

# Oral Contraceptive Used More than 5 Years is associated with Increased Risk of Breast Cancer: A Meta-Analysis of 28,776 South East Asian Women

RICVAN DANA NINDREA<sup>1,2</sup>, SUMADI LUKMAN ANWAR<sup>3,4</sup>, WIRSMA ARIF HARAHAP<sup>5</sup>, LUTFAN LAZUARDI<sup>6</sup>, IWAN DWIPRAHASTO<sup>7</sup>, TEGUH ARYANDONO<sup>3</sup>

<sup>1</sup>Doctoral Program, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

<sup>2</sup>Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

<sup>3</sup>Department of Surgical Oncology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

<sup>4</sup>PILAR Research and Education, 20 Station Road, Cambridge CB1 2JD, UK

<sup>5</sup>Department of Surgical Oncology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

<sup>6</sup>Department of Health Policy and Management, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

<sup>7</sup>Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.

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## ABSTRACT

Breast cancer associated with variety of hormonal inter-ethnic and reproductive factors. Duration of oral contraceptives use with breast cancer risk is not well understood in Southeast Asian women. A comprehensive literature search of published articles from January 2001 to June 2019 (PubMed, ProQuest, and EBSCO online article databases) and meta-analysis were performed to link the duration of oral contraceptive application with risk of breast cancer among women in Southeast Asia. We identified the reference category, being  $\leq 5$  years' duration and  $>5$  years' duration of oral contraceptive application. We use the Fixed and random-effect models to rely pooled odds ratios (OR). Egger's and Begg's test used for publication bias was presented with funnel plots. All analyzed data in Review Manager 5.3 (RevMan 5.3) and Stata version 14.2. A total of 385 studies were reviewed and 10 studies involving a total of 28,776 women were included in a meta-analysis. This study found a slight increase in breast cancer risk in Southeast Asian women with oral contraceptives application  $\leq 5$  years with OR = 1.21 (95% CI 0.96-1.52,  $p > 0.05$ ). A higher risk of breast cancer was found in women with oral contraceptive application  $>5$  years with OR = 2.66 (95% CI 1.79-3.94,  $p < 0.00001$ ).

Publication bias and heterogeneity were not found particularly in a group of Southeast Asian women with oral contraceptive application for more than 5 years. Oral contraceptives use more than 5 years are at a higher risk in breast cancer among women in Southeast Asia. Although other reproductive factors including age at first childbirth, menarche, menopause, and lactation might influence the risk of breast cancer.

**KEY WORDS:** Breast cancer, Five years, Oral contraceptive, Southeast Asia

**Correspondence:** Ricvan Dana Nindrea

Doctoral Program, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia/ Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

E-mail: ricvandana7@gmail.com

Tel: + 6274 902482

Fax: + 6274 545458

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## INTRODUCTION

Breast cancer is the most frequent cancer and the second leading cause of cancer-associated mortality among women worldwide. A total of 2,088,849 new cases and 626,679 deaths have been related to breast cancer in 2018 [1]. Multifactorial etiology has been identified as one of the risk factors known is oral contraceptive application [2],[3].

Previous studies have revealed that combined oral contraceptives reduce endometrial and ovarian cancer risks through ovulation suppression [4],[5]. These studies found contrary results of contraceptive pills use with occurrence of breast cancer. An increased breast cancer risk correlated with used in oral contraceptive pills [4,5,6], meanwhile other studies have shown inconclusive results [7,8,9,10].

Other determinants of oral contraceptive use and the occurrence of breast cancer are the length of the use, dose-response, and age of the users. Another study showed a significant elevate in the number of young women who use oral hormonal contraceptive as well as women who begin to use oral contraceptives before the age of 20 [2]. Furthermore, the studies found there is no association between breast cancer and oral contraceptives use [2,4]. Increased breast cancer risk particularly in women with oral contraception application for more than 4 years before the first pregnancy [5]. Another study

reported breast cancer risk increasing in the oral contraceptives pills use for more than eight years [6].

