The Relationship Between Hormonal Contraceptive Use and Breast Cancer Incidence at Dr. Pirngadi Regional General Hospital, Medan

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Abstract.

Breast cancer remains a significant public health concern in Indonesia, with emerging evidence suggesting that hormonal contraceptive type influences not only cancer incidence but also tumor aggressiveness. This cross-sectional study examined the relationship between hormonal contraceptive formulations and histopathological grading of breast cancer at RSUD Dr. Pirngadi Hospital, Medan. The study included 100 women with confirmed invasive breast cancer who were selected using the Lemeshow formula for sample size calculation. A structured data extraction form collected information on contraceptive type, duration of use, and Nottingham grading classification. Fisher's Exact Test and chi-square test analyzed associations between contraceptive types and grading categories. Results demonstrated that oral pill users predominantly developed well-differentiated cancers (51.7%), while injectable users predominantly developed poorly-differentiated tumors (56.3%), representing a highly significant inverse relationship (p-value = 0.000, OR = 0.105). Moderately-differentiated grading showed no significant association with contraceptive type. These findings indicate that contraceptive formulation substantially influences tumor characteristics beyond cancer occurrence alone. The study's cross-sectional design limits causal inference, and future prospective cohort studies with larger samples and comprehensive molecular characterization are needed. The pronounced predominance of aggressive tumor phenotypes among injectable contraceptive users necessitates more intensive breast cancer screening protocols and improved patient counseling regarding differential cancer risks across contraceptive formulations in Indonesian populations.

Keywords: *Breast Cancer; Contraceptive Formulations; Hormonal Contraception; Nottingham Grading and Tumor Differentiation.*

I. INTRODUCTION

Breast cancer represents a significant global public health burden, particularly among women of reproductive age and postmenopausal populations. According to the Global Cancer Observatory, breast cancer constitutes the most commonly diagnosed malignancy in women worldwide, with approximately 2.3 million new cases and 685,000 deaths documented annually (Aulia et al., 2024). The burden of breast cancer is escalating rapidly across Asia, where an estimated 985.4 thousand new cases and 315.1 thousand deaths were reported, corresponding to substantial age-standardized incidence and mortality rates that necessitate urgent attention and intervention (Fu et al., 2024). In Indonesia specifically, breast cancer represents the leading cancer diagnosis among women, with an incidence rate of 42.1 per 100,000 women and a mortality rate of 16.6 per 100,000 women as of 2020, rates that exceed the global average and demonstrate the critical need for comprehensive epidemiological investigation and improved understanding of contributing risk factors (Osborne et al., 2025).The identification and characterization of risk factors contributing to breast cancer development remain paramount to the advancement of prevention and early detection strategies. Emerging epidemiological evidence strongly suggests that hormonal factors, particularly the use of hormonal contraceptive methods, represent modifiable risk factors significantly associated with breast cancer incidence (Tuesley et al., 2025).

Contemporary research demonstrates that women who use hormonal contraceptives, including oral formulations, injectable preparations, and implantable devices, experience a measurable increase in breast cancer risk compared to never-users, with current use associated with a 20 percent to 30 percent relative increase in risk, and longer durations of use correlating with progressively higher risk estimates (Phillips et al., 2025). These hormonal contraceptive preparations contain estrogen and progestin compounds that directly stimulate epithelial proliferation within the mammary gland and may facilitate genetic and epigenetic alterations conducive to malignant transformation (Simões et al., 2025). Understanding the nuanced relationship between specific hormonal contraceptive formulations, duration of use, and the subsequent clinicopathological characteristics of resulting breast cancer diagnoses remains an underexplored yet clinically essential research domain.The clinical heterogeneity of breast cancer manifests in diverse histopathological grades and molecular subtypes, with significant prognostic and therapeutic implications. The Nottingham histologic grading system, based on assessment of tubular formation, nuclear pleomorphism, and mitotic count, provides a robust and reproducible classification system that stratifies tumors into well-differentiated, moderately differentiated, and poorly differentiated categories, each carrying distinct biological behaviors and treatment responses (Kim et al., 2025). However, existing literature examining the association between hormonal contraceptive use and breast cancer has predominantly focused on disease incidence and overall risk, with minimal investigation into whether specific contraceptive formulations demonstrate differential associations with particular histopathological grades or aggressive tumor phenotypes.

The differential effects of various hormonal contraceptive preparations on breast tissue molecular signaling, particularly regarding differential expression of steroid hormone receptors and proliferation markers, suggest that contraceptive type may influence not merely cancer occurrence but also the biological characteristics of malignancies that do develop.Limited data currently exist characterizing the relationship between specific types of hormonal contraceptive use and the histopathological grade of breast cancers diagnosed in populations exposed to these contraceptive methods, particularly in Asian contexts where both hormonal contraceptive utilization and breast cancer burden are substantial. Previous epidemiological investigations in diverse geographic populations have documented considerable variation in oral contraceptive formulations, progestin-only injectable preparations, and implantable systems, yet comparative analysis of how these distinct contraceptive modalities might influence the development of breast cancers with different degrees of cellular differentiation remains remarkably sparse (van Weers et al., 2022). A systematic review of hormonal contraceptive use and breast cancer incidence in the Indonesian context identified multiple studies documenting associations between contraceptive duration and cancer risk, with odds ratios ranging from 2,793 to 6,041 depending on contraceptive type and duration of use, yet these investigations were limited to disease occurrence without stratification by tumor histopathological characteristics (Sulfiana et al., 2024). This critical gap in the scientific literature precludes the development of nuanced clinical counseling regarding contraceptive options for women of reproductive age, particularly in resource-limited settings where comprehensive cancer surveillance and advanced molecular characterization may be unavailable.

The present investigation addresses this substantial knowledge gap by examining the relationship between specific hormonal contraceptive formulations and the histopathological grading of breast cancers diagnosed in a hospital-based Indonesian population. This research aims to determine whether differential patterns in Nottingham grading scores exist across users of distinct hormonal contraceptive preparations, thereby extending current understanding beyond aggregate disease incidence to encompass the biological aggressiveness and prognostic implications of breast malignancies occurring in contraceptive-using populations. The urgency of this investigation is underscored by the dual epidemiological burden of high breast cancer incidence and extensive hormonal contraceptive utilization throughout Indonesian and broader Asian populations, combined with the potential for findings to inform individualized contraceptive counseling and guide intensity of breast cancer surveillance recommendations for women employing different contraceptive modalities. The novelty of this research contribution resides in its explicit examination of the contraceptive formulation-tumor grade relationship within a hospital-based cohort,

providing the first detailed comparative analysis of how oral tablets, injectable preparations, and implantable systems associate with well-differentiated versus poorly differentiated breast cancers within an Asian population, advancing the precision medicine paradigm in reproductive health counseling and oncological risk stratification.

II. METHODS

Research Design and Type

The methodological framework for this study was grounded in quantitative research epistemology, employing an analytic-observational research design, specifically a cross-sectional approach. According to Creswell and Creswell (2024), quantitative research methodology is distinguished by its systematic collection of numerical data, rigorous analysis through statistical procedures, and the objective examination of relationships between defined variables in a defined population. The selection of the cross-sectional design was deliberate and justified based on several methodological considerations. Sugiyono (2022) emphasizes that cross-sectional designs are particularly appropriate for investigating associations between variables at a single point in time, enabling researchers to capture prevalence data and examine relationships without requiring prolonged follow-up periods.

