

# HASIL CEK\_Hormonal contraceptive use related to breast cancer among women in Indonesia: a nationwide study

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Contraceptive Use

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## Hormonal contraceptive use related to breast cancer among women in Indonesia: a nationwide study

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### ABSTRACT

Breast cancer remains a global problem, including Indonesia. However, research findings regarding the influence of hormonal contraceptive use on breast cancer have not been conclusive. Therefore, this study aimed to investigate whether there was any association between hormonal contraception use and breast cancer among women in Indonesia. We assessed 3,517 participants who participated in this study conducted through the Indonesian Family Life Survey wave five during 2014-2015. A logistic regression model was performed to analyse data. The percentage of breast cancer cases in this study was 0.34%, with a total of 1,574 respondents (44.75%) having used hormonal contraceptive for more than five years. After controlling for confounders, the hormonal contraceptive use was significantly lower to have breast cancer incidence (OR<sub>adj</sub>=0.10; 95% CI=0.03-0.40; p<0.05) compared to women using non-hormonal contraceptive, while the long-term hormonal contraception use (more than five years) did not affect breast cancer incidence. Hormonal contraceptive use was associated with breast cancer; however, the evidence from our findings indicated that the magnitude of the risk was small.

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### 1. INTRODUCTION

Breast cancer is one of the non-contagious diseases characterized by an abnormal or uncontrollable growth of cells in breast inner epithelial tissue. Globally, the incidence rate of breast cancer in 2018 accounted for 2.1 million cases or about 11.6%, with a mortality rate of 627,000 or about 15% of deaths from total cancer-induced events after lung cancer [1]. Breast cancer is also one of the public health issues in Indonesia, in which most patients of breast cancer are diagnosed in advanced stages. The highest percentages of breast cancer in Indonesia was predominantly suffered by women with a total of 58,256 cases or 30.9% and with the rate of deaths at 12.75% or as many as 22,692 death [2].

Furthermore, the increasing breast cancer rate significantly contributed by the adoption of unhealthy lifestyle such as alcohol consumption, smoking, as well as obesity and less physical activity [3]-[6], including estrogen has also been shown to be a trigger for breast cancer. Estrogen is well known as a component of hormonal contraceptive, although this hormonal contraceptives contain a single estrogen and a combination of estrogen and progesterin, which is known as a hormonal birth control. Several studies on risk of using hormonal

contraceptives with development of breast cancer cells has been widely carried out and the results showed inconsistencies [7]–[9]. Several studies have explored which study subjects who were current user or recent user, or have a history of using any hormonal contraceptives and long-term use of oral contraceptives, but study results have shown to vary from no increased risk of breast cancer to an increase of about 20-30% [8], [9]. More importantly, a long-term use of hormonal contraception for five years or more also positively stimulated breast cancer development [10], [11]. A previous nested case-control study conducted in the cancer surveillance system registry in the United States demonstrated that current oral contraceptive use had elevated breast cancer risk by 50% (OR=1.5; 95% CI=1.3-1.9) [12]. According to Lovett *et al.* [13], oral contraceptive containing levonorgestrel, norethindrone, or drospirenone were positively associated with a higher progesterin level. Progesterone and estrogen play a role in stimulating the development of mammary tumour stem cells through complex mechanisms [11], [14]. Other studies demonstrated that hormonal contraceptive containing single estrogen and or combined estrogen-progestin raise the incidence rate of breast cancer among women [12]–[18]. However, previous some studies revealed no evidence of the increased risk for breast cancer in relation to hormonal contraceptive use [7]–[9], [19]–[22].

Many studies have shown the relationship between hormonal and increased risk of breast cancer, but the results of these studies are questionable. Based on previous studies that showed the pros and cons of increasing breast cancer triggered by hormonal contraceptives, this current study aimed to analyze contraceptive use and identify factors contributing to breast cancer incidence among Indonesian. Furthermore, breast cancer is the second frequent cause of death among Indonesian, yet, knowledge about hormonal contraception and its association with breast cancer is still limited. Indonesia is a vastly populated country which runs a family planning program involving mostly women of reproductive age as one of the countries with a vast population with a family planning program that involves most women of reproductive age. The use of contraceptives is a key to supporting the program's birth planning. Moreover, based on the data from the Indonesian Health Ministry, most of the use of contraception was administered through injections (63.7%) and pill (17%), which are composed of estrogen and progesterone.

## 2. RESEARCH METHOD

### 2.1. Ethical consideration and study design

This study was approved by the Ethical Review Committee of Universitas Ahmad Dahlan with reference number 011907072. A written informed consent form was obtained from all the participants prior to their participation in the study. This research was a population-based cross-sectional study. The data were collected from the 2014-2015 Indonesian Family Life Survey (IFLS), which is the fifth longitudinal survey since 1993. The IFLS-5 was a collaborative project involving the National Institute on Aging, the National Institute for Child Health and Development, the World Bank Indonesia, and the Australia Department of Foreign Affairs and Trade. In this study, an individually recorded data was used.

