RESEARCH ARTICLE

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Oral Contraceptive and Breast Cancer Risks: a Case Control Study in Six Referral Hospitals in Indonesia

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Abstract

Objective: This study aimed to understand the effects of the use of oral contraceptive to breast cancer risk in six referral hospitals in Indonesia. **Methods:** The research design was hospital based case-control, conducted in 2013. Population was women patients aged 15 years and above in six cancer-referral hospitals in five provinces. Total of 762 people were included in this study consisting of 381 who are diagnosed with breast cancer as confirmed by histopathologic examination in inpatient surgery ward, and 381 people who are not diagnosed with breast cancer based on interview in outpatient surgery ward as control group. A set of data were collected including the use of oral contraceptives, age, early menarche, childbirth status, breastfeeding status, obesity, unhealthy diet, history of benign breast tumors, family history of breast cancer, and age of menopause. **Result:** Results showed that Odds Ratio (OR) of patients using oral contraceptive <6 years was 1.93 (95% CI 1.23 – 3.03) and OR of those using oral contraceptive ≥ 6 years was 2.90 (95% CI 1.65– 5.09) as compared to people who did not use oral contraceptive. **Conclusion:** Use of oral contraceptive in patients was indicated to increase the risk of breast cancer. Longer the duration of using oral contraceptive tend to have higher the risk of breast cancer.

Keywords: Oral contraceptive- estrogen- breast cancer risks- cancer-referral hospitals Indonesia

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Introduction

Breast cancer was the most common cancer in the world as well as in Indonesia. It was estimated that incidence of breast cancer in the world was 43.1 per 100,000 women with 12.9 per 100,000 deaths among them. The estimacy of beast cancer incidence in Indonesia was 40.3 per 100,000 women with mortality 16.6 per 100,000 among them (IARC, 2012a; IARC, 2012b). Breast cancer was also the highest inpatient cases in Indonesia with 12,014 cases or 21.4% among all cancer cases (Depkes, 2010). The causes of breast cancer was still unknown, but almost all it's risk factors have direct or indirect relationship with accumulation of estrogen hormones in human body and estrogen inbalance with progesterone (estrogen dominance). The efforts to fix estrogen dominance was the core prevention and treatment of breast cancer (Lee, 2008).

Oral contraceptive was one of contraceptive methods that use estrogen hormones. This method was used by 77,520,054 women aged 15 years and above in Indonesia by 2005. Oral contraceptives users was reported 17.5% among all contraceptive users (BKKBN, 2012). The most common pill used by Indonesian women was combination pill (estrogen and gestagen) with 92% users (BKKBN, 2013).

There were many researchs of influence of oral contraceptive and breast cancer. Evaluation of more than 10 cohort studies and 60 case control studies involving more than 60,000 women with breast cancer showed slight relationship but inconsistent among oral contraceptive ever users, and raised relative risk among current and recent users (IARC, 2007). A population based case control research in Britain by 2001 showed that users and ever users oral contraceptive were not associated with risk of breast cancer (Marchbanks et al., 2002). But, case-control study in Sweden (Jernstrom, 2005), population based case-control study in US (Sweeney et al., 2007), population based case-control study in 4 states in US (Newcomer et al., 2003) showed that oral contraceptive raised the risk of breast cancer. Similar resulat also reported from case control study among African American women in US (Bethea et al., 2015), Case control study in South Africa (Urban et al., 2012), and case control study di Seattle, US (Porter et al., 2015). Several researchs in Asia such as a hospital based case control study in Iran (Yavari et al., 2005), in Malaysia, (Norsa'adah et al., 2005), and in Turkey (Beji and Reis, 2007) also showed relationship between oral conraceptive use and breast cancer.

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Several researchs in Indonesia also showed inconsistent result. A case-control study ini Kariadi Hospital,Central Java (Indrati and Handojo, 2005), case-control study in Dharmais Hospital, Jakarta (Ambarwati, 2007), and case-control study ini Ciptomangunkusumo Hospital, Jakarta Harianto et al., (2005) showed that oral constraceptive was associated with breast cancer risk. These results were different research of Sirait et al.,(2009) which there was no significant association. But the sample of the research was obtained from survey, not from professional diagnosis in the hospital. Generally, these researchs in Indonesia did not included confounding factors in the analysis, which is very important to know pure association between oral contraceptive and beast cancer by controlling other related factors.