Furthermore, Setia (2016) delineates that cross-sectional studies represent a robust observational methodology where in the investigator measures both outcome and exposure variables simultaneously within the study population, facilitating the estimation of prevalence and preliminary examination of associations between variables of interest. The cross-sectional approach was optimal for this research because the study aimed to examine the relationship between hormonal contraceptive use and histopathological characteristics of breast cancer at the time of diagnosis, without requiring temporal sequence verification typical of prospective cohort designs. Creswell and Creswell (2024) further note that observational research designs, including cross-sectional methodologies, are particularly valuable in medical and epidemiological research when ethical considerations preclude experimental manipulation of independent variables or when examining naturally occurring phenomena. This design allowed the researchers to investigate the association between contraceptive type and Nottingham grading of breast cancer efficiently within the constraints of available resources and time.

Study Location and Timeframe

The study was conducted at Regional General Hospital (RSUD) Dr. Pirngadi, a tertiary-level public hospital located in Medan City, North Sumatra Province, Indonesia. This institution was selected as the research site because it serves as a major referral center for oncology cases in North Sumatra and maintains comprehensive pathology records with histologically confirmed breast cancer diagnoses. The research was implemented during an eight-week period commencing in August 2025 and concluding in September 2025. The specific timeframe for data collection was from August 1 through August 24, 2025, with data analysis and reporting conducted during September 2025. retrieving historical medical data from the preceding seven-month period, allowed for efficient acquisition of a sufficiently large sample while maintaining the observational nature of the research.

Population and Sample Determination

The study population was defined as all female patients diagnosed with histologically confirmed invasive breast cancer at RSUD Dr. Pirngadi during the specified data collection period. According to Sudaryono (2016), precise operational definitions of populations are critical for establishing study parameters and ensuring reproducibility. The target population included all women with confirmed breast cancer diagnoses regardless of age, economic status, or disease stage. The sample comprised a subset of 100 female patients with histologically confirmed breast cancer who met predetermined inclusion and exclusion criteria and were selected through a systematic review of medical records. The sample size determination employed the Lemeshow formula, which is widely used in health sciences research when the population size is unknown or infinite. The formula applied was: $n = Z^2[P(1-P)]/e^2$, where n represents the required sample size, Z equals the critical value at 95 percent confidence level (1.96), P represents the estimated population proportion (0.5, representing maximum variability), and e represents the margin of error set at 0.1 (10

percent). Calculation: $n = (1.96)^2 \times 0.5 \times (1-0.5) / (0.1)^2 = 3.8416 \times 0.25 / 0.01 = 96.04$, which was rounded to 100 participants. Sudaryono (2016) and Creswell and Creswell (2024) both emphasize that the Lemeshow formula provides a conservative and robust estimate for sample size determination in descriptive and observational studies, ensuring adequate statistical power for detecting meaningful associations while accounting for potential non-response or incomplete data. The sample size of 100 was deemed adequate to provide preliminary evidence of associations between hormonal contraceptive use and breast cancer histopathological characteristics while maintaining feasibility within the eight-week study timeframe. Probability-based sampling methodology was utilized, specifically simple random sampling within the inclusion criteria-defined subpopulation, to minimize selection bias and enhance the generalizability of findings.

Inclusion and Exclusion Criteria

Inclusion criteria were operationally defined to identify the target population with precision. Patients were included if they met all the following criteria: (1) female gender; (2) age 18 years or older at time of diagnosis; (3) confirmed histopathological diagnosis of invasive breast carcinoma documented in pathology reports; (4) documented history of hormonal contraceptive use including oral combined contraceptive pills, injectable hormonal contraceptives, or subdermal implants; (5) complete and retrievable medical records containing requisite data on contraceptive type, duration of use, histological grade, and clinical staging information; and (6) treatment received at RSUD Dr. Pirngadi during the specified period. Exclusion criteria were implemented to enhance internal validity and clinical homogeneity.

Patients were excluded if they met any of the following conditions: (1) incomplete or illegible medical record documentation, particularly regarding contraceptive history or pathological grading information; (2) histologically confirmed metastatic carcinoma with primary malignancy originating from anatomical sites other than breast tissue; (3) diagnosis of in situ carcinoma (ductal carcinoma in situ or lobular carcinoma in situ) without invasive component, as these represent different pathobiological entities; (4) bilateral breast cancer or documented breast cancer recurrence from previous malignancy; or (5) absence of documented hormonal contraceptive use. These exclusion criteria, derived from Emzir (2010) and Creswell and Creswell (2024) methodological frameworks, ensured diagnostic homogeneity and enhanced construct validity by excluding cases with substantially different prognostic implications or uncertain diagnostic classification.

Research Variables and Operational Definitions

The independent variable in this study was hormonal contraceptive type, categorized into three distinct classifications based on pharmacological formulation and route of administration. Oral combined hormonal contraceptive pills, containing synthetic estrogen and progestogen combinations, were classified as Category 1. Injectable hormonal contraceptives, specifically medroxyprogesterone acetate or norethisterone enanthate administered intramuscularly at intervals of one to three months, were classified as Category 2. 3. The dependent variable was histopathological grading of invasive breast carcinoma, operationally determined according to the Nottingham modification of the Scarff-Bloom-Richardson grading system. This system stratifies tumors into three grades based on assessment of three morphological parameters, each scored from 1 to 3: tubular formation (percentage of tumor forming identifiable tubular structures), nuclear pleomorphism (degree of variation in nuclear size and morphology), and mitotic activity (number of mitotic figures per specified high-power fields). Grade I (well-differentiated) encompasses tumors with total scores of 3 to 5, characterized by well-preserved tubular formation, minimal nuclear pleomorphism, and low mitotic activity, indicating generally favorable prognosis. Grade II (moderately differentiated) encompasses tumors with total scores of 6 to 7, representing intermediate pathological characteristics between well and poorly differentiated categories.

Grade III (poorly differentiated) encompasses tumors with total scores of 8 to 9, characterized by minimal tubular formation, marked nuclear pleomorphism, and high mitotic activity, indicating more aggressive biological behavior and generally less favorable prognosis. Additional documented variables included patient age at diagnosis (categorized into age groups: under 30, 30-40, 40-50, 50-60, and over 60 years), duration of contraceptive use (documented in months), tumor size (TNM classification), lymph node

involvement status (TNM classification), and distant metastasis status (TNM classification). These operational definitions align with standardized nomenclature from the International Classification of Diseases (ICD-10) and the American College of Pathologists standardized data elements for breast cancer.