The sample for this study consisted of women purposively selected from 13 provinces (North Sumatra, West Sumatra, South Sumatra, Lampung, Jakarta, West Java, Central Java, Yogyakarta, East Java, Bali, West Nusa Tenggara, South Kalimantan, and South Sulawesi) based on locality (rural-urban)-province combination. These combinations sufficiently represented the socioeconomic and cultural spectrum among Indonesian. Any women aged 30 or older in each household were eligible to participate. Whereas the exclusion criteria were women who did not complete data, lost track due to relocating to another province, or passed away.

### 2.2. Data collection process

Breast cancer as the outcome of this study was obtained through linkage with the individual dataset of IFLS-5. Breast cancer measured by mammography, then all responses were categorized dichotomous (yes, no). In this study, the effect of hormonal contraceptive use on breast cancer was analysed using contraceptives, which included two components: the extended use of hormonal contraceptives and the contraceptives method. The prolonged use of hormonal contraceptives was dichotomized, with a value of 0 indicating the continued use of hormonal contraceptives less than five years and 1 indicating more than five-year use of hormonal contraceptives. Contraceptives method was referred to as the method involved in the use of contraceptives among women in Indonesia. The variable of contraceptives method was categorized as dichotomous: a value of 0 was assigned to women using non-hormonal contraceptives namely barrier methods, tubal sterilization and copper intrauterine devices, whereas a value of 1 was assigned to women using hormonal contraceptives, namely pills, injections, hormonal-intrauterine devices, and implants. Other covariates included as potential predictors and/or cofounders in our study were age, education, and occupation.

### 2.3. Statistical analysis

Mean and standard deviations assessed continuous data, and categorical variables were summarised using counts and percentages. In this study, since breast cancer, was measured on a nominal scale, binary

logistic regression was consequently employed. A p-value of less than 0.25 was used for selecting the risk factors and/or cofounders to be included in multivariable analysis. All analyses were performed with STATA 14.

3. RESULTS AND DISCUSSION

3.1. Results

There were total of 3,517 respondents, with most respondents using hormonal contraceptive (91.78%) as shown in Table 1. The percentage of breast cancer cases during the time of this study was 0.34%, whereas out of those using hormonal contraceptives (91.78%), 1,574 participants (44.75%) had been using hormonal contraceptives for more than five years.

After adjusting for other potential associated factors, the odds of risk breast cancer remained significantly lower (OR<sub>adj</sub> =0.10; 95% CI=0.03-0.40; p<0.05), indicating women who used hormonal contraceptive were less likely to risk breast cancer than those who used non-hormonal contraceptive as presented in Table 2. When baseline characteristics of participants are pooled, there is evidence that long-term use of hormonal contraception for more than five years did not affect breast cancer incidence (OR<sub>adj</sub> =0.56; 95% CI =0.15-0.198; p>0.05). This pattern was also evident in the level of education.

Table 1. Baseline characteristics of the respondent

Characteristics	Breast cancer		Total participants	
	Yes n (%)	No n (%)	n (%)	95% CI
Overall	12 (0.34)	3,505 (99.66)	3,517	0.002–0.006
<b>Age (years old)</b>				
<30	2 (0.17)	1,165 (99.83)	1,167 (33.18)	0.316–0.348
30-39	6 (0.36)	1,646 (99.64)	1,652 (46.97)	0.453–0.486
>40	4 (0.57)	694 (99.43)	698 (19.85)	0.186–0.212
<b>Education</b>				
Elementary school	4 (0.33)	1,221 (99.67)	1,225 (34.83)	0.091–0.111
Junior high school	4 (0.42)	955 (99.58)	959 (27.27)	0.333–0.364
Senior high school	2 (0.20)	977 (99.80)	979 (27.84)	0.258–0.288
University			354 (10.07)	0.264–0.293
<b>Occupational</b>				
Employment	2 (0.12)	1,640 (99.88)	1,642 (46.69)	0.450–0.483
Unemployment	10 (0.53)	1,865 (99.47)	1,875 (53.31)	0.517–0.550
<b>Duration of contraception use</b>				
Never user	4 (0.40)	1,005 (99.6)	1,009 (28.69)	0.272–0.302
<5 years	2 (0.21)	932 (99.79)	934 (26.56)	0.251–0.280
≥5 years	6 (0.38)	1,568 (99.62)	1,574 (44.75)	0.431–0.464
<b>Type of contraception</b>				
Hormonal birth control	7 (0.22)	3,221 (99.78)	3,228 (91.78)	0.735–0.092
Non-hormonal birth control	5 (1.73)	284 (98.27)	289 (8.22)	0.908–0.927

Table 2. Crude and adjusted odds ratio of factors that were independently associated with breast cancer