Recently, information about influence of oral contraceptive use and breast cancer obtained from several locations and hospitals was still limited. This research was aimed to understand the effects of the use of oral contraceptive to breast cancer risk in six referral hospitals in Indonesia. There were six main cancer referral hospitals in 5 provinces of Indonesia: Dharmais Hospital and Cipto Mangunkusumo Hospital (Jakarta), Hasan Sadikin Hospital (West Java), Kariadi Hospital (Central Java), Sardjito Hospital (Jogjakarta), and Soetomo Hospital (East Java).

Materials and Methods

Design of the study was hospital based case-control study, conducted in January – March 2013. This study used data from Parent Study of Assessment of Risk Factors of Cervical and Breast Cancer in Sub Directorate of Cancer Control, Directorate of Non Communicable Disease Control, Directorate General of Disease Control and Environmental Health, Ministry of Health, Indonesia 2006.

Source population was women aged 15 years and above in six cancer referral hospitals in five provinces in Indonesia: Dharmais Hospital and Cipto Mangunkusumo Hospital (Jakarta), Hasan Sadikin Hospital (Bandung, West Java), Kariadi Hospital (Semarang, Central Java), Sardjito Hospital (Jogjakarta), and Soetomo Hospital (Surabaya, East Java). Study population was women patients aged 15 years and above in surgery ward in these six hospitals.

Total of 762 sample consisting of 381 people who were diagnosed breast cancer by medical doctors as corfirmed by histopatologic examination in inpatient surgical ward as case group, and 381 pepole who were not diagnosed breast cancer by medical doctors in outpatient surgical ward through interview (questionaire) as control group. Cases were taken from total number of breast cancer cases in the inpatient surgical ward from May – July 2006, meanwhile control was taken randomly (simple random) from patients but not breast cancer in the outpatient surgical ward in the same period. Inclusion criteria was women patient aged 15 years and above. Meanwhile, exclusion criteria were women patients using hormonal contraceptives but pill (injection or implant), and using hormone replacement therapy. Variables incuded in this study were oral contraceptive use, age, early menarche, childbirth status, breasfeeding status, obesity, unhealthy diet, benign breast tumor history, family history of breast cancer, and age of menopause.

Cut off point of contraceptive use determined by using Receiver Operating Characteristic (ROC), cut off point of uhealthy diet using median of 5 questions of diet (Hastono, 2006), cut off point of obesity using body mass index ≥25 (Kemkes 2013). Meanwhile, cut off point other variables were obtained directly from the questionaire. Data management and analyse using statistic software. Univariate analysis was conducted to know frequency among cases and controls. Bivariat analysis of association between oral contraceptive use and breast cancer used Chi Square test and Simple Logistic Regression in order to know significancy, Odds Ratio (OR) and 95% Confidence Interval. Variables which had p value < 0.25 in bivariate analysis were selected to multivariate analysis using multiple logistic regression (Hastono, 2006). Multivariate modelling was done through modelling of selected variables (Hierarchically Well Formulated Model/HWF Model) and elimination of interaction whis was not correlated and elimination of confounder, then forming the final model (Kleinbaum, 1998). There were 9 variables included in full model and only 2 variables were non included in the model because p value >0.25 (family history if breast cancer and age of menopause). In the final model, there were only 6 variables included: oral contraceptive use, age, unhealthy diet history of benign tumor, breastfeeding status, and hospital.

