademola MATTHEW [1*], Folakemi Mercy AKINWALE [2], Frank Nwaogelenya OPIA [3], Abiola Adenike ADEBIYI [4]

[1, 3] Accident and Emergency Department, Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria
[2] School of Science and Computer Studies, Department of Science, Federal Polytechnic, Ade-Ekiti, Nigeria
[4] Faculty of Dentistry, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria

* Corresponding Author: **Kayode Ademola MATTHEW**

Article Info

ISSN (online): 2582-7138
Volume: 02
Issue: 06
November-December 2021
Received: 06-11-2021
Accepted: 05-12-2021
Page No: 390-400

Abstract
One of the most used hormonal contraceptive treatments in the world, oral contraceptives (OCs) provide substantial advantages for hormone management and family planning. However, a lot of study has been done on their possible effects on breast tissue and long-term health hazards, including breast cancer. This study synthesizes data from epidemiological and clinical research to examine the intricate relationship between OC usage, mammographic breast density, and breast cancer risk. The hormonal makeup of OCs, especially estrogen and progestin, may have an impact on mammographic breast density, a known independent risk factor for breast cancer. The slightly increased risk of breast cancer seen in current or recent OC users is therefore believed to be partially mediated by higher breast density. Key findings highlight that the degree of risk varies depending on factors such as age, duration of OC use, hormonal formulation, and genetic predispositions. While the absolute increase in breast cancer risk associated with OCs remains small for most women, it holds greater significance for those with high-risk profiles. The review also identifies gaps in knowledge regarding the effects of modern low-dose OC formulations and variations across diverse populations. This synthesis emphasizes the importance of informed contraceptive choices, individualized risk assessments, and enhanced screening protocols for women at higher risk of breast cancer. Furthermore, it underscores the need for interdisciplinary research to explore molecular mechanisms, develop safer contraceptive options, and address unresolved questions. By advancing our understanding of these relationships, healthcare providers can better guide women in making decisions that prioritize both reproductive health and long-term well-being.

DOI: https://doi.org/10.54660/.IJMRGE.2021.2.6.390-400

Keywords: Oral Contraceptive, Use, Mammographic, Breast Density, Breast Cancer, Risk

1. Introduction

One of the most used methods of birth control in the world is oral contraceptives (OCs), sometimes known as birth control tablets. OCs have transformed reproductive health since they were first introduced in the 1960s, giving women a practical and efficient way to avoid unwanted pregnancies (Christin-Maitre, 2013). Oral contraceptives are a vital component of family planning efforts, with over 151 million women using them globally, according to the World Health Organization (WHO). About 14% of women between the ages of 15 and 49 in the US alone report using oral contraceptives (Daniels & Abma, 2020). The main ingredients of oral contraceptives are synthetic forms of the hormones progestin and estrogen. Oral contraceptives are primarily composed of synthetic versions of the hormones estrogen and progestin. These hormones work synergistically to inhibit ovulation, alter cervical mucus to prevent sperm penetration, and thin the endometrial lining to reduce the likelihood of

implantation (Burkman *et al*., 2011). Despite their benefits, the hormonal components of OCs have been linked to various side effects, including their potential impact on breast tissue. Hormonal fluctuations caused by OCs are known to affect breast physiology, raising questions about their relationship with mammographic breast density, a recognized risk factor for breast cancer (Grindlay *et al*., 2013). Mammographic breast density refers to the proportion of fibroglandular tissue relative to fatty tissue in the breast, as visualized on a mammogram. Breast density is categorized into four levels based on the Breast Imaging-Reporting and Data System (BI-RADS): almost entirely fatty, scattered fibroglandular densities, heterogeneously dense, and extremely dense (Boyd *et al*., 2007). Approximately 40–50% of women undergoing mammography have dense breasts, categorized as either heterogeneously or extremely dense (McCormack & dos Santos Silva, 2006). High breast density is a well-established risk factor for breast cancer. Women with extremely dense breasts are four to six times more likely to develop breast cancer compared to those with predominantly fatty breasts (Boyd *et al*., 2010). The increased risk is attributed to the higher concentration of glandular and stromal tissue, which are more susceptible to carcinogenic processes. Additionally, dense breast tissue can obscure lesions on mammograms, reducing the sensitivity of breast cancer screening and potentially delaying diagnosis (Kolb *et al*., 2002). Understanding the interplay between oral contraceptive use and mammographic breast density is critical for women's health. OCs are known to modulate hormonal levels, which may influence breast tissue composition and, consequently, breast density (Tamimi *et al*., 2006). This relationship has implications for breast cancer risk, as increased breast density is independently associated with higher cancer susceptibility. Given the widespread use of OCs, particularly among young women, investigating their potential impact on breast density and cancer risk is essential for developing evidence-based guidelines for contraceptive use and breast cancer screening. Furthermore, understanding this relationship can empower women to make informed decisions about their reproductive health while considering their long-term cancer risk (Kennedy *et al*., 2019).

This review aims to synthesize existing research on the relationships between oral contraceptive use, mammographic breast density, and breast cancer risk. Specifically, it seeks to evaluate how OCs influence breast density, examine the association between breast density and cancer risk, and explore the potential interplay among these factors (Upadhya *et al*., 2017). The review will critically analyze key findings from epidemiological and clinical studies, highlight inconsistencies and gaps in the literature, and provide recommendations for future research. By addressing these topics, the review aims to contribute to a deeper understanding of the implications of OC use for breast cancer risk and inform healthcare providers and policymakers about best practices for contraceptive counseling and cancer prevention (Shah *et al*., 2018).

2.0 Methodology

This study employs the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology to investigate the relationship between oral contraceptive (OC) use, mammographic breast density (MBD), and breast cancer risk. The systematic review was initiated with a comprehensive search of databases including PubMed, Scopus, and Web of Science to identify relevant peer-reviewed studies. The search strategy was constructed using keywords such as "oral contraceptives," "mammographic breast density," and "breast cancer risk," combined with Boolean operators. Inclusion criteria focused on studies published in English, with human subjects, that evaluated the association between OC use and either MBD or breast cancer risk. Exclusion criteria included studies with incomplete data, those involving non-human subjects, and studies with overlapping cohorts.

All retrieved studies were imported into a reference management system, and duplicates were removed. The remaining records were screened independently by two reviewers at the title and abstract levels, followed by a full-text review for eligibility. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer. Data extraction was performed using a standardized form to capture relevant information, including study design, population characteristics, OC usage details (duration, type, and dosage), mammographic density measurements, and breast cancer outcomes.

The quality of included studies was assessed using validated tools such as the Newcastle-Ottawa Scale for observational studies and the Cochrane risk-of-bias tool for randomized controlled trials. Key variables included OC usage patterns, percent mammographic density, dense area, and breast cancer incidence. Covariates such as age, body mass index, and hormonal levels were recorded to adjust for potential confounding factors.

Statistical analysis involved a meta-analysis of the extracted data. A random-effects model was applied to calculate pooled estimates of effect sizes, odds ratios, and 95% confidence intervals for the relationship between OC use, MBD, and breast cancer risk. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated through funnel plots and Egger's test. Sensitivity analyses were conducted to assess the robustness of results by excluding low-quality studies and studies with extreme effect sizes.