Oral contraception has recently emerged as the third most common method for family planning and the most widely distributed across the globe compared to other contraceptive methods. It is estimated that 6.4% of Asian women use contraceptive pills [11]. Meanwhile, the proportion of oral contraceptive users in Southeast Asia is 12.8% [12]. Oral contraceptive users by country in Southeast Asia revealed that Thailand as the highest users (35%), followed by Indonesia (13.6%) and Vietnam (8.6%) [11,13]. Therefore, oral contraceptive application in Southeast Asia is relatively high yet the correlation with breast cancer risk is still under study.

## MATERIALS AND METHODS

### Study design and research sample

In this meta-analysis study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [14]. The samples of this research included published research articles which were published from January 2001 to June 2019 in PubMed, ProQuest, and EBSCO of online article databases. In each study we identified the reference category, being  $\leq 5$  years' duration and  $>5$  years' duration of the application of oral contraceptive.

### Operational definitions

This study comprised of independent variables, (a)  $\leq 5$  years' duration and (b)  $> 5$  duration of oral contraceptive use, and a dependent variable, i.e. breast cancer risk.

### Research procedure

The procedure of this research was started by collecting data through published research articles identification on the oral contraceptive application length and the risk of breast cancer in Southeast Asian women on PubMed online article databases, ProQuest, and EBSCO (Figure 1).

These following keywords are used treating as title or abstract for the literature search: ("oral contraceptive" OR "hormonal oral") AND ("breast cancer" OR "breast neoplasms"). We found 385 articles were identified by examining the article titles, abstract and full-text. Furthermore, this study classified the research articles into two groups based on the oral contraceptive application length with  $\leq 5$  years' duration and  $> 5$  years' duration.

The article will be excluded if it is: (a) not breast cancer outcome, (b) conducted by using other study designs other than case-control or cohort study (c) included insufficient data for extraction.

### Data collection technique

Online searching was performed in data collection. The collected data was limited by the articles written in English. The article type was limited to original research one. The publication date of the articles was limited from January 2000 to May 2019. The research subject was limited to humans only. Conceivably significant title unique articles were inspected, while the insignificant articles were prohibited. Those possibly significant unique articles will be evaluated in full-content structure, while then the unessential articles were excluded. The sample inclusion criterias were researched on the duration of oral contraceptive application, including  $\leq 5$  years' duration or  $> 5$  years' duration, and breast cancer in Southeast Asian women with retrospective study and prospective study design. The exclusion criterias were (a) the inclusion criterias were unsatisfyingly fulfilled, (b) the articles were unavailable in full-text form, and/or (c) the data provided in the full-text form was not sufficient for extraction of datas. The following datas were also collected from the articles: the name of the original writer, study location, study type, and a number of several samples.

The information from all of the articles that fulfilled inclusion criterias per under a standardized protocol carefully extracted by two investigator, while contradictions were settled by three different investigators. Newcastle-Ottawa Quality Assessment Scale (NOS) was performed for evaluation quality of research articles. Articles were indicated poor (score 0-3), moderate (score 4-6) and high quality (score 7-9) [15].

### Data analysis

Data analysis was conducted to get pooled and combined odd ratios of the collected articles. Odd ratio with 95% confidence intervals (CIs) was utilized to pool the results. These test presented the minimum statistical power article with limited numbers and sample sizes was

indicated by  $I^2 > 50\%$  significantly heterogeneity. Assesment significant heterogeneity used a random-effect model and homogeneity used a fixed-effect model. Review Manager 5.3 (RevMan 5.3) was used to analyze the data. Publication bias was performed funnel plots and Egger's and Begg's tests, statistically significant publication bias p-value  $< 0.05$ . Stata version 14.2 was conducted to analyze publication bias. A two-tailed P-value of  $< 0.05$  was considered statistically significant.

## RESULTS

Reviewing process was held to select 10 studies related to the duration of oral contraceptive application with breast cancer risk in Southeast Asian women with a total 28,776 samples patients (Table 1) [13,16-24].