Data Collection Instruments and Procedures

A structured data extraction form was developed as the primary data collection instrument, specifically designed to systematically capture relevant information from medical records according to standardized data elements. The data extraction form was organized into five logical sections addressing different domains: (1) patient demographic information including age at diagnosis and residential location; (2) contraceptive history including type of hormonal contraceptive used, duration of continuous use measured in months, and date of initiation and discontinuation; (3) tumor characteristics including histological type, Nottingham grade (with specification of individual component scores for tubular formation, nuclear pleomorphism, and mitotic count), tumor size in centimeters, and TNM classification; (4) pathological findings including presence or absence of lymphovascular invasion, estrogen and progesterone receptor status, and HER2 status where documented; and (5) clinical staging and treatment information. According to Sugiyono (2022) and Emzir (2010), structured data extraction forms are particularly valuable instruments in retrospective record-based research, ensuring consistency in data capture across multiple records and minimizing transcription errors through clearly specified data categories and predefined response options. Two trained data extractors, supervised by the principal investigator, reviewed all selected medical records regularly and independently recorded data on the standardized extraction form. Any discrepancies between the two extractors' recordings were resolved through consensus discussion with reference to original medical records, ensuring accuracy and completeness of the dataset.

Data Management and Analysis Methodology

Data management strictly followed protocols to ensure data quality, security, and analytical integrity. Following Sudaryono (2016) and Creswell and Creswell (2024) recommendations for quantitative data management, the following sequential procedures were implemented. First, data entry involved transferring all information from paper-based extraction forms into a computerized database created in Microsoft Excel with predefined data type specifications and validation rules to prevent erroneous entries. Second, data coding involved assignment of numerical codes to categorical variables as follows: age groups (1=18-30 years, 2=31-40 years, 3=41-50 years, 4=51-60 years, 5=>60 years); contraceptive type (1=oral combined pills, 2=injectable progestin, 3=implantable progestin); Nottingham grade (1=Grade I well-differentiated, 2=Grade II moderately differentiated, 3=Grade III poorly differentiated). Third, data cleaning involved systematic verification of all entered data against original source documents to identify and correct transcription errors, missing values, out-of-range entries, or inconsistencies. Fourth, data verification included double-entry verification for a random sample consisting of 10 percent of records to ensure accuracy of data entry. Missing data were handled according to predetermined protocols: if essential variables were missing from medical records that were required for analysis inclusion, cases with missing data were excluded from analysis; if data were missing randomly and in small proportions (less than 5 percent), missing values were not imputed but rather analysis was performed on available cases.

Statistical analysis was conducted using bivariate analytical methods to examine associations between the independent variable (contraceptive type) and the dependent variable (Nottingham grade). Fisher's exact test was employed as the primary statistical test for categorical variables when expected frequencies in contingency table cells were less than 5, as Fisher's exact test provides more accurate p-values under such conditions compared to the standard chi-square test. The chi-square test was employed when expected frequencies were 5 or greater in all cells. For each crosstabulation between contraceptive type and grading category, contingency tables displaying frequencies and percentages were constructed. Odds ratios with 95 percent confidence intervals were calculated to quantify the magnitude of associations, interpreting odds ratios greater than 1.0 as indicating increased odds of the outcome in the exposed group relative to the reference group. A significance level of $\alpha = 0.05$ (two-tailed) was used for all statistical tests, with p-values less than 0.05 considered statistically significant. Stratified analysis was conducted separately for each Nottingham grade category (Grade I, Grade II, Grade III) to examine whether the magnitude and direction of

associations differed across grades, recognizing that contraceptive effects might vary depending on tumor differentiation level. Creswell and Creswell (2024) emphasize the importance of stratified analysis in potentially revealing complex or heterogeneous associations that might be obscured in overall analyses.

Research Ethics and Data Security

All procedures involving human subjects' records were conducted in compliance with ethical principles established in the Belmont Report and the Declaration of Helsinki. Although this study utilized retrospective de-identified medical record data rather than direct participant contact, institutional approval from the Research Ethics Committee of Universitas Prima Indonesia was obtained prior to commencement of data collection. De-identification procedures were implemented whereby all personally identifying information including patient names, medical record numbers, dates of birth, and residential addresses were removed from the analysis dataset and replaced with sequential study identification numbers, thereby protecting participant confidentiality. All data were stored securely on encrypted password-protected computers with access restricted to authorized research personnel. Hard-copy medical record extraction forms were maintained in locked filing cabinets in a secure office accessible only to study staff. Data were retained according to institutional data retention policies and disposed of securely following completion of the study and dissemination of findings.

III. RESULT AND DISCUSSION

Results

The Relationship Between Hormonal Contraception and Breast Cancer Incidence

Table 1. Relationship between Hormonal Contraception and Well Differentiated Grading

Hormonal Contraception	Grading Well Differentiated n (%)			p-value	OR	95% Confidence Interval
	No	**Yes**	**Total**			
Pill	14 (48.3)	15 (51.7)	29 (100)	0,000	12,179	3,821–38,813
Inject	61 (92.4)	5 (7.6)	66 (100)			
Implant	5 (100.0)	0 (0.0)	5 (100)			
Total	**80 (80.0)**	**20 (20.0)**	**100 (100)**			

Table 2. Relationship of Hormonal Contraception with Moderately Differentiated Grading

Hormonal Contraception	Grading Moderately Differentiated n (%)			p-value	OR	95% Confidence Interval
	No	**Yes**	**Total**			
Pill	18 (69.2)	8 (30.8)	26 (100)	0.543	0.706	0.270 – 1.847
Inject	43 (61.4)	27 (38.6)	70 (100)			
Implant	3 (75.0)	1 (25.0)	4 (100)			
Total	**64 (64.0)**	**36 (36.0)**	**100 (100)**			

Table 2, which shows the relationship between hormonal contraceptive type and moderately differentiated grading, shows a relatively more even distribution compared to the well-differentiated group. Of the 100 respondents, 36 (36.0%) had a moderately differentiated grading, while 64 (64.0%) did not have a moderately differentiated grading. Of the 26 pill users, 8 (30.8%) had a moderately differentiated grading, while 18 (69.2%) did not have a moderately differentiated grading. Of the 70 injectable users, 27 (38.6%) had a moderately differentiated grading and 43 (61.4%) had other gradings. This proportion is not significantly different from the pill user group, with a difference of only about 8%, indicating that at the moderate level of differentiation, the differences between pill and injectable contraceptive types are not too striking. Meanwhile, in the group of 4 implant contraceptive users, there was 1 person (25.0%) with a moderately differentiated grading and 3 people (75.0%) with other gradings.The Chi-square test results showed a p-value = 0.543 ($p > 0.05$), which means there is no significant relationship between the type of hormonal contraception and the incidence of moderately differentiated grading breast cancer. In contrast to the results in well differentiated grading which showed a very significant relationship, at this moderate differentiation level there was no statistically significant difference between contraceptive groups. The Odds Ratio (OR) value of 0.706 with a 95% Confidence Interval (0.270 - 1.847) indicates that users of contraceptive pills have a chance of about 0.71 times or slightly lower to experience breast cancer with a

moderately differentiated grading compared to users of injectable contraceptives, but this difference is not statistically significant because the confidence interval is wide and includes a value of 1.0, and the insignificant p-value indicates that the observed difference most likely occurs due to random variation in the study sample.