Data from eligible studies were also used to develop predictive models for breast cancer risk using machine learning techniques. Models such as logistic regression, random forest, and support vector machines were trained on combined datasets to evaluate the interaction between OC use, MBD, and breast cancer outcomes. Model performance was evaluated using metrics such as area under the curve (AUC) and accuracy, and external datasets were used for validation.

This PRISMA-guided approach ensures a transparent and reproducible methodology, integrating systematic review and advanced analytics to explore the complex relationship between OC use, mammographic density, and breast cancer risk. The findings will inform evidence-based guidelines for clinical practice and public health interventions. The flowchart is shown in figure 1.

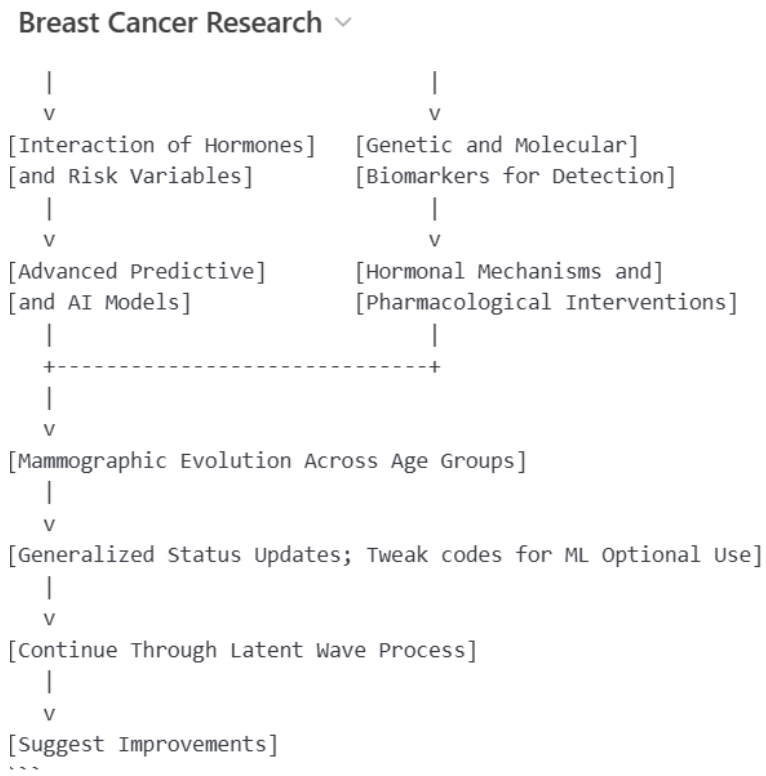

Fig 1: The flowchart of the methodology used

2.1 Oral Contraceptives (OCs)

According to their hormonal makeup, oral contraceptives (OCs) can be divided into two main categories: progestin-only pills (POPs) and combination oral contraceptives (COCs) (Renner & Jensen, 2011). Progestin, a synthetic version of progesterone, and estrogen, usually ethinyl estradiol, are the two artificial hormones found in COCs. The progestin thickens cervical mucus to limit sperm entrance and modifies the endometrial lining to prevent implantation, while the estrogen component suppresses ovulation by inhibiting follicle-stimulating hormone (FSH) (Burkman *et al*., 2011). Because of their great effectiveness and extra advantages, such controlling menstrual cycles and lowering the risk of ovarian and endometrial malignancies, COCs are the most often prescribed kind of OCs (Cipriani *et al*., 2020). Also known as "mini-pills," POPs contain only progestin, making them suitable for women who cannot tolerate estrogen or have contraindications such as a history of thromboembolic disorders (Shukla *et al*., 2017). POPs primarily work by thickening cervical mucus and altering the endometrial lining, with ovulation suppression occurring in approximately 50% of users (Nelson, 2019). POPs are often prescribed to breastfeeding women or those with specific health conditions. Beyond these two main types, there are newer formulations such as extended-cycle pills, which reduce the frequency of withdrawal bleeding, and low-dose pills, designed to minimize hormonal side effects.

Oral contraceptives exert their effects by manipulating the endocrine system to suppress the natural hormonal fluctuations of the menstrual cycle (Hampson, 2020). This hormonal alteration also affects breast tissue. Estrogen stimulates the proliferation of ductal and stromal cells in the breast, contributing to increased breast tissue density. The prolonged exposure to synthetic estrogen in COCs may amplify this effect, leading to changes in mammographic density (Greendale *et al*., 2003). Progestin has a dual effect: it promotes differentiation of breast tissue but may also enhance the proliferative effects of estrogen under certain conditions (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). These hormonal effects on breast tissue could potentially increase the susceptibility to DNA damage, a precursor to carcinogenesis (De Leo *et al*., 2016). The duration of oral contraceptive use is a critical factor in determining the cumulative hormonal exposure a woman receives. Women who begin using OCs at an early age or continue use for extended periods are exposed to higher cumulative doses of synthetic hormones. Several epidemiological studies have suggested that prolonged OC use, particularly over 10 years, may slightly increase the risk of breast cancer in premenopausal women (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). However, the risk appears to diminish over time after cessation of use, with no significant increase in risk observed after 10 years of discontinuation (Hunter *et al*., 2010). Women who initiate OC use during adolescence, a period of breast development, may be more susceptible to hormonal changes that affect breast tissue density. Long-term use has been associated with persistent increases in mammographic density, which is a known risk factor for breast cancer. Oral contraceptive formulations have evolved significantly since their introduction. Early formulations contained high doses of estrogen (50–150 micrograms of ethinyl estradiol) and were associated with a higher risk of side effects, including thromboembolic events and breast cancer (Harvey and Bovbjerg, 2004). Modern formulations now use much lower doses (10–35 micrograms), aiming to reduce adverse effects while maintaining contraceptive efficacy (Smith *et al*., 2003). Studies have shown that higher-dose estrogen formulations are more likely to increase breast density compared to low-dose alternatives. For example, Tamimi *et al*. (2006) reported that women using high-estrogen OCs had significantly higher mammographic density than non-users. Modern low-dose formulations may reduce this effect, although more research is needed to confirm their long-term impact on breast density. Differences in progestin types across formulations may also influence breast cancer risk. For instance, second-generation

progestins (e.g., levonorgestrel) have a stronger androgenic effect, while third-generation progestins (e.g., desogestrel) are more selective for progesterone receptors, potentially affecting breast tissue differently (Burkman *et al*., 2011). Understanding these variations is critical for evaluating the safety of newer contraceptive options.

2.2 Mammographic Breast Density

Mammographic breast density refers to the proportion of fibroglandular (dense) tissue relative to fatty (non-dense) tissue in the breast, as visualized on a mammogram. Dense breast tissue appears white or bright on a mammogram, while fatty tissue appears darker (Boyd *et al*., 2011). This density is determined by the relative amount of glandular, connective, and stromal tissue compared to fatty tissue in the breast (Boyd *et al*., 2007). Mammographic density is influenced by genetic, hormonal, and environmental factors, and it varies across individuals and age groups. The Breast Imaging-Reporting and Data System (BI-RADS), developed by the American College of Radiology, is the standard classification system used to categorize breast density. BI-RADS assigns breast density into four categories based on the proportion of dense tissue visible on a mammogram; The breast is almost entirely composed of fatty tissue, with minimal fibroglandular tissue (<25%). There are scattered areas of dense tissue, but the majority of the breast is fatty (25–50%). There is significant dense tissue that may obscure small masses (51–75%). The breast is composed of a high proportion of dense tissue, making it difficult to detect abnormalities (>75%) (American College of Radiology, 2013).

