The Association Between Combined Oral Contraceptive Use and the Incidence of High-Density Lesions on Digital Mammography

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Abstract

Background:
High mammographic density (MD) is an independent breast cancer risk factor that hinders early detection through the "masking effect." Global literature on the impact of combined oral contraceptives (COCs) remains inconsistent, with limited data available for the Indonesian population. This research aims to investigate the association between COC use and high-density lesions on digital mammography while evaluating the influence of family history.

Methods:
This cross-sectional study analysed 158 subjects at Siloam MRCCC Hospital (Dec 2025–Jan 2026) using purposive sampling. Statistical associations were assessed using Chi-square and Fisher's exact tests.

Result:
Long-term COC use (≥5 years) was significantly associated with a reduced risk of high-density lesions (OR=0.28; 95% CI: 0.14–0.55; p<0.001) in perimenopausal women (median age 53). In contrast, family history was a potent risk factor, with a 100% prevalence of high-density lesions (p=0.003). After adjusting for family history, the protective association of COC use persisted (aOR=0.43). BMI and reproductive history showed no statistically significant associations.

Conclusion:
Long-term COC use correlates with lower mammographic density in perimenopausal women, potentially mitigating diagnostic masking. However, family history remains a dominant factor that overrides these hormonal associations. These findings highlight the need for multifaceted screening strategies that integrate genetic predisposition and physiological tissue involution.

Introduction

Breast cancer is the primary driver of oncology-related mortality in Indonesia and a significant global health challenge, particularly in low- and middle-income countries. Although early detection through mammography can reduce mortality by 30–40%,[1–3] High mammographic density (MD) remains a potent independent risk factor, potentially increasing cancer risk sixfold. [1,5] As the gold standard for first-line diagnostic imaging, mammography

provides critical data on MD, which is essential for identifying high-risk patients and overcoming the limitations of late-stage diagnosis.

Current literature suggests that exogenous hormonal factors, such as combined oral contraceptives (COCs), may influence MD; however, scientific evidence remains inconclusive. [6,7] Disparities between studies reporting no significant risk and those indicating a clear correlation, most notably by Mørch et al, highlight a critical research gap regarding the impact of COCs on high-density mammographic lesions.[6] Consequently, this study investigates the association between COC use and the occurrence of these lesions to better elucidate breast cancer pathogenesis and provide an evidentiary basis for public health education and early detection strategies.

Material and Methods

This observational analytic study employed a cross-sectional design to evaluate the association between combined oral contraceptive (COC) use and the incidence of high-density lesions on mammography. The study was conducted at the Radiology Department of Mochtar Riady Comprehensive Cancer Centre (MRCCC) Siloam Hospitals Semanggi, Jakarta, with data collection spanning from December 2025 to January 2026.

The target population included women undergoing mammography with a history of contraceptive use for at least five years. The 5-year cut-off point value is used based on previous research data showing that 5 years is a sufficient period to determine the effect of hormonal birth control on breast cancer risk.[10] Subjects were selected using a retrospective purposive sampling technique to ensure alignment with specific study objectives. The minimum sample size was calculated at 80 subjects, determined using a categorical analytic formula for independent groups with a 5% significance level ($\alpha = 0.05$) and 80% statistical reference ($\beta = 0.20$), based on previously reported proportions of high-density lesions ($P_1 = 0.707$, $P_2 = 0.475$). Inclusion criteria comprised women aged ≥ 40 years with a history of COC use for at least five years who underwent mammography. Patients with incomplete medical records, missing imaging results, or who were pregnant at the time of examination were excluded.

Research Procedures

Following ethical clearance from the Universitas Pelita Harapan Ethics Committee and administrative approval from MRCCC Siloam, eligible subjects provided informed consent. Contraceptive history was collected via questionnaires, while mammographic density data were obtained through a specialist-led retrospective review of digital imaging and medical records. Data were processed using SPSS Version 27. The association between categorical variables, specifically COC use and the presence of high-density mammographic lesions, was assessed using the Chi-Square test. Statistical significance was defined as $p < 0.05$ at the appropriate degrees of freedom.