A meta-analysis study was performed to determine the duration of oral contraceptive application and breast cancer risk in Southeast Asian women (Figure 2). The figure presented an insignificant result of  $\leq 5$  years' duration of oral contraceptive application and breast cancer risk in Southeast Asian women with OR = 1.21 (95% CI 0.96-1.52,  $p > 0.05$ ). The Heterogeneity test in these studies ( $P_{\text{heterogeneity}} = 0.0004$ ;  $I^2 = 70\%$ ) resulted in a variety of heterogeneous results on the breast cancer risk. In contrast, oral contraceptive application for  $> 5$  years and breast cancer risk in Southeast Asian women had a significant result with OR = 2.66 (95% CI 1.79-3.94,  $p < 0.00001$ ). Different from the  $\leq 5$  years' application duration, heterogeneity tests in these studies ( $P_{\text{heterogeneity}} = 0.14$ ;  $I^2 = 45\%$ ) resulted in multifariousness of homogeneous research on breast cancer risk.

Publication bias in articles collected described by presenting Funnel plots on the duration of oral contraceptive application with breast cancer risk among women in Southeast Asia (Figure 3). In figure 3, results showed as significant publication bias detected in articles on oral contraceptive  $\leq 5$  years' duration of oral contraceptive and risiko of breast cancer among women in Southeast Asia with Egger's test ( $P = 0.011$ ) and Begg's test ( $P = 0.09$ ). In contrast, in articles on  $> 5$  years' duration of oral contraceptive use and risk of breast cancer among women in Southeast Asia (Figure 4), our study found that there was no significant publication bias with Egger's test ( $p = 0.270$ ) and Begg's test ( $p = 0.308$ ).

Subgroup analysis for oral contraceptive use and breast cancer risk in Southeast Asia (Table 2). Ten studies assessing oral contraceptive application and breast cancer risk, seven were case-control studies [13,16-18,21,22] with Pooled Odds Ratio (POR) 1.52 (1.06-2.18), heterogeneity test in these studies ( $P_{\text{heterogeneity}} = < 0.001$ ;  $I^2 = 90\%$ ) resulted in various heterogeneous research on breast cancer risk, and three were cohort studies [19,20] with POR 1.34 (0.98-1.84), heterogeneity test in these studies ( $P_{\text{heterogeneity}} = 0.28$ ;  $I^2 = 21\%$ ) resulted in a variety of homogeneous research on the breast cancer risk.

Study quality found eight studies with high NOS scores [13,18-24], POR 1.51 (1.09-2.10), heterogeneity test in these studies ( $P_{\text{heterogeneity}} = < 0.001$ ;  $I^2 = 88\%$ ) resulted various heterogeneous research on the breast cancer risk. Two studies with low NOS scores [16,17], POR 1.35

(0.80-2.27), heterogeneity test in these studies ( $P_{\text{heterogeneity}} = 0.17$ ;  $I^2 = 48\%$ ) resulted various homogeneous research. The oral contraceptive use duration and breast cancer risk in Southeast Asian countries was presented in Table 3. Our study found that there is an association of >5 years' duration of oral contraceptive application and breast cancer risk in Southeast Asian women, while  $\leq 5$  years' duration of oral contraceptives is not associated to breast cancer risk in Southeast Asian women.

Indonesia has the largest figure of women used oral contraceptives for >5 years with POR for breast cancer risk was 2.67 (1.62-4.40), followed by Thailand and Malaysia with POR for breast cancer risk were 2.56 (1.08-6.08) and 2.28 (0.84-6.16), respectively.

## DISCUSSION

This study result showed that >5 years' length of oral contraceptive pills use increased breast cancer risk in Southeast Asian women with risk opportunity was more than doubled. The results were also homogeneous which means the studies will give consistent or insignificantly different if the study performs at the same time and place.

Furthermore, Indonesia has been known that this country has the greatest risk opportunities for breast cancer, followed by Thailand and Malaysia. Our study findings described possibly relate to the high rates of oral contraceptive application in those country mentioned in advance [11,13,24].