Breast density is typically assessed during routine mammography screenings and has both diagnostic and prognostic implications (Azam *et al*., 2020). Women with heterogeneously or extremely dense breasts are considered to have high breast density, which is associated with an increased risk of breast cancer and reduced sensitivity of mammograms in detecting tumors (McCormack & dos Santos Silva, 2006). Breast Density as a Risk Factor for Breast Cancer, High mammographic breast density increases breast cancer risk through several biological mechanisms: Increased Cell Proliferation: Dense breast tissue contains higher amounts of epithelial and stromal cells, which are more susceptible to carcinogenic changes due to increased cell turnover and DNA replication errors (Yaghjyan *et al*., 2015). Hormonal Sensitivity: Dense tissue is more responsive to estrogen and other hormonal signals, which may promote the growth of estrogen receptor-positive (ER+) breast cancers (Boyd *et al*., 2010). Masking Effect: Dense tissue can obscure the presence of tumors on mammograms, leading to delayed detection and treatment. This reduced diagnostic accuracy can result in more advanced disease at diagnosis (Kolb *et al*., 2002). Microenvironment Changes: The stromal and glandular composition of dense tissue creates a pro-inflammatory microenvironment, which may enhance tumor initiation and progression.

Numerous studies have demonstrated that mammographic breast density is one of the strongest independent risk factors for breast cancer. For example, Boyd *et al*. (2007) found that women with extremely dense breasts are 4–6 times more likely to develop breast cancer than those with almost entirely fatty breasts (Yaghjyan *et al*., 2012). A meta-analysis by McCormack and dos Santos Silva (2006) further confirmed the association between breast density and breast cancer risk, reporting a significant dose-response relationship. Women with high-density breasts not only have a higher incidence of breast cancer but also face challenges in early detection, contributing to poorer outcomes (Tesic *et al*., 2013). The magnitude of the risk is comparable to or even greater than that of other established risk factors, such as a family history of breast cancer or carrying BRCA1/2 mutations. This makes breast density an important focus of cancer prevention and screening strategies.

Hormonal Influence on Breast Density, Hormones play a critical role in the regulation of breast tissue development and composition. Estrogen and progesterone, in particular, influence the proliferation and differentiation of epithelial and stromal cells in the breast (Kanadys *et al*., 2021). These hormones increase the amount of glandular and connective tissue, leading to higher breast density. Estrogen: Stimulates ductal growth and stromal cell proliferation, leading to an increase in fibroglandular tissue. Progesterone: Promotes lobular development and enhances the effects of estrogen, further contributing to increases in breast density (Tamimi *et al*., 2006). These hormonal effects are most pronounced during reproductive years and decrease with menopause as endogenous hormone levels decline. Oral contraceptives, which contain synthetic estrogen and progestin, mimic the effects of endogenous hormones and can influence breast tissue composition (Ramón *et al*., 2015). The degree of change in breast density associated with OCs depends on factors such as the dose and type of hormones, duration of use, and individual hormonal sensitivity. Evidence from Studies: Tamimi *et al*. (2006) found that premenopausal women using oral contraceptives had significantly higher mammographic density compared to non-users. However, the increase in density was often reversible upon discontinuation of OCs. Formulation Variations: Modern low-dose formulations may have a reduced impact on breast density compared to older high-dose formulations, although more research is needed to confirm these differences (Burkman *et al*., 2011). Prolonged OC use results in cumulative exposure to synthetic hormones, which may increase breast density over time. Women who begin using OCs at an early age, when breast tissue is still developing, may experience greater changes in density compared to women who initiate use later in life (Moore *et al*., 2020). The relationship between OC use, breast density, and breast cancer risk underscores the need for individualized contraceptive counseling, particularly for women with other risk factors for breast cancer. Screening strategies should also account for breast density to improve early detection rates in this population.

2.3 Breast Cancer Risk and Oral Contraceptives

2.3.1 Epidemiological Evidence

The relationship between oral contraceptive (OC) use and breast cancer risk has been extensively studied, with findings indicating a complex interplay between hormonal exposure and individual risk factors (Brinton *et al*., 1995). While OCs offer significant reproductive health benefits, such as contraception and regulation of menstrual cycles, their potential influence on breast cancer development remains a topic of concern. Epidemiological studies have consistently reported a slight increase in the risk of breast cancer among current and recent users of oral contraceptives, particularly in younger women. A meta-analysis conducted by the Collaborative Group on Hormonal Factors in Breast Cancer (1996) examined data from over 50 studies and found that women who were currently using OCs or had used them within the past 10 years had a 20–30% increased risk of breast cancer compared to non-users (Marchbanks *et al*., 2012). However, this increased risk diminishes gradually after cessation, with no significant excess risk observed 10 years after discontinuation. Similarly, a systematic review

by Gierisch *et al*. (2013) corroborated these findings, noting that OC use slightly elevates breast cancer risk, particularly for premenopausal women and those under 40 years of age (Beaber *et al*., 2014). The study highlighted that the relative risk (RR) is higher for estrogen receptor-positive (ER+) cancers, indicating that the hormonal components of OCs may stimulate breast tissue growth in susceptible individuals (White, 2018). Duration of Use: Prolonged OC use is associated with a cumulative increase in hormonal exposure, which may heighten breast cancer risk. Women who use OCs for more than 10 years show a marginally higher risk compared to those with shorter durations of use (Collaborative Group on Hormonal Factors in Breast Cancer, 2019). However, the absolute increase in risk remains small, and the benefits of OCs often outweigh these risks for many women. Age at First Use: The age at which a woman begins using OCs significantly influences her risk (Beaber *et al*., 2014). Initiating OC use during adolescence or early adulthood, when breast tissue is still developing, may result in greater hormonal sensitivity and an increased likelihood of carcinogenic changes (Hunter *et al*., 2010). Women who begin using OCs after their mid-20s, when breast tissue development stabilizes, appear to have a lower risk. Cessation of Use: The increased risk of breast cancer associated with OCs declines over time after discontinuation. Studies suggest that 10 years after stopping OC use, the risk of breast cancer returns to levels similar to those of women who have never used OCs (Iversen *et al*., 2017). This reversibility is an important consideration for women weighing the long-term risks and benefits of OCs. Hormonal Formulations and Breast Cancer Risk Changes in OC formulations over the decades have also influenced risk profiles (Mørch *et al*., 2017). Modern low-dose OCs are associated with a reduced risk of breast cancer compared to earlier high-dose formulations. However, the specific role of progestin type, dose, and combination with estrogen in modulating breast cancer risk is still under investigation (Benagiano *et al*., 2006).

2.3.2 Mechanisms of OC-Related Breast Cancer Risk

The potential link between OCs and breast cancer risk can be explained by the biological and molecular effects of synthetic hormones on breast tissue, as well as genetic and individual susceptibilities that modulate these effects (Del Pup *et al*., 2019). The pathways are shown in figure 2.

