

# The Role of Oral Contraceptive Pills on Increased Risk of Breast Cancer in Iranian Populations: A Meta-analysis

ORIGINAL  
ARTICLE

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**Background:** Cancer is one of the main public health issues in the world. Breast cancer is one of the most common types of cancer among women. It is also the second cause of mortality in women. The association between the use of oral contraceptive pills and breast cancer is controversial and a main issue in public health. Some findings have shown that taking these pills does not have a significant effect in increasing the risk of breast cancer, while others have confirmed the carcinogenic effect of these products. These contradictory findings necessitated this meta-analysis, through of all correlated studies in Iran.

**Methods:** All published studies were considered from June 2000 until June 2015, using reliable Latin databases like PubMed, Google Scholar, Google search, Scopus, and Science Direct, and Persian database like SID, Irandoc, IranMedex, and Magiran. Finally, 26 papers were selected: 24 studies were case control while two were population based studies. A total of 26 papers with 46,260 participants were assessed since 2001.

**Results:** Overall estimate of OR for the effect of oral contraceptive pills on breast cancer is 1.521 (CI = 1.25-1.85), which shows that the intervention group had more chance (52%) compared to the control group ( $P = 0.001$ ). Using these pills increased the risk of breast cancer up to 1.52 times.

**Conclusions:** Because of directly increasing levels of estrogen and the role of estrogen in gaining weight indirectly, oral contraceptive pills can stimulate the occurrence of breast cancer. More studies should be conducted for controlling the period of pill use.

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**Key Words:** Breast neoplasms, Oral contraceptive, Meta-analysis, Iran

## INTRODUCTION

Breast cancer is one of the main public health issues in the world. Incidence of the health problem is growing in majority of countries and, despite all measures to deal with the disease, the next 20 years will witness considerable increase in incidence of the disease.<sup>1</sup> Breast cancer is one of the most common types of cancer among women. It is also the second cause of mortality in women. Every year, about 1.4 million women are diagnosed with breast cancer and more than 450,000 die due to the disease.<sup>2,3</sup> In developing countries, breast cancer is the most prevalent type of

cancer among women aged between 20 to 56 years and one of the main causes of death in the world, accounting for 23% of all cancer cases and 14% of all mortalities.<sup>4,5</sup> According to statistics, one in every eight women suffers from breast cancer.<sup>6</sup> The incidence of breast cancer varies in different parts of the world, from 10.3 per 1,000 women in Southern Africa to 123.6 per 1,000 women in Central and Eastern Europe and 256.2 per 1,000 women in Northern America. It exhibits high incidence (more than 793.7 per 1,000 women) in more developed countries and low incidence in undeveloped countries (less than 40 per 1,000 women in Africa) and developed countries (less than 20 per 1,000

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women in Australia/New Zealand).<sup>7</sup> In comparison to the developed countries of the world, breast cancer in Asian countries has less prevalence, but is one of the main types of cancer in Asian women.<sup>8</sup> Breast cancer with the incidence of 24 per 100,000 women is the most prevalent cancer among Iranian women. However, incidence of 24 per 100,000 cases has one of the lowest prevalence of breast cancer in the world. With regard to changes in the patterns of risk factors and population, breast cancer is expected to increase drastically in Iran, over the next decades.<sup>9,10</sup>

Many studies have been conducted to investigate the relationship between risk factors and the prevalence of breast cancer. Some of these factors are: age of menarche, age at first pregnancy, multiple pregnancies, family history of breast cancer, genetic factors, alcohol, and nutrition. Although the severity of some risk factors have been validated by stronger evidences, detailed studies have been conducted in this field, especially in Western societies.<sup>11,12</sup> Some risk factors like family history and genetics are uncontrollable but other factors like lifestyle, smoking, obesity, and nutrition can be controlled.<sup>13</sup> The association between the use of oral contraceptive pills (OCPs) and breast cancer is controversial and a main issue in public health.<sup>14</sup> Among contraceptive methods, hormonal medicines are the most commonly used methods. Today, two-third of American women use OCPs.<sup>15,16</sup> In several hypotheses about the mechanism by which contraceptive pills influence breast cancer, one highlights the relationship between the pills and gaining weight. Cleary and Grossmann<sup>17</sup> argued that using the pills was a factor effective on gaining weight and obesity.