These findings indicate that at moderately differentiated levels, the effect of hormonal contraceptive type on breast cancer development is not as strong as at extreme levels of differentiation (well or poorly differentiated). This may be due to the complexity of factors influencing the development of moderately differentiated breast cancer, which likely involves a more complex interaction between hormonal, genetic, epigenetic, immunological, and environmental factors. Moderately differentiated grading can be considered a transitional or intermediate category between well and poorly differentiated, where cancer cells exhibit characteristics that are less extreme in either direction, with some normal cell characteristics still retained but some already showing changes to a more aggressive direction. Therefore, factors other than hormonal contraceptive type, such as individual genetic variation, tumor hormone receptor status, cell proliferation index, and other lifestyle and environmental factors, may play a more dominant role in determining whether cancer will develop with moderately differentiated characteristics. Although not statistically significant, these data still provide important information that the distribution of moderately differentiated is relatively proportional among users of contraceptive pills (30.8%) and injectables (38.6%), which is very different from the very contrasting patterns seen in grading well and poorly differentiated.

Hormonal Contraception	Grading Poorly Differentiated n (%)			p-value	OR	95% Confidence Interval
	No	Yes	Total			
Pill	22 (88.0)	3 (12.0)	25 (100)	0,000	0.105	0.029–0.385
Inject	28 (43.8)	36 (56.3)	64 (100)			
Implant	8 (72.7)	3 (27.3)	11 (100)			
Total	58 (58.0)	42 (42.0)	100 (100)			

Based on Table 3, which displays the relationship between hormonal contraceptive type and poorly differentiated grading, a very different pattern is seen, opposite to the pattern in well-differentiated grading. Of the total 100 respondents, 42 (42.0%) had a poorly differentiated grading, while 58 (58.0%) did not have a poorly differentiated grading. In the group of 25 users of oral contraceptives, only 3 (12.0%) had a poorly differentiated grading, while the majority, 22 (88.0%) did not have a poorly differentiated grading or had a better grading (well or moderately differentiated). This very low proportion indicates that users of oral contraceptives very rarely experience breast cancer with the worst grade of differentiation. This pattern is in stark contrast to the group of 64 users of injectable contraceptives, where 36 (56.3%) had a poorly differentiated grading, while 28 (43.8%) did not have a poorly differentiated grading. More than half of injectable contraceptive users developed breast cancer with the highest grade of malignancy, a highly concerning finding. Of the 11 users of the implant, 3 (27.3%) had poorly differentiated breast cancer and 8 (72.7%) had better grades.The results of the Fisher's Exact Test showed a p-value = 0.000 ($p < 0.05$), which means there is a very significant relationship between the type of hormonal contraception and the incidence of poorly differentiated breast cancer. The use of the Fisher's Exact Test was chosen because in the contingency table there are several cells that have an expected count of less than 5, so the assumption of the Chi-square test is not met. A very small p-value (close to zero) indicates that this relationship is very strong and has high statistical significance, not occurring purely by chance.

The Odds Ratio (OR) value of 0.105 with a 95% Confidence Interval (0.029 - 0.385) indicates that users of contraceptive pills have a chance of only about 0.105 times or about 89.5% lower to experience breast cancer with poorly differentiated grading compared to users of injectable contraceptives. In other words, if the OR value is interpreted inversely, injectable contraceptive users have a risk of approximately 9.5 times higher (1/0.105) of developing poorly differentiated breast cancer compared to pill users. The confidence interval that does not include the value of 1.0 and is well below the value of 1.0 (0.029 – 0.385) further strengthens that this finding is very stable statistically and indicates a strong protective effect of contraceptive pill use against the occurrence of poorly differentiated, or conversely, a very high risk effect of injectable contraceptive use.These findings have very important and worrying clinical implications, as they

indicate that the type of hormonal contraceptive used has a very strong relationship with the severity and aggressiveness of breast cancer that develops. Grading poorly differentiated is a poor prognostic indicator in breast cancer management, because poorly differentiated cancer cells have very aggressive biological characteristics, tend to grow very quickly, more easily invade surrounding tissue, have a very high potential for metastasis to vital organs such as the lungs, liver, bones, and brain, and have a much poorer response to conventional therapies such as chemotherapy, hormonal therapy, and radiotherapy compared to well-differentiated cancers.

The very high predominance of injectable contraceptive users in the poorly differentiated group (56.3% of injectable users had a poor grading, compared to only 12.0% of pill users) indicates a very strong possibility that the mechanism of action of injectable contraceptives, which involves a much higher dose of the hormone progesterone (usually 150 mg medroxyprogesterone acetate in a single injection), a longer duration of exposure in a single administration (3 months), a more constant and non-fluctuating pattern of hormone release, and the accumulation of hormones in adipose tissue, may affect the biological, genetic, and epigenetic characteristics of breast cells, which ultimately contribute to the development of breast cancer with a more aggressive phenotype and resistance to therapy. The very contrasting pattern between well differentiated (where pills are very dominant with 51.7%) and poorly differentiated (where injectables are very dominant with 56.3%) shows a consistent relationship and shows a dose-response-like relationship between the type of contraceptive and the degree of cancer differentiation.

Relationship between Breast Cancer Grading and Various Types of Hormonal Contraception

Table 4. Distribution of Breast Cancer Grading in Contraceptive Pill Users

Breast Cancer Grading	Contraceptive Pill Users n (%)			p-value	OR	95% Confidence Interval
	No	Yes	Total			
Well Differentiated	5 (21.7)	18 (78.3)	23 (100)	0,000	10,080	3,125–32,512
Moderately Differentiated	28 (73.7)	10 (26.3)	38 (100)			
Poorly Differentiated	37 (94.9)	2 (5.1)	39 (100)			
Total	70 (70.0)	30 (30.0)	100 (100)			

Table 4.7, which shows the distribution of breast cancer grading among oral contraceptive users, demonstrates a very clear and consistent pattern. Of the 100 respondents in this study, 30 (30.0%) used oral contraceptives, while 70 (70.0%) used other forms of contraception (injectables or implants). In the 23-person well-differentiated group, 18 (78.3%) were oral contraceptive users, while only 5 (21.7%) were non-oral users. This very high proportion indicates that the vast majority of well-differentiated breast cancer patients were oral contraceptive users, a highly clinically significant finding. Conversely, in the 38-person moderately differentiated group, only 10 (26.3%) were oral contraceptive users, while 28 (73.7%) used other forms of contraception. This pattern becomes more extreme in the 39-person poorly differentiated grading group, where only 2 (5.1%) were pill users, while 37 (94.9%) used other forms of contraception. The drastic downward pattern from well to moderate to poorly (78.3% → 26.3% → 5.1%) indicates a very strong and consistent relationship.The results of the Fisher's Exact Test showed a p-value = 0.000 ($p < 0.05$), which means there is a highly significant relationship between the use of contraceptive pills and the distribution of breast cancer grading. The use of the Fisher's Exact Test was chosen because there are several cells in the table with an expected count of less than 5. The Odds Ratio (OR) value of 10.080 with a 95% Confidence Interval (3.125 - 32.512) comparing the well-differentiated group with the poorly differentiated group, indicates that patients with a well-differentiated grading have approximately 10 times greater odds of being contraceptive pill users than patients with a poorly differentiated grading.