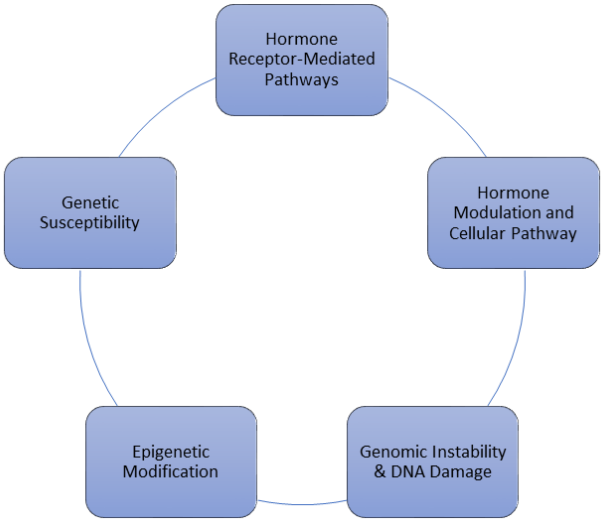

Fig 2: key pathways through which Oral contraceptives may impact breast cancer risk.

Oral contraceptives contain synthetic versions of estrogen and progestin, which mimic the effects of endogenous hormones. These hormones influence breast tissue in the following ways; Proliferation of Epithelial Cells: Estrogen and progestin promote the proliferation of epithelial cells in the mammary glands (Samson, 2016). Increased cell division raises the likelihood of DNA replication errors, which can lead to mutations and the initiation of carcinogenesis (Russo & Russo, 2004). Breast tissue exposed to synthetic hormones may experience prolonged periods of proliferative activity, creating conditions favorable for tumorigenesis (Passey, 2017). Enhanced Mammographic Density: As discussed earlier, higher breast density is associated with an increased risk of breast cancer. OCs, through their hormonal effects, can increase mammographic breast density in some women, thereby elevating cancer risk (Tamimi *et al*., 2006). Promotion of Estrogen-Receptor Positive (ER+) Tumors: Synthetic estrogen in OCs can stimulate the growth of ER+ breast cancers by binding to estrogen receptors and activating pathways that promote cell survival and proliferation (Kurta, 2013). This is particularly relevant for premenopausal women, whose breast tissue is more hormonally responsive (Van der Westhuizen & Van der Merwe, 2011). The risk associated with OC use is not uniform across all women; genetic predisposition and individual hormonal sensitivity play crucial roles in modulating risk. BRCA1/BRCA2 Mutations: Women with mutations in the BRCA1 or BRCA2 genes, which are associated with hereditary breast cancer, may face a higher risk of breast cancer if they use OCs, especially before the age of 30 (Quinn, 2020). A study by Narod *et al*. (2002) found that BRCA mutation carriers who used OCs had a moderately increased risk of breast cancer compared to non-carriers. However, more recent studies have suggested that modern low-dose OCs may pose a lower risk for BRCA carriers than earlier formulations (Hasyim, 2020). Variations in genes encoding estrogen and progesterone receptors may influence an individual's susceptibility to OC-related breast cancer. For example, certain polymorphisms in the estrogen receptor alpha (ESR1) gene are associated with increased breast cancer risk in OC users (Hankinson *et al*., 2004). Women with a strong family history of breast cancer may have an inherent predisposition to the disease, which could be amplified by the hormonal effects of OCs. However, the absolute increase in risk remains relatively small for most women in this group (Cipriani *et al*., 2020). Women with higher baseline levels of estrogen and progesterone may be more sensitive to the additional hormonal exposure from OCs. This sensitivity could result in greater changes in breast tissue composition and a higher risk of carcinogenesis (Pike *et al*., 1993). While the use of oral contraceptives is associated with a slight increase in breast cancer risk, it is important to consider the broader context. OCs confer significant protective effects against ovarian, endometrial, and colorectal cancers, which may offset the marginally increased risk of breast cancer for many women. The decision to use OCs should be based on an individualized assessment of risk factors, including family history, genetic predisposition, and personal health goals (García, 2020).

2.4 The Interplay between OCs, Breast Density, and Breast Cancer

Understanding the interplay between oral contraceptive (OC) use, mammographic breast density, and breast cancer risk requires integrating data on how OCs influence breast tissue composition and how this, in turn, mediates cancer risk (Wong *et al*., 2011). This section delves into how these

factors are interconnected, the evidence supporting their relationships, and the complexities surrounding this topic.

2.4.1 OCs and Breast Density

Mammographic breast density, defined as the proportion of fibroglandular tissue in the breast relative to fatty tissue, is influenced by hormonal factors, including those introduced by OCs. Given the hormonal composition of OCs, their use has been associated with changes in breast density, though the magnitude and nature of these changes vary depending on individual and contextual factors (De Hert *et al*., 2016). Several studies have investigated the impact of OC use on breast density, with results indicating that OCs can lead to modest increases in density. For instance, research by Vachon *et al*. (2000) found that current OC users had a higher percentage of mammographic density compared to non-users. The synthetic estrogen and progestin in OCs promote cell proliferation in the mammary gland, which can lead to increased fibroglandular tissue and, consequently, higher mammographic density. A more recent study by Engmann *et al*. (2017) also reported a positive association between OC use and mammographic density. The study noted that the increase in density was most pronounced in younger women and those who used OCs for extended durations (Monteiro *et al*., 2013). However, it also highlighted that the effect was reversible after discontinuation, with density returning to baseline levels over time.

The impact of OCs on breast density is more pronounced in younger women, whose breast tissue is more hormonally sensitive. Adolescents and women in their early 20s who use OCs are more likely to experience significant increases in density compared to older users (Boyd *et al*., 2009). Higher-dose formulations of OCs, which were common in earlier decades, are associated with greater increases in breast density compared to modern low-dose formulations. Advances in OC formulations aim to minimize these effects by reducing estrogen and progestin concentrations (Feng *et al*., 2016). Prolonged use of OCs has been linked to cumulative hormonal exposure, which may amplify changes in breast density. Women who use OCs for over five years may experience sustained increases in density, though these effects diminish after discontinuation (McCormack *et al*., 2010).

2.4.2 Breast Density as a Mediator for Cancer Risk

Breast density is one of the strongest independent risk factors for breast cancer, and it also serves as a potential mediator linking OC use to cancer risk. High breast density is characterized by increased epithelial and stromal tissue, both of which are more susceptible to hormonal stimulation and carcinogenic processes (Masarwah, 2016). Role of Increased Breast Density as a Pathway Linking OCs to Higher Cancer Risk. The relationship between OCs, breast density, and cancer risk can be conceptualized as follows, The synthetic estrogen and progestin in OCs stimulate breast cell proliferation, leading to increased density. This process may also elevate the number of cells at risk for malignant transformation (Verma *et al*., 2021). Women with dense breasts are four to six times more likely to develop breast cancer compared to those with fatty breasts (Boyd *et al*., 2007). Dense tissue provides a microenvironment conducive to tumorigenesis by increasing the number of proliferative cells and altering stromal-epithelial interactions. For women who use OCs, the increased density may amplify the carcinogenic potential of hormonal exposure (Dannhauser & Van den Berg, 2011). This creates a feedback loop wherein both the density and the hormonal stimulation act as co-factors in elevating cancer risk. Breast density naturally decreases with age, particularly after menopause, when hormonal levels decline. However, for premenopausal women using OCs, the maintenance or increase in breast density may prolong their period of elevated cancer risk (Stanczyk *et al*., 2013). Synthesizing the relationships between OCs, breast density, and breast cancer risk requires a multidisciplinary approach, drawing from epidemiology, biology, and clinical studies. While evidence points to clear associations, several unresolved questions and conflicting findings remain (OLULOPE, 2016).