There are several studies on the relationship between breast cancer and using contraceptive pills. Some have shown that using the pills only trivially increased breast cancer risk and this was limited to those who used the pills for a long time.<sup>18,19</sup> The other studies that have reported inconsistent results are not negligible.<sup>14,20-22</sup> Bethea et al.<sup>20</sup> examined the relationship between using contraceptive pills and emergence of breast cancer and found that using contraceptive pills and the term of using the pills were significantly related to development of breast cancer in African American women. Marchbanks et al.<sup>14</sup> studied women ranged from 35 to 64 years old and found no significant relationship between breast cancer risk and using contraceptive pills. Veisy et al.<sup>21</sup> found a significant relationship between the term of using contraceptive pills and breast cancer, while Zare et al.<sup>22</sup> found a that using the pills significantly decreased risk of breast cancer.

Some results show that the use of the pills has no significant

impact on increasing risk of breast cancer. Other evidences confirm their carcinogenic effect. Following national family planning programs in Iran, OCPs have been widely used by women in reproductive ages. Although OCPs were considered safe in many cases, some complications are rarely reported and its prescription is contraindicated in some disorders.<sup>23</sup> In most references, OCP is one of the probable predisposing factors for breast cancer.<sup>20,21</sup> Since there are no studies supporting a definite relationship between OCP and breast cancer in Iran, the present study was conducted to confirm this theory.

## MATERIALS AND METHODS

A case-control study was used to determine the correlation of oral contraceptives pills on breast cancer. All studies from June 2000 to June 2015 were assessed. Inclusion criteria: case-control studies, the study in one of the provinces of Iran in which the risk of breast cancer following use of contraceptive pills are reported. We also used all of studies which corresponding CI 95%, ORs were reported, and calculation was possible. Exclusion criteria: ecologic, cohort, and cross-sectional studies which corresponding 95% CI, OR were not reported and calculation was not possible.

Search strategy: Published papers were extracted in six reliable Latin databases namely Cochrane, PubMed, Google, Google Scholar, Scopus, and Science Direct. Persian databases like SID, IranMedex, and Magiran were also used. For the selection of the word to search, the PICO criterion was used. P is population of women in fertility age, I or intervention is the use of oral contraceptives, C or comparisons are the controls that do not use contraceptive pills, and O is outcome. Two Iran researchers were dedicated to searching studies to ensure the correct selection of articles.<sup>24</sup> In searching electronic databases, all articles were extracted, thereafter duplicated ones were excluded.

The articles were searched using the following keywords in Farsi and English: "Breast cancer", "Oral Contraceptive Use", "Pills", "Iran", and their combinations.

Based on the inclusion and exclusion criteria, headlines and abstracts, full texts of articles, and finally favorite articles were chosen. In the form of data extraction (in Excel), author's last name, year of publication, place of the study, age, sample size, cases and control, and OR (95% CI) were extracted. Extracted data was entered into Microsoft Excel. For data analysis, STATA 12 was used. Two statistical models (fixed and random effect) with CI of 95% were used with regard to the heterogeneity of studies (Cochran's Q-test, Higgins & Theompson I<sup>2</sup>) in data analysis. To assess the publication bias, Begg's and Egger's tests were used.<sup>25</sup>

Assessment of the quality of studies: To assess the quality of studies, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used. STROBE checklist includes 24 items. These items include: exact point to the study plan, stating precise way for measuring exposure and outcome, referring to calculation method of sample size and a flowchart of selecting subjects, referring to the time of data collection, and referring to the time of arrival and departure criteria. Thereafter, studies were divided into three groups: low orientation, middle, and low.<sup>26</sup> In this study, STROBE tool was used to assess the quality of studies for all observational studies. Also, quality assessment was based on expert opinion.