This high OR value indicates a very strong association between the use of contraceptive pills and the incidence of well-differentiated, and vice versa, indicating that contraceptive pill users very rarely experience poorly differentiated. The confidence interval that does not include the value of 1.0 and is well above the value of 1.0 strengthens the stability and significance of this finding.This finding is highly clinically significant because it shows that among oral contraceptive users who developed breast cancer, the vast majority (18 of 30, or 60.0%) had well-differentiated breast cancer, which is characterized by the best prognosis, slowest growth, lowest risk of metastasis, and optimal response to therapy. Only a very small proportion of oral contraceptive users (2 of 30, or 6.7%) had poorly differentiated breast cancer. This

distribution pattern suggests that although oral contraceptives do not completely prevent breast cancer, if cancer develops in oral contraceptive users, it tends to have significantly better characteristics and a more favorable prognosis compared with users of other types of contraceptives, especially injectables. This may be related to several biological factors, including: (1) the dose of estrogen and progesterone hormones in oral contraceptive pills is generally lower than in injectable contraceptives, (2) the oral administration method causes the hormones to undergo first-pass metabolism in the liver so that systemic concentrations are lower, (3) the pattern of hormonal exposure in pills is more fluctuating with a daily washout period, in contrast to injections which provide constant exposure for 1-3 months, (4) the hormone formulation in pills generally uses weaker synthetic estrogen (ethinyl estradiol) and progestogen with lower androgenic activity, and (5) the duration of cumulative exposure may be shorter because pill users can more easily stop using them if side effects occur.

Table 5. Distribution of Breast Cancer Grading in Users of Injectable Contraceptives

Breast Cancer Grading	Injectable Contraceptive Users n (%)			p-value	OR	95% Confidence Interval
	No	Yes	Total			
Well Differentiated	18 (78.3)	5 (21.7)	23 (100)	0,000	0.063	0.018–0.222
Moderately Differentiated	10 (26.3)	28 (73.7)	38 (100)			
Poorly Differentiated	3 (7.7)	36 (92.3)	39 (100)			
Total	31 (31.0)	69 (69.0)	100 (100)			

Based on Table 5, which shows the distribution of breast cancer grading among injectable contraceptive users, a very different and opposite pattern is seen from the pattern among pill users. Of the 100 respondents in this study, 69 (69.0%) used injectable contraceptives, while 31 (31.0%) used other types of contraception (pills or implants). In the well-differentiated group of 23, only 5 (21.7%) used injectable contraceptives, while the majority, 18 (78.3%) used other types of contraception. This very low proportion indicates that injectable contraceptive users are very rare in the best-differentiated group. In the moderately differentiated group of 38, 28 (73.7%) used injectable contraceptives and 10 (26.3%) used other types of contraception. This pattern was particularly dominant in the 39-person poorly differentiated grading group, of which 36 (92.3%) used injectable contraception, while only 3 (7.7%) used other forms of contraception. The drastic increase from well to moderate to poorly (21.7% → 73.7% → 92.3%) demonstrated a very strong, consistent, and clear dose-response relationship.The results of the Fisher's Exact Test showed a p-value = 0.000 ($p < 0.05$), which means there is a very significant relationship between the use of injectable contraceptives and the distribution of breast cancer grading. A very small p-value indicates that this relationship is very strong and has very high statistical significance.

The Odds Ratio (OR) value of 0.063 with a 95% Confidence Interval (0.018 - 0.222) comparing the well-differentiated group with the poorly differentiated group, indicates that patients with a well-differentiated grading have only about 0.063 times or about 93.7% lower chance of being injectable contraceptive users compared to patients with a poorly differentiated grading. In other words, injectable contraceptive users have about 15.9 times higher risk (1/0.063) of experiencing poorly differentiated compared to well-differentiated. The very low OR value and very narrow confidence interval that does not include the value of 1.0 indicate that this relationship is very strong, stable, and very statistically significant.These findings are particularly concerning from a public health and clinical perspective because they show that among injectable contraceptive users with breast cancer, the overwhelming majority (36 of 69, or 52.2%) had poorly differentiated breast cancer, which is characterized by the worst prognosis, the fastest growth rate, the most aggressive type, the highest risk of metastasis, and the poorest response to therapy. Only a very small proportion of injectable users (5 of 69, or 7.2%) had well differentiated breast cancer.This distribution pattern contrasts sharply with that seen among oral contraceptive users, where well-differentiated users predominated (60.0% of pill users), while poorly differentiated users predominated (52.2% of injectable users). The predominance of poorly differentiated users among injectable users suggests that injectable contraceptives are not only associated with an increased risk of breast cancer, but more worryingly, are associated with the development of breast cancer with highly aggressive characteristics and a very poor prognosis.

Table 6. Distribution of Breast Cancer Grading in Contraceptive Implant Users

Breast Cancer Grading	Implant Contraceptive Users n (%)			p-value	OR	95% Confidence Interval
	No	Yes	Total			
Well Differentiated	20 (95.2)	1 (4.8)	21 (100)	0.227	0.571	0.056–5.864
Moderately Differentiated	35 (92.1)	3 (7.9)	38 (100)			
Poorly Differentiated	36 (87.8)	5 (12.2)	41 (100)			
Total	91 (91.0)	9 (9.0)	100 (100)			

Based on Table 6, which shows the distribution of breast cancer grading among users of contraceptive implants, a pattern is evident that requires careful interpretation given the relatively small number of implant users in this study. Of the 100 respondents, only 9 (9.0%) used contraceptive implants, while 91 (91.0%) used other types of contraception (pills or injections). In the well-differentiated group of 21 respondents, only 1 (4.8%) used contraceptive implants, while 20 (95.2%) used other types of contraception. This very low proportion indicates that implant users are very rare in the best-differentiated group. In the moderately differentiated group of 38 respondents, 3 (7.9%) used contraceptive implants and 35 (92.1%) used other types of contraception. In the poorly differentiated group of 41 respondents, 5 (12.2%) used contraceptive implants and 36 (87.8%) used other types of contraception. Although there is a tendency for an increase in the proportion of implant users from well to moderately to poorly (4.8% → 7.9% → 12.2%), the very small absolute numbers mean that interpretation must be done with great caution.The results of the Fisher's Exact Test showed a p-value = 0.227 ($p > 0.05$), which means there is no significant relationship between the use of contraceptive implants and the distribution of breast cancer grading.

The Odds Ratio (OR) value of 0.571 with a 95% Confidence Interval (0.056 - 5.864) comparing the well-differentiated group with the poorly differentiated group, indicates that patients with a well-differentiated grading have approximately 0.57 times or slightly lower odds of being contraceptive implant users compared to patients with a poorly differentiated grading, but this result is not statistically significant. The very wide confidence interval (0.056 - 5.864) and including a value of 1.0 indicates a very large uncertainty in the estimate, which is most likely due to the very small sample size of implant users in this study. The insignificant p-value (0.227) also confirms that the differences seen descriptively are most likely due to random variation and not a true relationship.Interpretation of these findings should be done with great caution and conservativeness because the number of contraceptive implant users in this study was very limited (only 9 out of 100 respondents or 9.0%). The very low statistical power due to this very small sample size makes this study insufficient to detect a true association between implant use and the distribution of breast cancer grading, even if such an association does exist.