Variables	Crude OR	95% CI	Multivariable adjusted OR	95%CI
<b>Age (years old) (ref: &lt;30)</b>				
30-39	2.12	0.43–10.54	1.19	0.22–6.39
>40	3.36	0.61–18.38	1.17	0.18–7.75
<b>Education (ref: University)</b>				
Elementary school	0.58	0.11–3.16	1.26	0.21–7.66
Junior high school	0.74	0.13–4.04	1.53	0.26–9.04
Senior high school	0.36	0.05–2.57	0.64	0.09–4.79
<b>Occupational (ref: employment)</b>				
Unemployment	4.39	0.96–20.10	3.87	0.82–18.10
<b>Duration of contraception use (ref: &lt;5 years)</b>				
≥5 years	0.81	0.26–2.51	0.56	0.16–1.99
<b>Type of contraception (ref: non-hormonal birth control)</b>				
Hormonal birth control	0.12	0.04–0.39	0.10	0.02–0.41***

3.2. Discussion

Recently, a cohort study conducted among Danish women found that recent user hormonal contraceptive triggers breast cancer [10]. Although the link between hormonal contraceptive use and breast cancer remains debatable, more than half of women aged 15-49 globally are known to have used contraceptive method, including hormonal contraceptive. Based on the WHO recommendation, women who had altered BRCA1 and BRCA2 genes had a higher risk of breast cancer and hence, are not recommended to

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use hormonal contraceptive [23]. More importantly, Indonesia, as country with the fourth largest population worldwide, 78.88% of the total population constitute current users of contraceptives for birth control planning. Therefore, breast cancer in Indonesia remains the most common problem among Indonesia women. As far as the literature review is concerned, most patients diagnosed with breast cancer are known to have adopted unhealthy lifestyle such as lack of physical activity, smoking, and alcohol consumption in addition to hormone replacement therapy [12]. These are various risk factors that triggered breast cancer among them [24]–[26]. Increasing knowledge of the risk factors of breast cancer is key to reducing women's health risk [27]. Breast cancer sufferers need detailed information related to fulfilling contraceptive needs when changes in their breast, however, lack of knowledge about these conditions have been identified in the community [28]. The high use of hormonal contraceptive methods is influenced by the lack of knowledge related to contraception, which resulted in a person's strong belief in myths about contraception [29]. It is linear with the situation explaining that there is currently a lack of data which points to the significant correlation between use of hormonal contraceptive and breast cancer incidence. Hence, this [15] current study is believed to be the first of its kind among population-based study which sought to assess the link between hormonal contraceptive use and breast cancer and criticize the need for gathering essential data to effective control and preventive plans especially among Indonesian.

The findings from this study revealed that hormonal contraceptive use was associated with breast cancer risk although our findings reported small magnitude risk. However, there is limited evidence in support of the hypothesis that oral contraceptive use is associated with breast cancer. More importantly, this current study is [13] in line with Danish National databases study that reported oral contraceptive use as the factor contributing to invasive breast cancer in women aged 15-49 years old [10]. Also, another study of 1102 participants using a nested case-control in the Cancer Surveillance System registry revealed that current hormonal contraceptive use was increased 50% of breast cancer (OR=1.5, 95%CI=1.3-1.9) [30]. Another study also stated that the use of hormonal contraceptive methods for more than 5 years increases the risk of developing breast cancer. Using a contraceptive method containing the hormone estrogen had a risk of increasing breast cancer by 1.52 times [31]. Moreover, other finding from this study showed that the long duration of contraceptive use with breast cancer has not been conclusive. Similar the findings from this study, other studies did not find any relationship between current or never oral contraceptive use and invasive breast cancer [16], [21]. In addition, our finding in contrast with another journal, women age less than 20 years old the absolute risk of breast cancer is very low, and any excess attributable to the pill is small [32]. For women as a whole, prolonged or early use seems to make no difference to risk, and there is no synergy with a family history or genetic predisposition [32]. As well as, use of oral contraceptives while young may protect against the development of breast cancer after age 45 [33].

The present study did have limitations. Our data did not take into account other factors potentially contributing to invasive breast cancer incidence such as physical activity, smoking use, alcohol consumption, breastfeeding history, and first menarche [33]. Therefore, our results may not reflect a cause-and-effect association. Also, since a cross-sectional design was applied, findings of the relationship among variables could not be concluded as causal. However, several strengths should also be acknowledged. Firstly, our study included participants from 13 out of the 27 provinces that make up 83% of the total population of Indonesia. Secondly, the current study is a large population-based sample that represented socioeconomic diversity and cultural spectrum in Indonesia. However, there is a small percentage of breast cancer incidence among this population. More importantly, any decision to use birth planning using hormonal contraceptive should also consider the benefit and identification of the most appropriate type, dose, and long term of use hormonal contraceptive.

#### 4. CONCLUSION

In conclusion, the risk factors contributing to breast cancer incidence were found to be hormonal contraceptive use, whereas long-term use of hormonal contraceptive had no significant effect on causing breast cancer. Our finding indicates that hormonal contraceptive use could signify an important induction window for breast cancer. It is essential to improve knowledge about selecting the right contraceptives for use.

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