Results

The study result showed that oral contraceptive use ≥6 years among cases was 1.5 times higher than among control. Meanwhile, oral contraceptive use <6 years among cases 2.4 times higher than among control. Based on age, the respondent among cases was bigger in 40-49 years of age, meanwhile in control was bigger in <40 years of age. In the point of menarche, respondent who were early menarche (<13 years of age) among control 1.4 timer higher than among cases. This ratio was same in the term of never had chilbirth among control and cases. Respondent who were never give breastfeeding among cases was 5 timer higher than control. It showed that obesity among cases were 1.2 timer higher than among control. Unhealthy diet was almost same among cases and control. In term of history of benign breast tumor, the number among cases was 4 timer higher than among control. Respondent with family history of breast cancer among cases 1.2 times higher than among control. Then, age of menopause were almost same among cases and control (Table 1)

Resulf of bivariat analysis showed that oral contraceptive use ≥6 years indicated raised risk of breast cancer (p 0.000) with Odds Ratio 2.99 times compared with never use. Meanwhile oral contraceptive use <6 years had Odds Ratio 1.79 times compared with never use. There are several factor associated with breast cancer: age (p 0.000), early menarche (p 0. 003), childbirth status (p 0.016), breastfeeding status (p 0,025), history of

Table 1. Frequency Distribution of Variables

Variable	Case (%)	Control (%)
Oral Contraceptive use		
Never use	246 (64. 6)	304 (79. 8)
Use < 6 years	77 (20. 2)	53 (13. 9)
Use ≥ 6 years	58 (15. 2)	24 (6. 3)
Total	381 (100)	381 (100)
Age		
<40 years	75 (19. 7)	170 (44. 6)
40 49 years	145 (38. 1)	97 (25. 5)
≥ 50 years	161 (42. 3)	114 (29. 9)
Total	381 (100)	381 (100)
Early menarche (< 13 years)		
No	271 (71. 7)	232 (60. 9)
Yes	110 (28. 9)	149 (39. 1)
Total	381 (100)	381 (100)
Childbrith status		
Ever	335 (89. 7)	311 (81. 6)
Never	46 (12. 1)	70 (18. 4)
Total	381 (100)	381 (100)
Breastfeeding status		
Ever	270 (70. 9)	297 (78. 0)
Never	111 (29. 1. 2)	84 (22.0)
Total	381 (100)	381 (100)
Obesity (BMI ≥ 25 kg/m^2)		
No	277 (72. 7)	295 (77. 4)
Yes	104 (27. 3)	86 (22. 6)
Total	381 (100)	381 (100)
Unhealthy diet		
No	171 (44. 9)	196 (51. 4)
Yes	210 (55. 1)	185 (48. 6)
Total	381 (100)	381 (100)
History of benign breast tumor		
No	236 (61. 9)	345 (90. 6)
Yes	145 (38. 1)	36 (9. 4)
Total	381 (100)	381 (100)
Family history of breast cancer		
No	326 (85. 6)	335 (87. 9)
Yes	55 (14. 4)	46 (12. 1)
Total	381 (100)	381 (100)
Age of menopause		
≤ 50 years	257 (76. 9)	224 (76. 7)
>50 years	77 (23. 1)	68 (23. 3)
Total	334 (100)	292 (100)
Missing	47 (12. 3)	89 (23. 3)

benign breast tumor (p 0.000). Other variables were not associated with beasat cancer i.e obesity, unhealthy diet, family history of breast cancer, and age of menaopause (Table 2)

Based on multivariate analysis, oral contraceptive use raised the risk of breast cancer in the final model. After

Table 2. Bivariate Analysis of Association of Oral Contraceptive and Breast Cancer

Variable	Case	Control	Odds Ratio (OR)	95% Confidence Interval	p value
Oral contraceptive use					0.000
Use < 6 years	77	53	1.79	1.22 – 2.65	
Use ≥ 6 years	58	24	2.99	1.80 – 4.95	
Never use	246	304	1		
Age					0.000
≥ 50 tahun	161	114	3.20	2.23 – 4.60	
40 49 tahun	145	97	3.39	2.33 – 4.93	
<40 tahun	75	170	1		
Early menarche (< 13 yrs)					0.003
Yes	110	149	0.63	0.47 – 0.86)	
No	271	232	1		
Childbrith status					0.016
Never	46	70	0.61	0.40 – 0.91	
Ever	335	311	1		
Breastfeeding status					0.025
Never	111	84	1.45	1.05 – 2.02	
Ever	270	297	1		
Obesity (IMT ≥ 25 kg/m^2)					0.132
Yes	104	86	1.29	0.93 – 1.79	
No	277	295	1		
Unhealthy diet					0.070
Yes	210	185	1.30	0.98 – 1.73	
No	171	196	1		
History of benign breast tumor					0.000
Yes	145	36	5.89	3.94 – 8.79	
No	236	345	1		
Family history of breast cancer					0.336
Yes	55	46	1.23	0.81 – 1.87	
No	326	335	1		
Age of menopause					
> 50 tahun	77	68	0.99	0.68 – 1.43	0.945
≤ 50 tahun	257	224	1		