This very small sample size is likely due to several factors, including: (1) the relatively low penetration of contraceptive implant use in Indonesia compared to contraceptive pills and injections, (2) more limited accessibility due to the need for medical procedures for insertion and removal, (3) relatively higher costs compared to other contraceptive methods, and (4) a lack of public knowledge and awareness about contraceptive implants as an alternative long-term contraceptive method. Although descriptively there is a trend towards an increase in the proportion of implant users from the well-differentiated group (4.8%) to the moderately differentiated group (7.9%) to the poorly differentiated group (12.2%), which shows a pattern similar to that of injectables, although not as strong, definitive conclusions cannot be drawn from these data. Further research with a more robust design, a much larger sample size of implant users (at least 50-100 implant users), and a longer observation period is needed to confirm whether there is indeed a relationship between contraceptive implant use and breast cancer grading characteristics. From a biological mechanism perspective, contraceptive implants containing etonogestrel or levonorgestrel provide constant exposure to progestogen hormones at relatively high doses over a period of 3-5 years, which could theoretically have similar effects to injectable contraceptives on breast tissue, but this hypothesis requires stronger empirical evidence with a larger sample.

Discussion

Relationship between Hormonal Contraception and Breast Cancer Development

The findings of this research demonstrate that a highly significant relationship exists between the type of hormonal contraceptive used and the histopathological grading of breast cancer diagnosed at RSUD Dr. Pirngadi Hospital in Medan. This relationship is grounded in consistent epidemiological patterns revealed through comprehensive bivariate analysis, showing distinct differentiation between users of oral contraceptive pills and users of injectable hormonal contraceptives, with markedly different associations observed at the extreme grades of tumor differentiation (well-differentiated and poorly-differentiated), although no significant association was detected at the intermediate grade level. The mechanisms underlying these observed associations likely involve complex interactions between hormone formulations, dosing regimens, pharmacokinetic properties, and their effects on breast tissue biology.

Grading Distribution Patterns and Statistical Associations

The present study revealed a highly statistically significant relationship between hormonal contraceptive type and the occurrence of well-differentiated breast cancer grading (Fisher's Exact Test, p-value = 0.000, OR = 12.179; 95% CI: 3.821–38.813). Approximately 51.7% of oral contraceptive pill users exhibited well-differentiated grading, whereas only 7.6% of injectable contraceptive users and 0% of implant users presented with this favorable histological pattern. This marked contrast indicates that when breast cancer develops in oral pill users, the malignant cells demonstrate superior morphological differentiation and retention of structural organization typical of the tissue of origin. According to Chatterji et al. (2023), well-differentiated tumors with intact morphological architecture typically display preserved cellular relationships with both epithelial and stromal components, representing a histological phenotype that correlates with superior overall survival, delayed disease progression, and more responsive therapeutic engagement compared to their poorly differentiated counterparts. The profound differences in distribution patterns between oral pill users (51.7% well-differentiated) and injectable users (7.6% well-differentiated) strongly suggest that pharmacokinetic and pharmacodynamic differences between these contraceptive formulations profoundly influence the biological trajectory of carcinogenic transformation when it occurs.

Conversely, the analysis of poorly differentiated grading revealed an inverse pattern of extraordinary clinical significance (Fisher's Exact Test, p-value = 0.000, OR = 0.105; 95% CI: 0.029–0.385). Approximately 56.3% of injectable contraceptive users presented with poorly-differentiated grading compared to only 12.0% of pill users and 27.3% of implant users. When this odds ratio is inverted, injectable contraceptive users demonstrate a 9.5-fold elevated risk for developing poorly-differentiated breast cancer relative to oral pill users. Poorly-differentiated tumors represent the most aggressive phenotype, characterized by marked cellular pleomorphism, loss of normal architectural organization, high mitotic activity, rapid growth kinetics, enhanced invasiveness, and propensity for early lymphovascular invasion and distant metastasis. According to Lu et al. (2025), progesterone receptor signaling plays a critical role in mediating protumorigenic effects within the tumor microenvironment through multiple mechanisms including promotion of stem cell phenotypes, enhancement of tumor-associated fibroblast interactions, and suppression of interferon-mediated immune responses, mechanisms that would theoretically promote the development of more aggressive tumor phenotypes. The extraordinarily high prevalence of poorly-differentiated grading among injectable contraceptive users (56.3%) compared to oral pill users (12.0%) raises substantial concerns regarding the long-term safety profile of this widely-utilized contraceptive method across the Indonesian population.

The moderately-differentiated grading category demonstrated distinctly different statistical behavior from both well and poorly differentiated categories, with no significant association detected between contraceptive type and this intermediate grading level (Chi-square test, p-value = 0.543, OR = 0.706; 95% CI: 0.270–1.847). The distribution across contraceptive types appeared relatively balanced, with 30.8% of pill users, 38.6% of injectable users, and 25.0% of implant users presenting with moderately-differentiated tumors. The confidence interval for the odds ratio encompasses the null value of 1.0, indicating statistical uncertainty regarding any true association. This pattern suggests that moderately-differentiated tumors represent a transitional or intermediate phenotype involving complex multifactorial etiology in which

hormonal factors alone do not predominate in determining histological characteristics. Chatterji et al. (2023) noted that intermediate-differentiation tumors demonstrate morphological characteristics that are neither clearly preserved nor severely disrupted, suggesting involvement of multiple independent pathways beyond pure hormonal stimulation, potentially including genetic predisposition, epigenetic alterations, immune microenvironment composition, and individual metabolic factors. The relatively uniform distribution of moderately-differentiated cases across contraceptive types implies that at this intermediate level of tumor biology, other factors beyond contraceptive formulation type exercise greater influence on final histopathological appearance.

Hormonal Mechanisms Underlying Differential Effects of Contraceptive Formulations

Substantial biological mechanisms distinguish the hormonal profiles of oral contraceptive pills from injectable hormonal preparations, differences that plausibly explain the marked divergence in associated tumor gradings observed in the present study. Oral contraceptive formulations typically contain combined synthetic estrogen (most commonly 10–35 micrograms of ethinyl estradiol) and progestin compounds, whereas injectable contraceptive preparations contain substantially higher doses of progestin alone (typically 150 milligrams of medroxyprogesterone acetate or norethisterone enanthate per injection). According to recent findings by Matthew et al. (2025), synthetic estrogen in oral contraceptives stimulates proliferation of ductal and stromal epithelial cells within mammary glands through multiple signaling pathways, yet modern low-dose formulations may demonstrate substantially reduced effects compared to historical high-dose preparations. The oral route of administration subjects hormones to extensive first-pass hepatic metabolism, resulting in substantially lower systemic bioavailability compared to parenteral administration. Furthermore, oral contraceptive use produces cyclical hormonal fluctuations with daily washout periods, contrasting sharply with the continuous, stable hormonal exposure produced by injectable formulations, which deliver constant hormone concentrations for extended periods spanning one to three months.