Research designs such as the Nurses' Health Study and other large cohorts have provided valuable insights into how OC use influences breast density and cancer risk over time. These studies emphasize the dynamic nature of these relationships, particularly the reversibility of effects after OC cessation (Iversen *et al*., 2017). Experimental studies on breast tissue samples have elucidated the molecular pathways through which synthetic hormones alter tissue composition. These findings complement epidemiological data by providing biological plausibility for observed associations. Integrating breast density into risk prediction models has improved the accuracy of breast cancer risk assessments (Wiegratz & Kuhl, 2004). Tools such as the Breast Cancer Surveillance Consortium (BCSC) risk calculator incorporate density as a key variable, highlighting its importance as a mediator (White, 2015).

2.4.3 Conflicting Findings and Unresolved Questions

Not all women experience increases in breast density with OC use. Genetic and hormonal factors likely influence individual responses, but these factors are not yet fully understood. The relationship between OCs, density, and cancer risk may vary by breast cancer subtype. For example, estrogen receptor-positive (ER+) cancers are more strongly associated with hormonal exposure, while triple-negative cancers may have weaker links to density. Most existing studies focus on older, higher-dose OC formulations (Oskar, 2021). There is limited data on the long-term effects of modern low-dose formulations, which may have different risk profiles. Breast density and cancer risk vary by ethnicity, with African-American women often having denser breasts compared to other groups (Burke, 2010). However, most studies have been conducted in predominantly Caucasian populations, limiting the generalizability of findings. The interplay between OCs, breast density, and breast cancer risk is complex and multifactorial. Evidence suggests that OC use can modestly increase breast density, particularly in younger women and those using higher-dose formulations (Sitruk *et al*., 2013). This increase in density may partially mediate the elevated breast cancer risk observed among OC users. However, significant variability exists in individual responses, highlighting the need for personalized risk assessments (Brooks *et al*., 2021). Future research should focus on elucidating the mechanisms underlying these relationships, with an emphasis on modern OC formulations, genetic susceptibility, and diverse populations.

2.6 Implications for Practice and Future Research

The relationship between oral contraceptives (OCs), mammographic breast density, and breast cancer risk presents significant implications for clinical practice and research. Clinicians face the challenge of balancing the benefits of OCs for family planning and hormone regulation against potential long-term health risks, particularly for women with predisposing factors for breast cancer (Fischer,

2016). Simultaneously, researchers are tasked with addressing the knowledge gaps to provide evidence-based guidance and explore innovative approaches for minimizing risks.

2.6.1 Clinical Recommendations

Healthcare providers play a pivotal role in guiding women through contraceptive choices while considering individual risk factors (Dias *et al*., 2016). The following recommendations are essential for translating current evidence into clinical practice; Considerations for OC Prescriptions in Women at High Risk of Breast Cancer. Women with a family history of breast cancer, genetic predispositions (e.g., BRCA1 or BRCA2 mutations), or other high-risk factors require personalized contraceptive counseling. While OCs are generally safe for most women, high-risk individuals may face an elevated likelihood of breast cancer due to hormonal exposure (Mahboobnia *et al*., 2021). Clinicians should conduct comprehensive risk assessments, including evaluations of family history, genetic markers, and breast density, before prescribing OCs. For high-risk women, non-hormonal contraceptive options such as intrauterine devices (IUDs) or barrier methods may be preferable alternatives. Counseling should include discussions on how hormonal contraceptives may temporarily increase breast density and, potentially, breast cancer risk (Santen *et al*., 2010). Patients should be informed about the reversibility of these changes upon discontinuation and the importance of regular monitoring. Modern low-dose OCs, which contain reduced levels of estrogen and progestin, may offer safer alternatives for women at moderate risk (Shukla *et al*., 2017). These formulations aim to minimize hormonal stimulation of breast tissue while maintaining contraceptive efficacy. Mammographic breast density is an established risk factor for breast cancer and poses diagnostic challenges, as dense tissue can mask malignancies on mammograms (Rajaneesh, 2021). For OC users with higher breast density, enhanced screening protocols are recommended, Women with dense breasts may benefit from adjunctive imaging techniques, such as breast ultrasound or magnetic resonance imaging (MRI), to improve cancer detection (Thompson *et al*., 2019). These modalities are particularly important for high-risk OC users, as mammograms alone may be insufficient (Wu *et al*., 2015). High-risk OC users with increased breast density should begin breast cancer screening earlier than the general population, with more frequent follow-ups (Burkman *et al*., 2011). Clinical breast exams and self-examinations should also be encouraged as complementary practices. Regular assessment of breast density through mammography can help track changes over time and guide individualized risk management strategies (Mathew *et al*., 2021).

2.6.2 Research Priorities

Despite advances in understanding the relationships between OCs, breast density, and breast cancer risk, significant gaps remain. Addressing these gaps through targeted research is critical for improving patient outcomes and informing clinical guidelines (Dalene, 2020). Investigating Newer OC Formulations with Lower Hormonal Doses. Over the years, OC formulations have evolved to contain lower doses of synthetic hormones, reducing adverse effects while maintaining contraceptive effectiveness (Dragoman, 2014). However, the long-term impact of these modern formulations on breast density and cancer risk requires further investigation. Research should compare the effects of older high-dose OCs with newer low-dose options on breast density and cancer risk. Such studies could clarify whether reduced hormonal exposure translates to lower breast cancer incidence (Westbrook & Stearns, 2013). Progestin-only contraceptives, including pills, implants, and injections, may have a different risk profile compared to combined estrogen-progestin formulations. Future studies should explore their impact on breast density and cancer risk, particularly in women with contraindications to estrogen use (Tenti *et al*., 2020). Large-scale, long-term cohort studies are needed to track the effects of low-dose OCs on breast density and cancer risk over decades. These studies should account for variations in age, ethnicity, and genetic predispositions. Developing Interventions to Mitigate Breast Density Increases in OC Users. As breast density is a modifiable risk factor, interventions to reduce or prevent density increases in OC users could significantly lower cancer risk. Potential avenues for research include; Investigating the role of diet, exercise, and weight management in counteracting the density-increasing effects of OCs (Helland, 2019). For instance, higher physical activity levels and lower body fat percentages are associated with reduced breast density (Haber, 2010). Exploring the use of medications or supplements that mitigate hormonal stimulation of breast tissue. Selective estrogen receptor modulators (SERMs) or aromatase inhibitors may have potential as protective agents for high-risk OC users (Seo *et al*., 2015). Research should focus on identifying genetic and hormonal markers that predict individual responses to OCs (Yang *et al*., 2013). This knowledge could enable the development of personalized interventions, such as customized contraceptive formulations or targeted screening protocols (Elebro, 2017). Most existing studies on OCs, breast density, and cancer risk have been conducted in predominantly Caucasian populations. To ensure the generalizability of findings, future research should include diverse populations, accounting for variations in breast density and cancer risk across different ethnic and racial groups (Riondino *et al*., 2019). Advances in molecular biology and imaging technologies provide opportunities to unravel the mechanisms through which OCs influence breast tissue. Investigating the cellular and genetic pathways involved could shed light on why some women experience greater density increases and cancer risk than others. The interplay between OCs, breast density, and breast cancer risk underscores the importance of evidence-based clinical practices and targeted research efforts. For clinicians, prescribing OCs requires a nuanced understanding of individual risk factors, particularly for women with high breast density or a predisposition to breast cancer. Enhanced screening protocols and personalized counseling can help mitigate potential risks while ensuring effective contraception. For researchers, priorities include investigating the safety profiles of newer OC formulations, developing interventions to address density increases, and exploring the molecular underpinnings of these relationships. By addressing these challenges, future research can contribute to more informed decision-making and improved health outcomes for women worldwide.