Result

Subject Characteristics and Distribution

The study included 158 subjects who met the eligibility criteria, with a median age of 53 years (IQR 12). Long-term use of Combined Oral Contraceptives (COCs) for ≥ 5 years was reported by 53 participants (33.5%), while high-density lesions were identified in 95 person (60.1%). A family history of cancer was present in 20.9% (n=33) of the study population. Bivariate Analysis of High-Density Lesions in table 1 revealed that long-term COC use (> 5 years) was

significantly associated with a reduced risk of high-density lesions (*OR = 0.28; CI: 0.14–0.55; p < 0.001*).
Conversely, a family history of cancer was significantly associated with an increased risk (*p = 0.003*), where 100% of subjects with such a history exhibited high-density lesions. Other variables, including BMI, history of menstrual disorders, hormone therapy, IVF programs, breastfeeding history, and parity, demonstrated no statistically significant association with the incidence of high-density lesions (all *p > 0.05*).

Table 1. Bivariate Analysis of Factors Associated with High-Density Lesions

Variable	High-Density Lesions		OR	95% CI	*p Value*
	Yes	No			
Age, median (IQR)	53,00 (12,00)	54,00 (11,00)	-	-	0,720
Combined Oral Contraceptive Use					
Yes	39,6%	60,4%			
No	70,5%	29,5%	0,28	0,14 – 0,55	<0,001
Family History of Cancer					
Yes	100,0%	0,0%	68,07	4,08 -	0.003
No	49,6%	50,4%		1135,45	
History of Menstrual Disorders					
Ya	71,4%	28,6%	1,69	0,32 – 9,02	0,703*
Tidak	59,6%	40,4%			
History of Hormone Therapy					
Yes	25,0%	75,0%			
No	61,0%	39,0%	0,21	0,02 – 2,09	0,302*
History of IVF Program					
Yes	50,0%	50,0%	0,66	0,09 – 4,78	1,000*
No	60,4%	39,6%			
Breastfeeding History					
Yes	56,1%	43,9%	0,44	0,19 – 1,02	0,081
No	74,3%	25,7%			
Parity (Number of Children)					
None	75,9%	24,1%	Ref.	Ref.	0,068
1 - 2 Children	60,7%	39,3%	0,49	0,19 - 1,28	
≥ 3 Children	48,9%	51,1%	0,30	0,11 - 0,85	

*Notes: *Did not meet Chi-square requirements; Fisher's exact test was utilized instead.*
OR: Odds Ratio; CI: Confidence Interval; IQR: Interquartile Range; Ref: Reference group.

Stratified Analysis by Family History of Cancer Stratification was performed to control for the confounding effect of family history of cancer. Within the strata of subjects with a positive family history (n=33), all participants (100%) presented with high-density lesions, rendering the calculation of an OR statistically non-applicable. In the strata without a family history of cancer (n=125), COC use maintained a significant protective association (OR = 0.43; 95% CI: 0.21–0.89; p = 0.035) as seen in table 2. Although the effect estimate shifted slightly compared to the crude analysis, the protective trend remained consistent.

Table 2. Stratified Analysis of the Association Between COC Use and High-Density Lesions Based on Family History of Cancer

Variable	High-Density Lesions		OR	95% CI	P Value
	Yes	No			
Family History of Cancer (+)					
Combined Oral Contraceptive	100,0%	-	NA	NA	NA
No Combined Oral Contraceptive	100,0%	-			
Family History of Cancer (-)					
Combined Oral Contraceptive	37,3%	62,7%	0,43	0,21 - 0,89	0,035
No Combined Oral Contraceptive	58,1%	41,9%			

Discussion

This study evaluated the association between long-term combined oral contraceptive (COC) use and the incidence of high-density lesions on digital mammography, the primary gold-standard tool for early detection capable of reducing breast cancer mortality by 30–40%.

Our findings indicate that COC use for ≥ 5 years serves as a significant protective factor against the development of high-density lesions (OR = 0.28; 95% CI: 0.14–0.55; p < 0.001). In this radiological context, high-density lesions were classified as findings corresponding to BI-RADS Breast Density (heterogeneously or extremely dense tissue).