The previous studies found breast cancer incidence related to oral contraceptive application in several ethnicities. Non-Hispanic Caucasians have the highest percentage of oral contraceptive application (55%) as well as the highest number of incidence of breast cancer (6%). Interestingly, the lowest proportion of oral contraception application (37.5%) yet being the second-highest in the percentage of breast cancer incidence (5.7%) in non-Hispanic/Pacific Islanders. Non-Hispanic African-Americans and Hispanics have the same percentage of oral contraceptive application (52.2%) with a relatively lower figure of breast cancer incidence with 3.8% and 4.7%, respectively [25]. Our study had found the percentage of oral contraceptive application with breast cancer incidence followed by a range of 3.7-13.9%. The figure was higher in some ethnic than others as we had described, possibly due to oral contraception application percentage is known was also relatively high in the Southeast Asian region with 12.8% [12].

Based on the risk opportunities found, it was demonstrated that there was a higher breast cancer risk in Southeast Asian regions with  $\leq 5$  years' duration of oral contraceptive application was OR = 1.21 (95% CI 0.96-1.52), while >5 years' duration of oral contraceptive use was OR = 2.66 (95% CI 1.79-3.94). Previous study also had found risk opportunities of breast cancer related to oral contraceptive included non-Hispanic Caucasians (HR = 1.09 (95% CI 1.01-1.18), non-Hispanic African Americans (HR = 0.95 (95% CI 0.64-1.42), and non-Hispanic Asian / Pacific Islander (HR = 0.93 (95% CI 0.63-1.39) [25].

Data from 39 case-control studies led from 1980 to 2006 have discovered a association of contraceptive pills with breast cancer among premenopausal [26]. Another study recommended that present utilization of contraceptive pills which substance is estrogen appears to somewhat elevate the breast cancer risk. A few factors adding to the advancement of breast disease incorporate hormones, which is estrogen itself [27-29]. The use of contraceptive pills which contains estrogen the breast tissue to be presented to large amounts of hormones for longer periods. That estrogen stimulates growth factors that exist in breast cancer cells resulting in tumor progression [30,31].

The previous research on the impact of age at beginning of utilization of the pill on the rate of breast cancer growth presumed that ladies that had begun utilizing the pill before 18 years old contracted disease 4 years sooner [32]. In a study, the researcher accepts prolonged use increases the risk. Another study found a relative risk of 2.2 with over 10 years of length of using [33]. The other study found the affinity between breast cancer and contraceptive pills use (OR=2.11). The investigation results show that women that utilization preventative pills have more noteworthy requirements for preventive and screening measures [34].

Based on data oral contraceptive is the most common means of contraception in the world and Southeast Asian countries, utilized by millions of women [35-37]. According to the duration of oral hormonal contraceptives use more than 5 years will increase breast cancer risk which will be higher compared to those who have never used hormonal contraception. If a person stops taking hormonal contraception for 5 years then she will have no risk of breast cancer. This result is supported by a theory found about the imbalance of the hormones estrogen and progesterone used in hormonal contraception [4,38,39]. This hormonal imbalance has resulted in a feedback mechanism that can physiologically control the number of hormones in the body when it is not functioning properly [40]. It was triggered by the estrogen receptors up regulation so that the number of hormones continues to increase. Exposure to sexual hormones over a period of more than 5 years will increase the proliferation of breast cells and increase breast cancer stem cell mitosis [41].

A meta-analysis data in this study has several limitations. First, there were 2 potential articles should be included in this study but the full-text articles are unavailable. Second, there were 2 studies are also potentially included in data analysis yet the data presented were incomplete and different risk factors in the calculations were also performed.

Based on our analysis, as we found of the significant association of oral hormonal contraceptives use with breast cancer risk as well as increase for more than five years' duration of contraceptive pills use, we suggest people to select effective and efficient long-term contraceptive methods to prevent pregnancy, yet safe in accordance with infertility and breast cancer risk. Another suggestion is breast cancer screening programs are necessary for Southeast Asian countries.