controlling confounder factors i.e age, breast feeding status, unhalthy diet, history of benign tumor, and other variables (eliminated in multivariate analysis), p value of oral contraceptive use <6 years was 0.004 (< α 0,05) and Odds Ratio 1.93 (95% CI 1.23 – 3.03). It mean that the risk of breast cancer among people who use oral contraceptive <6 years was 1.93 times higher than never use. Meanwhile, p value of oral contraceptive use ≥ 6 years was 0.000 (< α 0,05) and Odds Ratio 2,90 (95% CI 1.65 – 5.09), which mean the risk of breast cancer among people who use oral contraceptive ≥ 6 years was 2.90 times higher that never use. These results showed that there was relationship between duration of oral contraceptive use and breast cancer. Longer the duration of using oral contraceptives tend to have higher the risk of breast cancer (Table 3).

Discussion

The result of this study indicated oral contraceptive use raised the risk of breast cancer. This result was inline

Table 3. Final Model of Multivariate Analysis of Association of Oral Contraceptive and Breast Cancer Controlled by Other Variables

Variable	OR (Adjusted)	95% Confidence Interval	p value
Oral contraceptive use			
(Reference: never use)			
Use < 6 years	1.93	1.23 – 3.03	0.004
Use ≥ 6 years	2.90	1.65 – 5.09	0.000
Never use	1		
Unhealthy diet			
Yes	1.46	1.04 – 2.05	0.028
No	1		
History of benign breast tumor			0.000
Yes	7.24	4.58 – 11.4	
No	1		
Age			
40 49 years	3.98	2.60 – 6.10	0.000
≥ 50 years	3.65	2.42 – 5.50	0.000
< 40 years	1		
Breast feeding status			
Yes	1.83	1.23 – 2.72	0.003
No	1		
Hospital			
Ciptomangunkusumo	1.21	0.56 – 2.65	0.621
Hasan Sadikin	0.85	0.39 – 1.89	0.696
Kariadi	0.89	0.39 – 2.04	0.788
Sardjito	0.56	0.25 – 1.25	0.158
Soetomo	0.59	0.26 – 1.31	0.196
Dharmais	1		

with monograph of International Agency for Research on Cancer (IARC) that there were raised relative risk of breast cancer among current and recent users of oral contraceptive (IARC, 2007). Several findings of case control studies showed similar results. Study in US resulted Odds Ratio using oral contraceptive 5 years 1.27 and 20 years 1.5 (Sweeney et al., 2007), another study in US with Odds Ratio of using oral contraceptive 2.6 for lobural carcinoma and 1.2 for ductal carcinoma (Newcomer et al., 2003). Study in Iran with Odd Ratio 1.95 (Yavari et al., 2005), study in Kelantan, Malaysia with Odds Ratio 2.5 (Norsa'adah et al., 2005). Similar results are also reported from studies in Indonesia, such as study in Dharmais Hospital Jakarta with Odds Ratio 3.13 (Ambarwati, 2007), study in Kariadi Hospital, Central Java with Odds Ratio of oral contaceptive use for 10 years 3.1 (Indrati and Handojo, 2005), and study in Ciptomangunkusumo Hospital Jakarta with Odds Ratio 1.86 (Harianto et al., 2005).