2.7 Conclusion

Women's health is greatly impacted by the complex interaction that exists between oral contraceptives (OCs), mammographic breast density, and breast cancer risk. Given that OCs are still one of the most used forms of birth control in the world, it is crucial to comprehend how they may affect breast tissue and the risk of developing cancer in the long run. This conclusion summarizes the main conclusions, emphasizes the value of individualized treatment, and

stresses the necessity of more study and cooperation. Several important conclusions about the relationship between OCs, breast density, and cancer risk may be drawn from a thorough analysis of the literature. OCs, especially those that contain estrogen and progestin, have hormonal effects that affect the composition of breast tissue. Among these consequences might be a rise in glandular tissue growth, which could lead to a larger breast density on mammograms. The extent of these changes appears to vary based on factors such as age, duration of OC use, and the specific hormonal formulation. Mammographic breast density is a well-established independent risk factor for breast cancer. Women with high breast density face a four to six times greater risk of developing breast cancer compared to those with low density. The hormonal stimulation from OCs may transiently elevate breast density, thereby increasing short-term cancer risk, particularly in younger women. Epidemiological evidence shows a modest but consistent association between current or recent OC use and an elevated risk of breast cancer. This risk diminishes over time after discontinuing OCs. Factors such as the age of initiation, duration of use, and hormonal dosage influence the degree of risk. Notably, the absolute risk increase remains small for most women, particularly those without additional risk factors. Higher breast density is thought to mediate part of the link between OC use and increased breast cancer risk. However, the strength of this relationship varies across studies, with conflicting findings and unresolved questions. This highlights the need for further investigation into individual variability and molecular mechanisms underlying these effects.

The connection between OCs, breast density, and the risk of breast cancer emphasizes how crucial individualized treatment and well-informed choices are. Although OCs provide many advantages for family planning, controlling menstruation, and managing hormones, their possible hazards should be carefully considered, especially for women who have risk factors for breast cancer. Comprehensive information on the advantages and disadvantages of OCs, including possible impacts on breast density and cancer risk, should be made available to women. This allows people to interact with healthcare specialists and make well-informed decisions. For the purpose of directing contraceptive options, personalized risk evaluations that take into account variables including genetic predisposition, family history, and breast density are essential. OCs that include estrogen might not be the best option for high-risk individuals. It is essential to maintain a balanced perspective when interpreting the risks associated with OCs. For most women, the benefits of OCs outweigh the potential risks, particularly when their use is carefully monitored and tailored to individual needs. Advancing our understanding of the complex relationships between OCs, breast density, and cancer risk requires a collaborative and interdisciplinary approach. Policymakers, researchers, healthcare providers, and patient advocacy groups must work together to address existing knowledge gaps and improve outcomes for women globally. Collaboration between epidemiologists, oncologists, endocrinologists, and radiologists is essential for elucidating the mechanisms by which OCs influence breast density and cancer risk. Integrating expertise from these fields can help develop more effective screening, prevention, and treatment strategies. Large-scale, long-term studies are needed to examine the effects of modern low-dose OC formulations on breast density and cancer risk over decades. Research should include diverse populations to ensure findings are generalizable across different racial, ethnic, and genetic backgrounds. Research efforts should focus on creating interventions to mitigate the potential risks associated with OCs. This includes exploring new contraceptive formulations with lower hormonal doses, as well as adjunctive therapies that counteract increases in breast density. Policymakers and health organizations should prioritize public health campaigns that raise awareness about breast cancer risk factors, including the role of OCs and breast density. Educational initiatives can empower women to seek regular screenings and engage in proactive risk management. Advances in genetics and molecular biology provide opportunities to tailor contraceptive recommendations and cancer prevention strategies to individual risk profiles. Investment in precision medicine approaches could revolutionize care for women at varying levels of risk.

The complex interplay between OCs, breast density, and breast cancer risk highlights the need for a nuanced and individualized approach to women's health. While OCs offer invaluable benefits, their potential risks should not be overlooked, particularly for women with higher breast density or other risk factors. By fostering interdisciplinary collaboration and advancing research, we can address current uncertainties, develop safer contraceptive options, and ensure optimal care for women worldwide. Through informed decision-making, personalized assessments, and continued innovation, the healthcare community can empower women to make choices that support their health and well-being across their lifespan.

3. References

1. Ahmad MA. Mining health data for breast cancer diagnosis using machine learning. Canberra, Australia: University of Canberra; c2013.
2. Azam S, Eriksson M, Sjölander A, Hellgren R, Gabrielson M, Czene K, *et al*. Mammographic density change and risk of breast cancer. JNCI: Journal of the National Cancer Institute. 2020;112(4):391–9.
3. Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer Research. 2014;74(15):4078–89.
4. Beaber EF, Malone KE, Tang MTC, Barlow WE, Porter PL, Daling JR, *et al*. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiology, Biomarkers & Prevention. 2014;23(5):755–64.
5. Benagiano G, Bastianelli C, Farris M. Contraception today. Annals of the New York Academy of Sciences. 2006;1092(1):1–32.
6. Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, *et al*. Mammographic density and the risk and detection of breast cancer. New England Journal of Medicine. 2007;356(3):227–36.
7. Boyd NF, Martin LJ, Sun L, Guo H, Chiarelli A, Hislop G, *et al*. Breast tissue composition and susceptibility to breast cancer. Journal of the National Cancer Institute. 2010;102(16):1224–37.
8. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. Mammographic density and breast cancer risk: current understanding and future prospects. Breast Cancer Research. 2009;11(6):223.
9. Boyd NF, Melnichouk O, Martin LJ, Hislop G, Chiarelli AM, Yaffe MJ, *et al*. Mammographic density, response to hormones, and breast cancer risk. Journal of Clinical Oncology. 2011;29(22):2985–92.
10. Brinton LA, Daling JR, Liff JM, Schoenberg JB, Malone KE, Stanford JL, *et al*. Oral contraceptives and breast cancer risk among younger women. JNCI: Journal of the