## CONCLUSION

This study confirms the significant correlation of more than five years' duration of oral hormonal contraceptives use and breast cancer risk in Southeast Asia. Therefore, we recommend fertile women who want to prevent pregnancy for a relatively long period, should use long-term contraception methods.

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## ABBREVIATIONS

CIs: Confidence Intervals

HR: Hazard Ratio

NOS: Newcastle–Ottawa Quality Assessment Scale

OR: Odds Ratios

POR: Pooled Odds Ratios

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

RevMan: Review Manager

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**Table 1:** Systematic review of duration of oral contraceptive use with breast cancer risk in Southeast Asian women

First Author	Region	Study Type	Patients Characteristic	Duration (years)	Number of Sample				NOS
					Cases		Control		
					Total	Exposure	Total	Exposure	
Norsaadah et al [16]	Malaysia	Case control	Aged 26-70 years	≤5	147	53	147	36	6
Gibson et al [17]	Philippines	Case control	Aged 35-64 years	≤5	123	16	978	125	6
Matalqah et al (a) [18]	Malaysia	Case control	Aged 23-83 years, three ethnic groups (Malay, Chinese and Indian)	≤5	150	27	150	21	7
Matalqah et al (b) [18]	Malaysia	Case control	Aged 23-83 years, three ethnic groups (Malay, Chinese and Indian)	>5	150	13	150	6	7
Poosari et al (a) [19]	Thailand	Cohort	Aged 30-69 years	≤5	3,664	14	2,153	11	8
Poosari et al (b) [19]	Thailand	Cohort	Aged 30-69 years	>5	5,597	45	2,153	11	8
Lee et al [20]	Singapore	Cohort	Aged 45-74 years, Chinese population	≤5	411	39	1,212	81	7
Nguyen et al [13]	Vietnam	Case control	Aged 25-75 years	≤5	294	25	294	13	7
Trieu et al [21]	Vietnam	Case control	Aged 27-74 years	≤5	269	79	519	134	7
Chaveepojnkornjorn et al (a) [22]	Thailand	Case control	Aged <45 years	≤5	257	42	257	44	7
Chaveepojnkornjorn et al (b) [22]	Thailand	Case control	Aged <45 years	>5	257	125	257	51	7
Tan et al [23]	Malaysia	Case control	Aged 40-74 years, three ethnic groups (Malay, Chinese and Indian)	≤5	3,683	935	3,980	1,145	8
Wahidi et al (a) [24]	Indonesia	Case control	Aged 40-49 years	≤5	381	77	381	53	7
Wahidi et al (b) [24]	Indonesia	Case control	Aged 40-49 years	>5	381	58	381	24	7
<b>Total</b>					<b>15,764</b>	<b>1,548</b>	<b>13,012</b>	<b>1,755</b>	

Abbreviation: NOS, Newcastle–Ottawa Quality Assessment Scale

**Table 2:** Subgroup analysis for oral contraceptive use and breast cancer risk in Southeast Asia

Subgroups	Number of studies	Pooled OR (95% CI)	Heterogeneity	
			I <sup>2</sup> (%)	p
Study design				
Cohort	3	1.34 (0.98-1.84)	21	0.28
Case control	7	1.52 (1.06-2.18)	90	<0.001
Study quality				
High (NOS scores ≥7)	8	1.51 (1.09-2.10)	88	<0.001
Low (NOS scores <7)	2	1.35 (0.80-2.27)	48	0.17

Abbreviation: CI, confidence interval; OR, odds ratio; p <0.05 considered statistically significant; significant heterogeneity >50%