This result is considered interesting to explore as it contrasts with landmark oncological studies, such as the cohort by Mørch et al. (2017), which observed a 20% increased risk of malignancy among hormonal contraceptive users.

From an imaging standpoint, the presence of high-density tissue acts as a "double-edged sword". Beyond being an independent biological risk factor in carrying a nearly sixfold increase in cancer risk, high mammographic density (MD) creates significant technical hurdles through "anatomical noise" or the "masking effect." This phenomenon occurs when dense fibroglandular tissue obscures underlying pathologies, contributing to an estimated 28% miss rate for cancers during standard screenings. Radiologists identify suspicious masses by looking for irregular shapes, spiculated margins, and high radiopacity, whereas benign masses typically appear round with circumscribed borders. The protective trend observed here suggests that long-term COC use in this specific cohort may correlate with a more favorable imaging environment, potentially reducing the density-related masking effect that often complicates early diagnosis.

From an oncological perspective, the divergence from traditional theories of estrogen-induced epithelial proliferation may be explained by the evolution of pharmacology and the physiological context of our cohort. While estrogen is known to stimulate the proliferation of breast epithelial cells, potentially leading to DNA damage and carcinogenesis, the transition from high-dose (150 mcg) to ultra-low-dose (10–20 mcg) estrogen formulations has modified the risk profile[20,21]. As suggested by Samson et al., progestin-dominant components in

modern COCs may attenuate cellular proliferative stimulation. [22,23]

Furthermore, the median age of 53 years in this study suggests a population undergoing physiological involution, where fibroglandular tissue is progressively replaced by adipose tissue. This process naturally decreases MD and is negatively correlated with Body Mass Index (BMI). Our findings align with Hunt et al. (2023) and Yaghjyan et al. (2022), supporting the hypothesis that modern low-dose COCs do not necessarily translate to increased mammographic density in perimenopausal populations. [18, 19]

Additionally, this study also identifies a family history of cancer as a formidable independent risk factor; notably, 100% of subjects with such a history presented with high-density lesions ($p = 0.003$), These findings are in line with several studies that have been conducted previously, one of which is a study by Brewer, et al. showing that the risk of breast cancer is not only related to a history of breast cancer but also other cancers.[11] This absolute prevalence also indicates a biological link likely rooted in autosomal dominant mutations (e.g., BRCA1/BRCA2)[12] that trigger increased collagen deposition in the breast stroma, radiologically manifesting as heightened MD. [13,14]

Stratified analysis confirmed that family history is a critical confounder; adjusting for this variable shifted the effect estimate from a crude OR of 0.28 to an adjusted OR (aOR) of 0.43. This emphasizes that genetic predisposition can override the relative protective associations of exogenous hormones and may be linked to specific tumor subtypes that are less influenced by the hormonal mechanisms governing density.

While variables such as BMI, breastfeeding, and parity showed descriptive protective trends, likely due to mechanisms like ovulation suppression and reduced cumulative estrogen exposure, [27] they did not reach statistical significance. This limitation is likely due to restricted statistical limitations within specific subgroups, such as nulliparous women (n=29). Nonetheless, the integration of these findings underscores that interpreting high-density lesions requires a multifaceted approach that considers the technical limitations of imaging, the biological stage of the patient, and the evolving landscape of oncological risk.

Conclusion

This study demonstrates a significant association between the use of combined oral contraceptives (COCs) and the incidence of high-density lesions on digital mammography, Specifically, COC use for $\geq$ 5 years was identified as a significant protective factor, correlating with a lower incidence of high mammographic density compared to non-users within this perimenopausal cohort. Conversely, a positive family history of breast cancer was established as a potent independent factor, with a 100% prevalence of high-density lesions among affected subjects. These findings suggest that while modern ultra-low-dose hormonal contraceptives may not increase and may even correlate with lower mammographic density in older populations, the relationship is heavily influenced by hereditary risk factors and physiological involution, necessitating further research to refine clinical screening guidelines and address the technical masking effects of dense tissue.

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