National Cancer Institute. 1995;87(11):827–35.
11. Brooks JD, Nabi H, Andrulis IL, Antoniou AC, Chiquette J, Després P, *et al*. Personalized risk assessment for prevention and early detection of breast cancer: integration and implementation (PERSPECTIVE I&I). Journal of Personalized Medicine. 2021;11(6):511.
12. Burke MM. Functional polymorphisms in the epidermal growth factor family genes and their relationship to the risk and severity of breast cancer. Manchester, UK: The University of Manchester; 2010.
13. Burkman RT, Bell C, Serfaty D. The evolution of combined oral contraception: improving the risk-to-benefit ratio. Contraception. 2011;84(1):19–34.
14. Christin-Maitre S. History of oral contraceptive drugs and their use worldwide. Best Practice & Research Clinical Endocrinology & Metabolism. 2013;27(1):3–12.
15. Cipriani S, Todisco T, Scavello I, Di Stasi V, Maseroli E, Vignozzi L. Obesity and hormonal contraception: an overview and a clinician's practical guide. Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity. 2020;25:1129–40.
16. Dalene Skarping I. Mammographic density. A marker of treatment outcome in breast cancer? Lund, Sweden: Lund University; 2020.
17. Daniels K, Abma JC. Current contraceptive status among women aged 15–49: United States, 2017–2019. National Center for Health Statistics Data Brief. 2020;388:1–8.
18. Dannhauser A, Van den Berg VL. Prevalence of the known risk factors in women diagnosed with breast cancer at Queen II Hospital, Maseru. Bloemfontein, South Africa: University of the Free State; 2011.
19. De Hert M, Peuskens J, Sabbe T, Mitchell AJ, Stubbs B, Neven P, *et al*. Relationship between prolactin, breast cancer risk, and antipsychotics in patients with schizophrenia: a critical review. Acta Psychiatrica Scandinavica. 2016;133(1):5–22.
20. De Leo V, Musacchio MC, Cappelli V, Piomboni P, Morgante G. Hormonal contraceptives: pharmacology tailored to women's health. Human Reproduction Update. 2016;22(5):634–46.
21. Del Pup L, Codacci-Pisanelli G, Peccatori F. Breast cancer risk of hormonal contraception: counselling considering new evidence. Critical Reviews in Oncology/Hematology. 2019;137:123–30.
22. Dias JA, Fredrikson GN, Ericson U, Gullberg B, Hedblad B, Engström G, *et al*. Low-grade inflammation, oxidative stress and risk of invasive post-menopausal breast cancer—a nested case-control study from the Malmö Diet and Cancer Cohort. PLOS One. 2016;11(7):e0158959.
23. Dragoman MV. The combined oral contraceptive pill—recent developments, risks and benefits. Best Practice & Research Clinical Obstetrics & Gynaecology. 2014;28(6):825–34.
24. Elebro K. Androgen and estrogen receptors in breast cancer. Impact on risk, prognosis and treatment prediction. Lund, Sweden: Lund University; 2017.
25. Dragoman MV. The combined oral contraceptive pill—recent developments, risks and benefits. Best Pract Res Clin Obstet Gynaecol. 2014;28(6):825-34.
26. Elebro K. Androgen and estrogen receptors in breast cancer: Impact on risk, prognosis and treatment prediction [dissertation]. 2017.
27. Engmann NJ, Scott CG, Jensen MR, Ma L, Brandt KR, Vachon CM. Combined effect of volumetric mammographic density and body mass index on breast cancer risk. Breast Cancer Res. 2017;19(1):1-9.
28. Feng MX, Hong JX, Wang Q, Fan YY, Yuan CT, Lei XH, *et al*. Dihydroartemisinin prevents breast cancer-induced osteolysis via inhibiting both breast cancer cells and osteoclasts. Sci Rep. 2016;6(1):19074.
29. Fischer A. Life events, perceived stress and breast cancer risk in the hereditary breast and ovarian cancer study of Orange County, CA [dissertation]. UC Irvine; 2016.
30. García Damián A. Disease biomarkers in metabolomics. 2020.
31. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, *et al*. Oral contraceptive use and breast cancer risk: A systematic review. Cancer Epidemiol Biomarkers Prev. 2013;22(11):1931-9.
32. Greendale GA, Reboussin BA, Sie A, Singh HR, Olson LK, Gatewood O, *et al*. Effects of estrogen and estrogen-progestin on mammographic density. Ann Intern Med. 2003;130(4):262-9.
33. Grindlay K, Burns B, Grossman D. Prescription requirements and over-the-counter access to oral contraceptives: A global review. Contraception. 2013;88(1):91-6.
34. Haber G. Use of structural equation modeling to examine the association between breast cancer risk perception and repeat screening mammography among United States women [dissertation]. Florida International University; 2010.
35. Hampson E. A brief guide to the menstrual cycle and oral contraceptive use for researchers in behavioral endocrinology. Horm Behav. 2020;119:104655.
36. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density: Relationship with breast cancer risk. Radiology. 2004;230(1):29-41.
37. Hasyim NA. MAGEB2 antibody as a potential diagnostic and predictive tool in the progression of oral cancer [master's thesis]. University of Malaya (Malaysia); 2020.
38. Helland T. Tamoxifen in the treatment of luminal breast cancer: Implications of active metabolites on gene expression, side effects and clinical outcome. 2019.
39. Hunter DJ, Colditz GA, Hankinson SE. Oral contraceptive use and breast cancer: A comprehensive review of epidemiological evidence. J Natl Cancer Inst. 2010;102(15):1143-50.
40. Iversen L, Fielding S, Lidegaard Ø, Hannaford PC. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med. 2017;377(23):2228-39.
41. Iversen L, Hannaford PC, Vatten LJ. Long-term effects of oral contraceptive use on cancer risk. Lancet Oncol. 2017;18(1):103-12.
42. Kanadys W, Barańska A, Malm M, Błaszczuk A, Polz-Dacewicz M, Janiszewska M, *et al*. Use of oral contraceptives as a potential risk factor for breast cancer: A systematic review and meta-analysis of case-control studies up to 2010. Int J Environ Res Public Health. 2021;18(9):4638.
43. Kennedy CE, Yeh PT, Gonsalves L, Jafri H, Gaffield ME, Kiarie J, *et al*. Should oral contraceptive pills be available without a prescription? A systematic review of over-the-counter and pharmacy access availability. BMJ Glob Health. 2019;4(3):e001402.
44. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: An analysis of 27,825 patient