**Table 3:** The Duration of oral contraceptive use and breast cancer risk in Southeast Asian countries

Countries	Number of studies	Pooled OR (95% CI)	Heterogeneity	
			I <sup>2</sup> (%)	p
<b>Oral contraceptive for ≤ 5 years</b>				
Indonesia	1	1.57 (1.07-2.30)	n/a	n/a
Malaysia	3	1.19 (0.71-1.99)	79	0.009
Philippines	1	1.02 (0.58-1.78)	n/a	n/a
Thailand	2	0.89 (0.60-1.33)	0	0.61
Singapore	1	1.46 (0.98-2.18)	n/a	n/a
Vietnam	2	1.41 (0.88-2.27)	44	0.18
<b>Oral contraceptive for &gt;5 years</b>				
Indonesia	1	2.67 (1.62-4.40)	n/a	n/a
Malaysia	1	2.28 (0.84-6.16)	n/a	n/a
Thailand	2	2.56 (1.08-6.08)	80	0.02

**Abbreviation:** CI, confidence interval; n/a, not available; OR, odds ratio; p <0.05 considered statistically significant; significant heterogeneity >50%



Figure 1: Flow diagram of research procedure

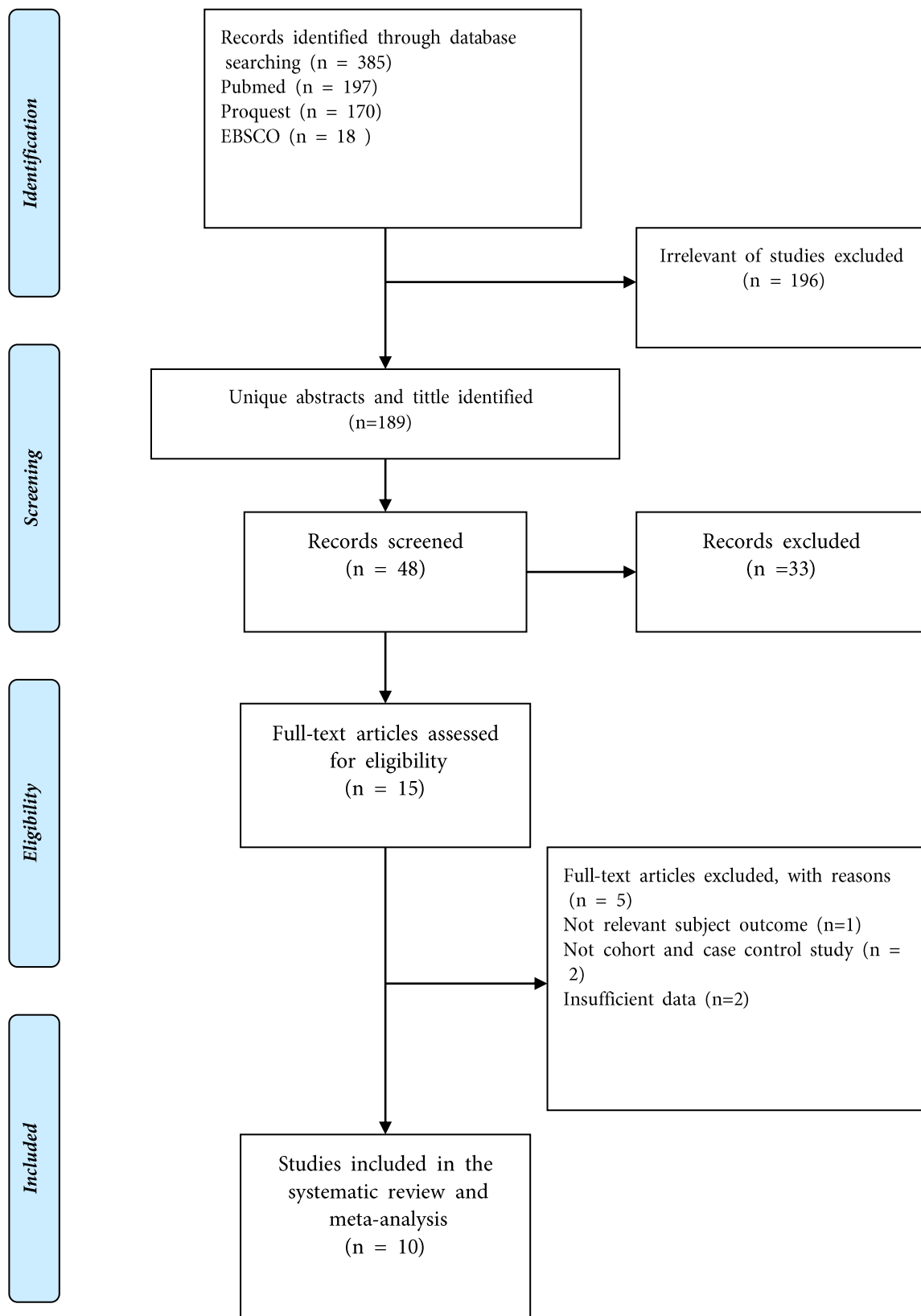