In total, 290 articles were initially found and 213 articles were excluded in the initial evaluation. In the next step, 77 articles were entered but 51 articles were excluded because of low quality of reports or failure to report the results. The final assessment was performed on 26 remaining articles in which 24 were case-control and two were population based studies. In these 26 articles, the number of cases, controls, and exposures were extracted and the OR was calculated using these values.

## RESULTS

Evaluation was carried out for 26 articles (24 were case-control studies and 2 were population based case-control studies).<sup>21,22,27-50</sup> Studies were evaluated with 460,260 participants during 2001 to 2015. The mean age of patients in the control group and case group was 47.81 and 46.13 years old, respectively. The least obtained OR (0.278) in different studies is related to Hosseinzadeh et al.<sup>47</sup> while the most OR (5.714) is related to Kihanian et al.<sup>35</sup> (Table 1). In the results of meta-analysis and use of random model, overall estimate of OR for the effect of OCPs on breast cancer is 1.521 (CI = 1.25-1.85) (Table 2). The ORs were extracted from different studies and according to exposures in the case and control group. The random effect model and fixed model were used. Heterogeneity in studies was carried out by two indexes and I<sup>2</sup> Cochran's Q statistics, Heterogeneity test was used to evaluate the null hypothesis that all studies were evaluated for similar effects. Heterogeneity effect was determined by using chi-square I<sup>2</sup>, which provides the contradiction between studies. It determines that changes in studies are the result of the heterogeneity, not by chance. I<sup>2</sup>-value greater than 50% showed

**Table 1.** Study characteristics of published population base study and case-control studies on breast cancer and oral contraceptive pills in the meta-analysis

Author' name	Province	Publication year	Samples size	Study
Razmara et al. <sup>29</sup>	Ahvaz	2010	394	Case-control
Yavari et al. <sup>30</sup>	Tehran	2006	606	Case-control
Ebrahimi et al. <sup>31</sup>	Tehran	2002	621	Case-control
Nojomi et al. <sup>32</sup>	Tehran-mashhad	2004	570	Case-control
Tehrani et al. <sup>33</sup>	Tehran	2009	624	Case-control
AttarParsaei et al. <sup>34</sup>	Tabriz	2001	323	Case-control
Kihanian et al. <sup>35</sup>	Mazandran	2010	120	Case-control
Holakoei et al. <sup>36</sup>	Mazandran	2006	750	Case-control
Adib et al. <sup>37</sup>	Rasht	2012	189	Case-control
Lotfi et al. <sup>38</sup>	Yazd	2008	160	Case-control
Eslamian et al. <sup>39</sup>	Tehran	2013	285	Case-control
Esfarjani et al. <sup>40</sup>	Ahvaz	2010	484	Case-control
Kashfi et al. <sup>28</sup>	Tehran	2001	240	Case-control
Sharif Zadeh et al. <sup>41</sup>	Birjand	2011	170	Case-control
Emamimeybodi et al. <sup>42</sup>	Yazd	2011	302	Case-control
Veisy et al. <sup>21</sup>	Urmia	2015	470	Case-control
Montazeri et al. <sup>43</sup>	Tehran	2008	232	Case-control
Ghiasvand et al. <sup>44</sup>	Shiraz	2011	938	Case-control
Sepandi et al. <sup>45</sup>	Shiraz	2014	11,850	Case-control
Motie et al. <sup>46</sup>	Golestan	2011	206	Case-control
Zare et al. <sup>22</sup>	Tehran	2013	24,477	Case-control
Hosseinzadeh et al. <sup>47</sup>	Tabriz	2014	420	Case-control
Ghorbani et al. <sup>48</sup>	Isfahan	2015	647	Case-control
Tazhibi et al. <sup>49</sup>	Isfahan	2014	257	Case-control
Ehsanpour et al. <sup>27</sup>	Esfahan	2013	525	Case-control
Pourzand et al. <sup>50</sup>	Tabriz	2013	400	Case-control

**Table 2.** Pooled results for 24 case-control and 2 population base studies of breast cancer and oral contraceptive pills