Recent studies also showed association of oral contraceptive use and breast cancer risk. Case control study included African American women with subtypes of breast cancer showed there was association of recent 5 years oral contraceptive use with breast cancer with OR 1.46 among estrogen receptor positive, OR 1.57 among estrogen receptor negative, and OR 1.78 among triple negative (Bethea et al., 2015). Study in South Africa showed there was raised of breast cancer risk among current and recent users of oral contraceptive with OR 1.57 (Urban et al., 2012). Study in Seattle, US for young women (20-44 years of age) showed that lifetime duration of OC use for ≥15 years was associated with an increased breast cancer risk with OR=1.5, current OC use (within 1 year of reference date) for ≥5 years was associated with an increased risk with OR=1.6 (Porter et al., 2015).

Several cohorts studies showed that oral contraceptive use was not associated with breast cancer risk. Study in England from 1968 – 2004 (Vessey and Painter, 2006) resulted Relative Risk 1.0, another study in England in 2007 resulted Relative Risk 0.98 (Hannaford et al., 2007), and study in China showed Relative Risk 1,00 (Rosenblatt et al., 2009). But, cohort study in Norwegia showed defference risk among types of oral contraceptive and breast cancer. Progestin oral contraceptive (POC) use ≥5 years was associated with Estrogen receptor (ER) positive with Hazard Ratio (HR) 1.59 and ER positive /Progestin receptor (PR) positive cancer with HR 1.6. Combination oral contraceptive use was associated with ER prositve and ER negative /PR negative cancer (Busund et al., 2018).

Result of this study contributed to knowledge about risk of oral contraceptive use to occurance of breast cancer which was still controversy. There was controversy about role of oral contraceptive to development of breast cancer, but several studies showed that oral contraceptive have role in raising breast cancer among premenopause women, but not for pasca manopause women (Rasjidi, 2010). Oral contraceptive use for long period influenced breast cancer occurance (Lee, 2008).

There were 2 steps of cancer development, initiation phase and promotion phase. In the initiation phase, there was mutation of normal genes that could caused by carcinogenes such as hormones, chemicals, virus, radiation, trauma, or combination of these factors. In the promotion phase, there was proliferation of the mutation genes (tumor). Estrogen could raise process in promotion phase (Lee, 2008).

Cancer was caused by DNA damage of gene which manages development and separation of cells. Although estrogen was not directly cause gene mutation that leading to cancer, but it stimulated cell proliferation. If breast cells have DNA mutation that raised risk of breast cancer, the cells will proliferated (with other normal cells) as respond to estrogen. Estrogen dominance was the condition that estrogen that has no or few progesteron to keep balance the effects of the estrogen. Estrogen dominance could lead to breast cancer (Lee, 2008). Oral contraceptive use could raised chance for estrogen dominance.

Result of multivariate analysis showed that unhealty diet, history of benign breast tumor, age, and breastfeeding status have roles in association of oral contraceptive use and breast cancer as confounder factors. Fat that easily oxidated has harm potential because it create free radicals. Fatty acid in the food have role in the risk of breast cancer (Lee, 2008). Study in Malaysia showed that fat intake associated with breast cancer with Odds Ratio 3.84

(Kamarudin et al., 2005).

Some benign breast tumors could mutate to be malignant/breast cancer (Rasjidi, 2010). Women whom diagnosed certain benign breast tumor might have raised breast cancer risk. One of eight breast cancer cases was in the age of less than 45 years, and two of three invasive breast cancer founded in the age more than 55 years (ACS, 2012). Longer duration of live higher the risk of breast cancer (Lee, 2008). Longer duration of breastfeeding could reduce the risk of breast cancer because of lowering level of estrogen and secretion of carcinogenic matters during breastfeeding (Rasjidi, 2010).

Type of oral contraceptive commonly used in Indonesia was combination pill (estrogen and gestagen) with 92% users. The rest (3%) was minipil containing progestin (BKKBN, 2013). This research was not spesifically studied types or dose of oral contraceptive. However, this study result gave general view about association of oral contraceptive and risk of breast cancer from several main cancer referral hospitals in Indonesia. Breast cancer risk did not vary significantly by oral contraceptive formulation, and no formulation was associated with a significantly increased breast cancer risk (Folger et al., 2013).

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