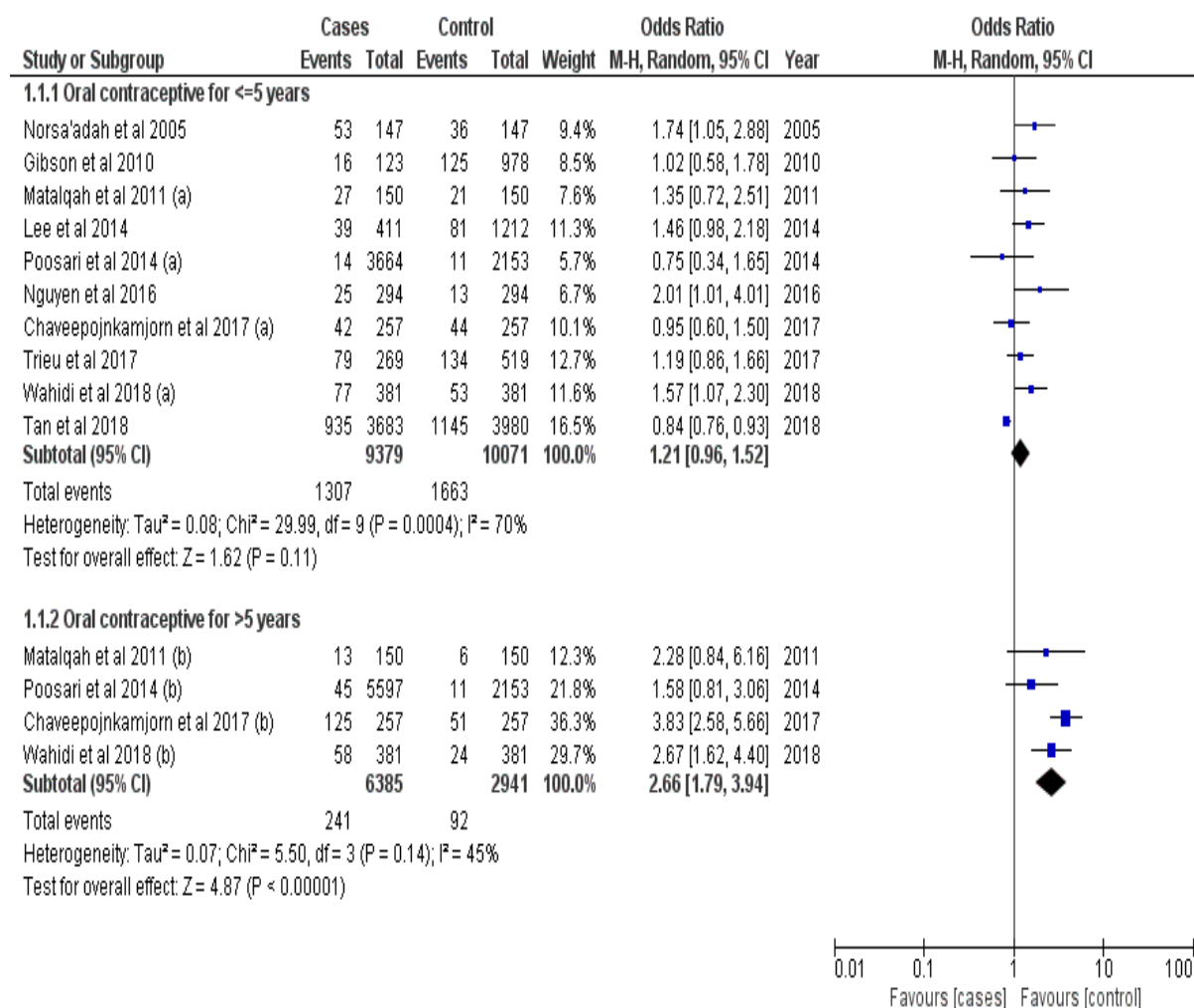
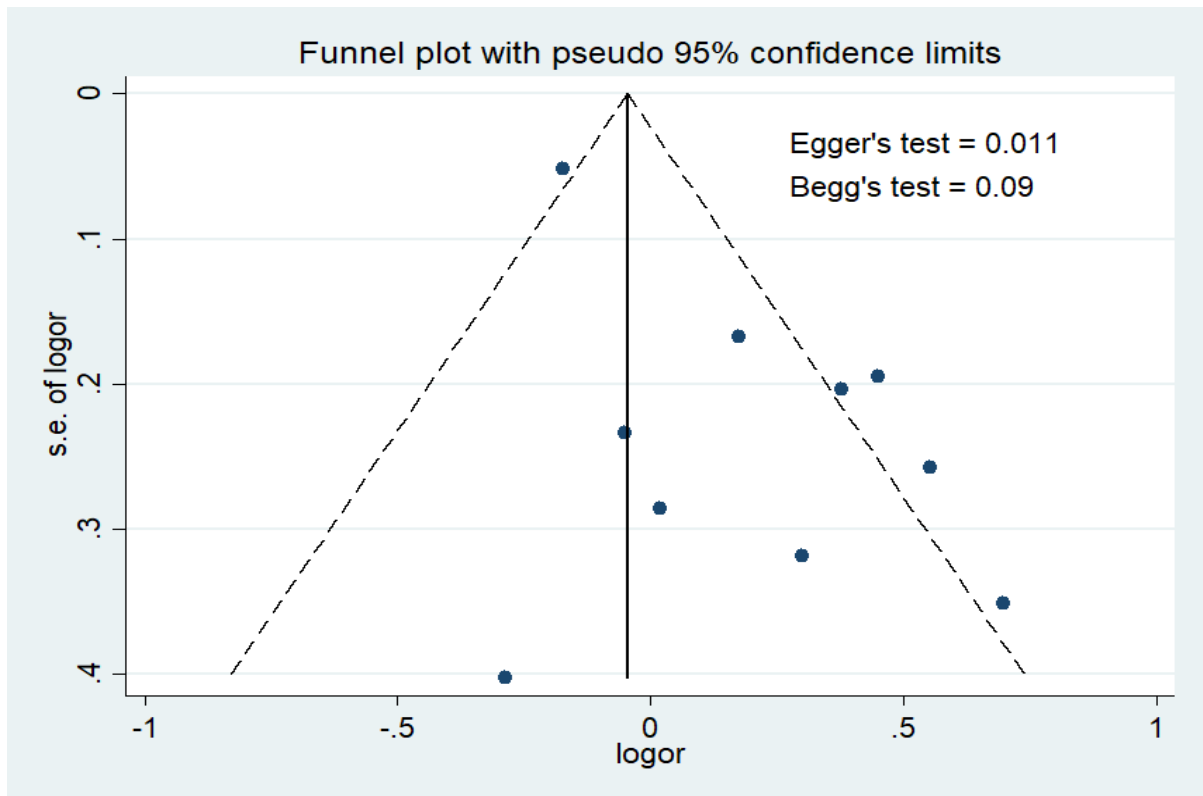


Figure i2: Forest plots of duration of oral contraceptive use and breast cancer risk in Southeast Asian women



**Figure 13:** Funnel plots of  $\leq 5$  years' duration of oral contraceptive use and breast cancer risk in Southeast Asian women



**Figure i4.** Funnel plots of >5 years' duration of oral contraceptive use and breast cancer risk in Southeast Asian women