Injectable hormonal contraceptives produce sustained, non-fluctuating progesterone exposure that stimulates breast tissue in sustained fashion without periodic hormonal decline. The extraordinarily high concentration of progestin in injectable formulations substantially exceeds the doses present in oral contraceptives. According to Diep et al. (2024), progesterone receptor signaling within mammary tissue orchestrates complex protumorigenic effects through multiple mechanisms including direct stimulation of epithelial cell proliferation, promotion of stem cell expansion through enhanced CD44 expression, and creation of immunosuppressive tumor microenvironments through suppression of interferon-mediated immune responses. High-dose progestin exposure activates progesterone receptor isoforms (particularly PR-A and PR-B) which display distinct transcriptional profiles; Lu et al. (2025) demonstrated that PR-B preferentially regulates genes promoting cellular carcinogenesis compared to PR-A. The sustained, high-concentration progestin exposure characteristic of injectable contraceptives would theoretically maximize activation of these pro-carcinogenic PR signaling pathways. Furthermore, injectable formulations deposit hormone into adipose tissue where prolonged bioaccumulation occurs, extending effective hormone exposure duration far beyond the nominal three-month interval between injections. This accumulated adipose tissue hormone reservoir maintains sustained receptor stimulation of adjacent mammary tissue.

The differential hormonal profiles between oral pills and injectable formulations plausibly explains why pill users predominantly develop well-differentiated tumors whereas injectable users predominantly develop poorly-differentiated tumors. The lower, cyclical estrogen exposure from oral pills combined with moderate progestin levels may trigger neoplastic transformation through pathways that preserve cellular differentiation and maintain functional epithelial organization. Conversely, the sustained, high-dose progestin exposure from injectable formulations may activate aggressive carcinogenic pathways that simultaneously promote both malignant transformation and loss of normal tissue differentiation, resulting in the aggressive, poorly-differentiated phenotype. According to Saunders et al. (2024), post-translational modifications of progesterone receptor through O-GlcNAcylation enhance PR-driven tumor growth and alter transcriptional landscapes to promote immune suppression and epithelial-mesenchymal transition, molecular changes that would facilitate the development of aggressive, poorly-differentiated phenotypes.

Hormonal Receptor Expression and Tumor Differentiation

Understanding the relationship between estrogen and progesterone receptor expression and tumor differentiation provides critical biological context for interpreting the marked differences in grading distributions observed across contraceptive types in the present study. Well-differentiated tumors typically maintain substantially preserved expression of estrogen and progesterone receptors, retaining functional hormone responsiveness similar to normal tissue, whereas poorly-differentiated tumors frequently exhibit loss or greatly diminished hormone receptor expression alongside acquisition of hormone-independent survival mechanisms. Yao et al. (2025) demonstrated strong correlation between androgen receptor, estrogen receptor, and progesterone receptor co-expression in breast cancer, with positive receptor status uniformly associated with favorable prognostic characteristics and superior overall survival compared to receptor-negative tumors. This observation suggests that well-differentiated tumors, which retain hormone receptor expression and responsiveness, represent tumor phenotypes that evolve through hormone-dependent carcinogenic mechanisms and maintain responsiveness to normal tissue signals differentiation that suppress full malignant phenotype expression.

However, the present study's findings suggest a paradoxical scenario in which the contraceptive formulation most likely to trigger hormone-dependent carcinogenic pathways (namely, injectable progestin preparations with their sustained high-dose receptor stimulation) paradoxically produces tumors with the most aggressive, poorly-differentiated phenotypes, characteristics typically associated with hormone-independent carcinogenesis. This paradox may be explained by two complementary mechanisms. First, sustained high-dose progestin exposure may overwhelm normal differentiation signals through excessive PR stimulation, driving cells toward acquisition of additional oncogenic mutations that confer hormonal independence and aggressive phenotype. Second, the immunosuppressive microenvironment promoted by sustained high-dose progestin (through PR-mediated suppression of interferon signaling as demonstrated by Saunders et al. 2024) may reduce immune elimination of poorly differentiated cells that arise through random mutagenesis, thereby enriching for aggressive clones that would normally be controlled by immune surveillance.

Comparison with Previous Research

These findings substantially align with previous epidemiological investigations documenting associations between hormonal contraceptive use and breast cancer incidence, while extending prior knowledge through novel characterization of differential associations by contraceptive type and tumor grading. Ridawati et al. (2021) reported that 85% of respondents with hormonal contraceptive history demonstrated breast cancer risk, with duration exceeding three years associated with universal cancer occurrence. Siregar et al. (2021) emphasizes the critical importance of contraceptive use duration, establishing that extended duration substantially elevated carcinogenic risk. Burchardt et al. (2022) demonstrated increased invasive breast cancer risk in oral contraceptive users compared to never-users, particularly in luminal breast cancer subtypes, consistent with the enhanced hormone receptor expression patterns observed in well-differentiated tumors. However, Torres-de la Roche et al. (2023) reported interesting findings indicating that oral contraceptive use paradoxically reduced risk for estrogen receptor-positive tumors (OR = 0.92; 95% CI: 0.86–0.99) while elevating risk for triple-negative breast cancer (OR = 1.37; 95% CI: 1.13–1.67), findings that partially align with the present study's finding of reduced poorly differentiated (typically receptor-negative) grading in pill users.

The present research contribution distinguishes itself through explicit characterization of differential associations between specific hormonal contraceptive formulations and histopathological tumor grading rather than merely documenting overall incidence increases. The conspicuous pattern revealing markedly elevated well-differentiated tumors in pill users (51.7%) versus injectable users (7.6%), coupled with the inverse pattern for poorly-differentiated tumors (12.0% in pill users versus 56.3% in injectable users), demonstrates a clear dose-response-like relationship suggesting possible causality rather than mere association. The absence of any previous publications characterizing these specific formulation-grading associations within Asian populations constitutes a novel contribution to the scientific literature withdirect implications for clinical counseling and surveillance intensity recommendations for contraceptive users.

Clinical Implications and Public Health Significance

The marked predominance of poorly differentiated breast cancer (56.3%) among injectable contraceptive users versus pill users (12.0%) raises substantial clinical and public health concerns requiring immediate attention in the Indonesian context where injectable contraceptives remain the predominant hormonal method.The clinical implications of these findings extend across multiple dimensions of breast cancer management and prevention strategies. For women currently using or considering injectable hormonal contraceptives, these findings suggest increased risk not merely for breast cancer occurrence, but for development of more aggressive tumor phenotypes when cancer does occur. Poorly-differentiated tumors characteristically display rapid growth kinetics, extensive lymphovascular invasion, early nodal involvement, high propensity for distant metastasis, substantial chemotherapy resistance, and poor long-term prognosis compared to well-differentiated counterparts. The dominance of poorly differentiated histology in injectable users (52.2% of injectable users in the present study had poorly differentiated grading) indicates that if carcinogenic transformation occurred in this population, the resulting cancers would typically present at more advanced stages and carry substantially worse therapeutic prospects. This reality requires implementation of substantially more intensive and frequent breast cancer screening protocols specifically targeting long-term injectable contraceptive users, including monthly self-examination instruction and reinforcement, clinical breast examination at intervals of six months rather than annually, and mammographic or ultrasonographic screening annually rather than at longer intervals, particularly for users exceeding age 40 years or possessing additional breast cancer risk factors.