Study (first author, year <sup>a</sup> )	OR	95% CI	Weight (%)
Montazeri (1996) <sup>43</sup>	1.078	0.631-1.841	3.72
AttarParsaei (1998) <sup>34</sup>	5.265	2.919-9.495	3.51
Tehrani (1998) <sup>33</sup>	2.830	1.887-4.245	4.22
Kashfi (1999) <sup>28</sup>	1.330	0.787-2.246	3.76
Ebrahimi (1999) <sup>31</sup>	0.857	0.385-1.910	2.77
Nojomi (1999) <sup>32</sup>	1.522	1.043-2.221	4.32
Tazhibi (1999) <sup>49</sup>	0.571	0.266-1.226	2.89
Yavari (2004) <sup>30</sup>	1.452	1.053-2.001	4.52
Holakoei (2004) <sup>36</sup>	1.095	0.804-1.492	4.56
Esfarjani (2004-2005) <sup>40</sup>	1.279	0.812-2.014	4.03
Motie (2004) <sup>46</sup>	1.794	1.026-3.138	3.63
Kihanian (2004) <sup>35</sup>	5.714	2.449-13.336	2.62
Sepandi (2004) <sup>45</sup>	1.086	0.816-1.444	4.64
Ghiasvand (2005) <sup>44</sup>	1.513	1.167-1.960	4.72
Lotfi (2006) <sup>38</sup>	0.532	0.280-1.011	3.32
Emamimeybodi (2006-2008) <sup>42</sup>	1.933	1.190-3.142	3.91
Sharif Zadeh GR (2006-2008) <sup>41</sup>	0.788	0.429-1.444	3.45
Zare (2007) <sup>22</sup>	0.660	0.449-0.970	4.29
Razmara (2008) <sup>29</sup>	1.508	1.012-2.246	4.24
Adib (2009) <sup>37</sup>	2.395	1.334-4.300	3.53
Ghorbani (2010) <sup>48</sup>	0.856	0.451-1.624	3.32
Pourzand (2010) <sup>50</sup>	1.244	0.696-2.222	3.55
Ehsanpour (2011) <sup>27</sup>	2.251	1.534-3.304	4.30
Eslamian (2011) <sup>39</sup>	2.555	1.516-4.307	3.77
Hosseinzadeh (2011) <sup>47</sup>	3.593	2.332-5.535	4.11
Veisy (2013) <sup>21</sup>	2.110	1.444-3.083	4.31
Dersimonian + Laird pooled OR	1.521	1.250-1.850	100.00

<sup>a</sup>All of year are years of study and collection data.

inconsistency among studies (heterogeneity). In this study, according to the index of heterogeneity,  $I^2 = 79.5\%$  and  $P < 0.001$ , the random effect model as well as Dersimonian and Laird were used. The amount of integrated OR was 1.521, this indicates that the chance of exposure was 52% more in the exposure group than in the control group ( $P = 0.001$ ) (Fig. 1). To assess the publication bias, Egger's and Begg's tests were used (Fig. 2).

## DISCUSSION

This study investigated the relationship between the consumption of OCPs and breast cancer. To this end, 26 studies were investigated. The result indicates that using these pills increases the risk of breast cancer up to 1.52 times.

A meta-analysis study by Kahlenborn et al.<sup>51</sup> on 34 case/control studies showed that OR of breast cancer increased by 1.19 times in the women who used contraceptive pills. In addition, results of the present study indicated that using contraceptive pills for

more than 4 years increased OR of breast cancer by 1.52 times. Consistently, Nelson et al.<sup>11</sup> conducted a meta-analysis study on 61 studies and examined 8 factors. The 12 studies showed that using the pills increased the risk of breast cancer by 30% times (relative risk = 1.30, CI = 1.13-1.49).

Moreover, a case-control study by Bethea et al.<sup>20</sup> estimated the relationship between OCP usage and breast cancer in African-American women. The results confirmed that OR of breast cancer in women who used the pills for more than five years was equal to 1.46. To create a wide perspective, all studies conducted in Iran on the relationship between using contraceptive pills and breast cancer were examined by the present study.