evaluations. Radiology. 2002;225(1):165-75.
45. Kurta ML. Ovarian cancer epidemiology: Risk, diagnosis, and prognosis [dissertation]. University of Pittsburgh; 2013.
46. Mahboobnia K, Pirro M, Marini E, Grignani F, Bezsonov EE, Jamialahmadi T, *et al*. PCSK9 and cancer: Rethinking the link. Biomed Pharmacother. 2021;140:111758.
47. Marchbanks PA, Curtis KM, Mandel MG, Wilson HG, Jeng G, Folger SG, *et al*. Oral contraceptive formulation and risk of breast cancer. Contraception. 2012;85(4):342-50.
48. Masarwah A. Mammographic breast density, tumour characteristics and the expression of hyaluronan as prognostic surrogate markers for breast cancer [dissertation]. Itä-Suomen yliopisto; 2016.
49. Mathew A, Doorenbos AZ, Li H, Jang MK, Park CG, Bronas UG. Allostatic load in cancer: A systematic review and mini meta-analysis. Biol Res Nurs. 2021;23(3):341-61.
50. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: A meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159-69.
51. Monteiro AC, Leal AC, Gonçalves-Silva T, Mercadante ACT, Kestelman F, Chaves SB, *et al*. T cells induce pre-metastatic osteolytic disease and help bone metastases establishment in a mouse model of metastatic breast cancer. PLoS One. 2013;8(7):e68171.
52. Moore JX, Han Y, Appleton C, Colditz G, Toriola AT. Determinants of mammographic breast density by race among a large screening population. JNCI Cancer Spectrum. 2020;4(2):pkaa010.
53. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med. 2017;377(23):2228-39.
54. Narod SA, Dubé MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, *et al*. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2002;94(23):1773–9.
55. Nelson AL. Menstrual suppression for adolescents. Pediatrics. 2019;144(5):e20193024.
56. Olulope OA. The relationship of endocrine disruptors with pituitary, gonadal, thyroid hormones and some receptors in Nigerian women with breast cancer [dissertation]. [location unknown]: [publisher unknown]; 2016.
57. Oskar S. Exposure to phthalates during critical windows of susceptibility and breast tissue composition: implications for breast cancer risk [dissertation]. [location unknown]: Columbia University; 2021.
58. Passey A. Epigenetic biomarkers for clinical outcomes and mechanisms driving emergence of drug resistance in ovarian cancer [dissertation]. London: Imperial College London; 2017.
59. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, breast tissue age, and the age-incidence of breast cancer. Nature. 1993;303(5920):767–70.
60. Quinn J. Evaluation of the role of autophagy in ovarian cancer chemoresistance [dissertation]. [location unknown]: [publisher unknown]; 2020.
61. Rajaneesh N. Risk factors in breast cancer: work on preventing recurrence. [place unknown]: Notion Press; 2021.
62. Ramón y Cajal T, Chirivella I, Miranda J, Teule A, Izquierdo Á, Balmaña J, *et al*. Mammographic density and breast cancer in women from high-risk families. Breast Cancer Res. 2015;17:1-11.
63. Renner RM, Jensen JT. Progestin-only oral contraceptive pills. Contraception. 2011;[pages unknown].
64. Riondino S, Ferroni P, Zanzotto FM, Roselli M, Guadagni F. Predicting VTE in cancer patients: candidate biomarkers and risk assessment models. Cancers. 2019;11(1):95.
65. Russo J, Russo IH. The role of estrogen in the initiation of breast cancer. J Steroid Biochem Mol Biol. 2004;86(3-5):449–56.
66. Samson ME. Progesterone-only oral contraceptive pill, breast cancer, heart disease, and stroke [dissertation]. [location unknown]: [publisher unknown]; 2016.
67. Santen RJ, Allred DC, Ardoin SP, Archer DF, Boyd N, Braunstein GD, *et al*. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab. 2010;95(7 Suppl 1):s1-66.
68. Seo BR, Bhardwaj P, Choi S, Gonzalez JA, Andresen Eguiluz RC, Wang K, *et al*. Obesity-dependent changes in interstitial ECM mechanics promote breast tumorigenesis. Sci Transl Med. 2015;7(301):301ra130.
69. Shah D, Patil M, National PCOS Working Group. Consensus statement on the use of oral contraceptive pills in polycystic ovarian syndrome women in India. J Hum Reprod Sci. 2018;11(2):96-118.
70. Shukla AK, Jamwal R, Bala K. Adverse effect of combined oral contraceptive pills. Asian J Pharm Clin Res. 2017;10:17-21.
71. Sitruk-Ware R, Nath A, Mishell DR Jr. Contraception technology: past, present and future. Contraception. 2013;87(3):319-30.
72. Smith NL, Heckbert SR, Lemaitre RN. Oral contraceptive use and breast cancer risk. JAMA. 2003;289(3):326–30.
73. Sprague BL, Trentham-Dietz A, Gangnon RE. The role of body mass index in the relationship between mammographic density and breast cancer. Cancer Causes Control. 2010;21(11):2001–11.
74. Stanczyk FZ, Archer DF, Bhavnani BR. Ethinyl estradiol and 17β-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics, and risk assessment. Contraception. 2013;87(6):706-27.
75. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2006;99(15):1178–87.
76. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Hormonal contraceptives and breast cancer risk in premenopausal women. Cancer Epidemiol Biomarkers Prev. 2006;15(11):2249–54.
77. Tenti S, Correale P, Cheleschi S, Fioravanti A, Pirtoli L. Aromatase inhibitors—induced musculoskeletal disorders: current knowledge on clinical and molecular aspects. Int J Mol Sci. 2020;21(16):5625.
78. Tesic V, Kolaric B, Znaor A, Kuna SK, Brkljacic B. Mammographic density and estimation of breast cancer risk in intermediate risk population. Breast J. 2013;19(1):71-8.
79. Tesic V, Kolaric B, Znaor A, Kuna SK, Brkljacic B. Mammographic density and estimation of breast cancer risk in intermediate risk population. The Breast Journal. 2013;19(1):71-8.
80. Thompson PA, Preece C, Stopeck AT. Breast cancer prevention. Fundamentals of Cancer Prevention.

2019;543-606.
81. Upadhya KK, Santelli JS, Raine-Bennett TR, Kottke MJ, Grossman D. Over-the-counter access to oral contraceptives for adolescents. Journal of Adolescent Health. 2017;60(6):634-40.
82. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes & Control. 2000;11(7):653-62.
83. Van der Westhuizen E, Van der Merwe E. The safety and efficacy of low-dose oral contraceptives: CPD article. South African Family Practice. 2011;53(5):403-11.
84. Verma N, Cwiak C, Kaunitz AM. Hormonal contraception: systemic estrogen and progestin preparations. Clinical Obstetrics and Gynecology. 2021;64(4):721-38.
85. Westbrook K, Stearns V. Pharmacogenomics of breast cancer therapy: an update. Pharmacology & Therapeutics. 2013;139(1):1-11.
86. White A. Multiple sources of PAH exposure, DNA methylation and breast cancer. Cancer Epidemiology, Biomarkers & Prevention. 2015;[journal volume and page numbers needed].
87. White ND. Hormonal contraception and breast cancer risk. American Journal of Lifestyle Medicine. 2018;12(3):224-6.
88. Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. Drugs. 2004;64:2447-62.
89. Wong CS, Lim GH, Gao F, Jakes RW, Offman J, Chia KS, Duffy SW. Mammographic density and its interaction with other breast cancer risk factors in an Asian population. British Journal of Cancer. 2011;104(5):871-4.
90. Wu L, Janagam DR, Mandrell TD, Johnson JR, Lowe TL. Long-acting injectable hormonal dosage forms for contraception. Pharmaceutical Research. 2015;32:2180-91.
91. Yaghjyan L, Colditz GA, Rosner B, Tamimi RM. Mammographic breast density and breast cancer risk: interactions of percent density, absolute dense, and non-dense areas with breast cancer risk factors. Breast Cancer Research and Treatment. 2015;150:181-9.
92. Yaghjyan L, Mahoney MC, Succop P, Wones R, Buckholz J, Pinney S. Relationship between breast cancer risk factors and mammographic breast density in the Fernald Community Cohort. British Journal of Cancer. 2012;106(5):996-1003.
93. Yang G, Nowsheen S, Aziz K, Georgakilas AG. Toxicity and adverse effects of Tamoxifen and other anti-estrogen drugs. Pharmacology & Therapeutics. 2013;139(3):392-404.