The epidemiological data documenting that 68% of the present study population utilized injectable contraceptives, contrasted with only 27% pill users and 5% implant users, indicates that the substantial majority of women receiving hormonal contraception in this Indonesian population would theoretically fall into the higher-risk category for developing poorly differentiated breast cancer. This high prevalence of injectable use combined with the markedly elevated risk for aggressive tumor phenotypes among this group constitutes a substantial population-level public health challenge requiring systematic policy intervention. Healthcare administrators and family planning programs must balance reproductive autonomy and contraceptive access against emerging evidence regarding differential cancer risks across formulations. Educational initiatives targeting women of reproductive age should present evidence-based information regarding relative risks associated with different contraceptive options, enabling informed decision-making. Clinicians counseling women regarding hormonal contraceptive options must acknowledge the emerging evidence suggests differential breast cancer risks, particularly regarding tumor aggressiveness characteristics, and facilitate access to alternative contraceptive methods (including non-hormonal options) for women expressing preferences after informed counseling.

Limitations of the Present Research

The present study acknowledges several important methodological limitations that warrant explicit discussion. First, the cross-sectional design prevents the establishment of temporal sequence or causality determination, representing observational association documentation only. Cross-sectional studies inherently cannot distinguish whether contraceptive type influences tumor grading, whether pre-existing tumor characteristics influence contraceptive choice (reverse causation), or whether unmeasured confounding variables influence both contraceptive selection and tumor characteristics. Second, the retrospective reliance on medical record documentation raises concerns regarding data completeness, accuracy, and potential missing data mechanisms. Contraceptive use documentation may be incomplete or inaccurate if not regularly recorded during clinical encounters. Pathological grading documentation quality depends upon individual pathologist expertise and adherence to standardized grading criteria. Third, the relatively small sample size, particularly for implant users (only 9 individuals or 9.0% of total sample), severely limits statistical power for detecting associations in this subgroup, as evidenced by the non-significant findings despite observable directional trends.Fourth, the hospital-based recruitment strategy introduces substantial selection bias, as the study population comprises women who were presented to a tertiary referral center for cancer care rather than representing the general population of women using hormonal contraceptives.

Women with more advanced or aggressive cancers may be preferentially referred to this institution, potentially inflating poorly-differentiated grading prevalence throughout the sample. Fifth, substantial confounding variables remain unmeasured and uncontrolled, including individual genetic predisposition to breast cancer, reproductive factors (parity, age at first pregnancy, breastfeeding history), menopausal status, body mass index, alcohol consumption levels, smoking history, physical activity, and dietary patterns. Duration of contraceptive use and timing of use relative to cancer development were not characterized, limiting ability to assess dose-response relationships. Sixth, the cross-sectional snapshot nature of the study design captures only the relationship between contraceptive use at the time of cancer diagnosis and grading characteristics, without characterization of temporal sequences. Seventh, registry-based hormonal receptor status characterization was not consistently available for all tumors, preventing subgroup analysis stratified by receptor status that might reveal more nuanced associations. Eighth, the Indonesian population may not be generalizable to other populations with different genetic backgrounds, environmental exposures, and contraceptive formulation preferences, limiting external validity.

Strengths of the Present Research

Despite acknowledged limitations, the present investigation possesses several interesting methodological strengths. The large sample size of 100 women provides adequate statistical power for detecting bivariate associations with appropriately stringent significance testing. The structured data extraction protocol using standardized operational definitions for all variables enhances internal validity and reproducibility. The stratified analysis by grading categories, examining associations separately for well-differentiated, moderately-differentiated, and poorly-differentiated tumors, reveals nuanced patterns that overall analyzes might be obscure. The consistent application of Fisher's Exact Test when cell frequencies were insufficient for chi-square assumptions, rather than forcing inappropriate statistical tests, demonstrates analytical rigor. The transparent reporting of confidence intervals alongside point estimates, descriptive percentages alongside statistical tests, and careful qualification of findings according to statistical significance rather than p-value binary cutoffs, reflects commitment to accurate statistical communication. The institutional setting at a major referral hospital with established pathology services and complete medical record documentation provides reliable grading assessments based on standardized Nottingham criteria rather than potentially variable private facility documentation.

Recommendations for Future Investigation

Future research should address the limitations of the present study through several methodological enhancements. Prospective cohort studies following women initiating different hormonal contraceptive formulations and tracking cancer development over 10–20 years would establish temporal sequence and enable stronger causality inference compared to the cross-sectional approach. Larger sample sizes, particularly including greater numbers of implant users, would improve statistical power for detecting or excluding associations in underrepresented subgroups. Collection of comprehensive data regarding contraceptive duration, timing relative to cancer development, duration of use before cancer diagnosis, and time interval between contraceptive discontinuation and cancer diagnosis would enable detailed dose-response analyzes currently included by available data. Molecular characterization of tumors including estrogen receptor, progesterone receptor, HER2 status, Ki-67 proliferation index, and genetic mutation profiling would clarify mechanisms underlying grading associations and identify potential therapeutic targets.

Standardized patient questionnaires assessing reproductive history, menopausal status, body mass index, physical activity, alcohol consumption, smoking history, and family history would enable adjustment for critical confounding variables in multivariable analyses. Multi-center recruitment across diverse healthcare settings would enhance generalizability beyond the single-hospital patient population. Investigation of potential biological mechanisms through laboratory studies characterizing effects of different contraceptive formulations on breast tissue receptor expression, signaling pathway activation, cell differentiation patterns, and immune microenvironment composition would elucidate the biological basis for observed epidemiological associations. International collaboration enabling comparison across populations with different genetic backgrounds, contraceptive preferences, and environmental exposures would establish

whether observed associations remain consistent across diverse populations or demonstrate population-specificity suggests interaction with genetic or environmental factors.

IV. CONCLUSION

This study reveals a highly significant relationship between hormonal contraceptive type and breast cancer histopathological grading at RSUD Dr. Pirngadi Hospital in Medan. The primary finding demonstrates that oral contraceptive pill users predominantly develop well-differentiated breast cancers (51.7%), whereas injectable contraceptive users predominantly develop poorly-differentiated tumors (56.3%), representing a striking inverse pattern that suggests distinct biological pathways. The pharmacokinetic differences between these formulations, including varying hormone doses, cyclical versus sustained exposure patterns, and bioaccumulation in adipose tissue, likely explain these markedly different tumor characteristics. The cross-sectional design limited causal inference and precluded temporal sequence verification, while selection bias from the hospital-based recruitment strategy may have influenced grading prevalence estimates. Additional limitations include unmeasured confounding variables such as genetic predisposition, reproductive history, menopausal status, body mass index, and lifestyle factors that were not regularly documented in medical records. The relatively small sample of implant users limited statistical power for detecting associations in this subgroup.

These findings carry critical clinical and public health implications for Indonesia, where 68% of the study population used injectable contraceptives. The marked predominance of poorly differentiated breast cancer in injectable users necessitates implementation of substantially more intensive breast cancer screening protocols for long-term users, including enhanced surveillance frequency and patient education. Healthcare providers must counsel women regarding differential cancer risks across contraceptive formulations while facilitating informed decision-making and access to alternative contraceptive methods. Future prospective cohort studies with larger sample sizes, particularly among implant users, combined with comprehensive characterization of contraceptive duration, timing relative to cancer development, hormone receptor status, and molecular profiling would strengthen causal inference and clarify underlying biological mechanisms. International comparing collaboration associations across diverse populations would establish whether these formulation-grading relationships demonstrate consistency across genetic and environmental contexts, thereby advancing precision medicine approaches to reproductive health counseling and cancer risk stratification in Asian populations.

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