Several assumptions about the relationship between the use of oral contraceptives and breast cancer have been proposed. The first assumption is that breast cancer is caused by the increase of estrogen in the body, which is caused by two factors. One is that oral contraceptives are mainly composed of estrogen and progesterone, another factor is numerous pregnancies for more exposure with female hormones.<sup>18</sup> Hence, these pills are likely to increase estrogen levels and then enhance the risk of breast cancer. Another mechanism justifies the impact of high levels of estrogen on the incidence of breast cancer after using pills; reduction and control of estrogen levels is possible by doing physical activities. Those who exercise while using these pills are less exposed to the increase of the level of estrogen and also incidence of breast cancer.<sup>52,53</sup>

The next assumption is that oral contraceptives contribute to a state of weight gain and the use of these pills is a factor for obesity.<sup>17</sup> These pills by increasing estrogen levels and regional estrogen production are the first causes of overweight. Several studies have shown a relationship between obesity and breast cancer, hence increased estrogen by consumption of these pills, directly leads to overweight and indirectly to breast cancer.<sup>54-56</sup>

Other studies also provide additional information about this relationship.<sup>22,38,57,58</sup> Based on an earlier report, there is a negative relationship between oral contraceptives and breast cancer. Vessey and Painter<sup>58</sup> in a large cohort study studied 17,032 women and found that these pills not only have adverse effects but also may have positive impact on this disease. This study found that women, who consumed these pills, had less advanced tumors compared to those who did not use such drugs. Moradzadeh et al.<sup>59</sup> stated that the possibility of protective effects against the disease increases dramatically, when the history of oral contraceptives and family history of breast cancer are simultaneous. Studies by Zare et al.<sup>22</sup> and Lotfi et al.<sup>38</sup> confirmed

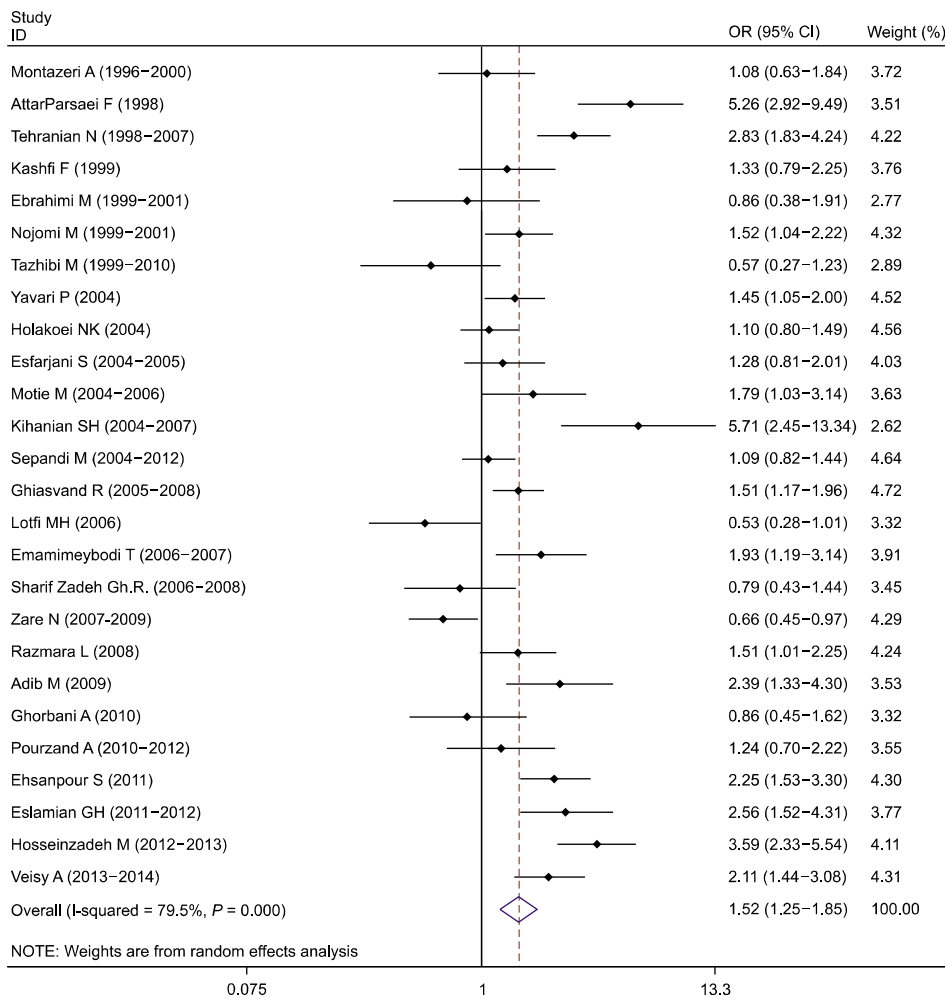


Figure 1. A forest plot of the association between breast cancer and oral contraceptive pills.

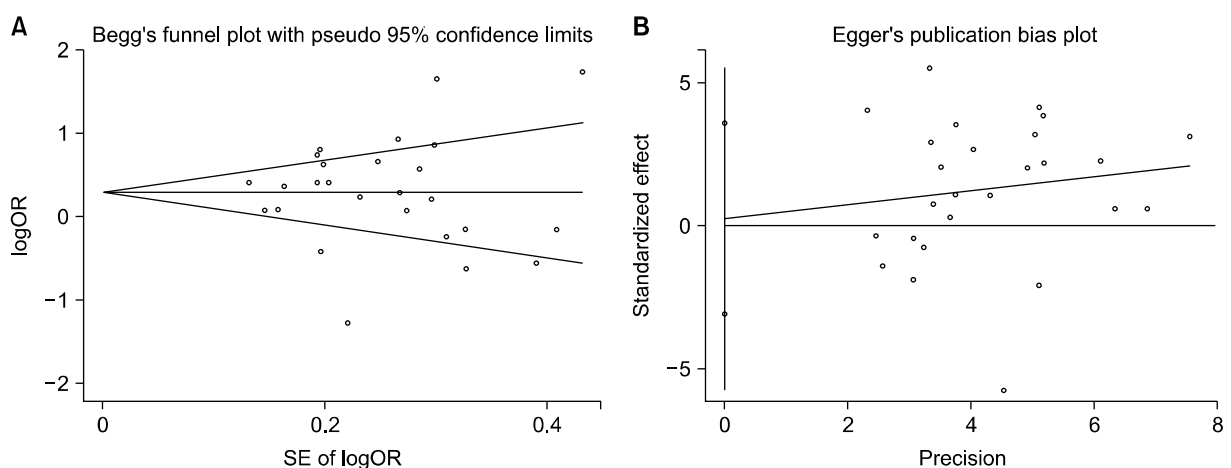


Figure 2. Publication bias which was estimated by Begg's test (A) and Egger's test (B).

this conclusion. These results are inconsistent with our findings.

Some studies show that there is no relationship between the use of oral contraceptives and breast cancer. Marchbanks et al.<sup>52</sup> carried out a meta-analysis in 2002 and reviewed 54 studies that represented 4,574 and 4,682 case and control subjects among women from 35 to 64 years of age, including white and black races. They concluded that current or former oral-contraceptive use was not associated with a significantly increased risk of breast cancer. OR for the women who used pills for long-term or continuously was equal to 1 (95% CI = 0.8-1.3) and for the those who had stopped using the pills was equal to 0.9 (95% CI = 0.8-1.0).<sup>52</sup> Wingo et al.<sup>60</sup> found no significant association between using oral contraceptives and mortality rate caused by breast cancer. That is, using OCPs was not effective on increase or decrease of the mortality rate caused by breast cancer. In other words, there was no association between using contraceptive pills and breast cancer.

The results of the current study show that OCPs is associated with increased risk of the breast cancer so that the OR of breast cancer in the women used OCPs is 1.5 greater than that in the women who didn't use of pills. Future cohort studies are recommended to evaluate this association with controlling confounding factors like duration of using oral contraceptives, family history of breast cancer, and oral contraceptives.

Although the results indicated that use of OCPs in women increases OR of breast cancer to 1.5, interpreting the data of the OCPs is not easy due to confounding variables, such as duration of using oral contraceptives, family history of breast cancer, and/or other similar factors.

## CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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