# Breast cancer incidence after hormonal treatment for infertility

## *A meta-analysis of population-based studies*

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## ABSTRACT

**الأهداف**: فهم العلاقة بين أدوية العقم وخطر الإصابة بسرطان الثدي لدى النساء بشكل شامل.

**المنهجية**: أُجري بحث في الأدبيات ذات الصلة باستخدام قواعد بيانات مختلفة (PubMed، ومكتبة كوكرين، وEmbase، وScopus، وWeb of Sciences) باتباع عناصر التقارير المفضلة للمراجعات المنهجية وإرشادات التحليل التلوي خلال الفترة من 2003م إلى 2023م. وشمل البحث دراسات قائمة على السكان قارنت معدل الإصابة بسرطان الثدي بعد العلاج الهرموني للخصوبة بمجموعة ضابطة. بالإضافة إلى ذلك، استُخدمت نماذج التأثير العشوائي والثابت لإجراء التحليل التلوي.

**النتائج**: شمل هذا البحث 15 دراسة شملت 92,555 امرأة. ولم يُظهر التحليل المجمع باستخدام نسب المخاطر (RRs) أي دليل على زيادة خطر الإصابة بسرطان الثدي المرتبط بأدوية الخصوبة الهرمونية (RR=1.00، فاصل ثقة 95% : [0.97-1.02]، قيمة $p$=0.83). كان مستوى التباين، كما هو موضح بإحصاء $I^2$، منخفضًا (32%)، ولم يكن اختبار Q ذا دلالة إحصائية. أسفر تحليل الحساسية باستخدام نموذج التأثيرات العشوائية عن نتائج متسقة، مما يشير إلى عدم وجود زيادة في خطر الإصابة بسرطان الثدي مع أدوية العقم. من بين الدراسات الأربع التي أبلغت عن نسب المخاطر (HRs)، لوحظ تأثير وقائي كبير على خطر الإصابة بسرطان الثدي (HR=0.91, 95% فترة الثقة: [0.88-0.94]، $p$<0.001). كان التباين مرتفعًا بشكل كبير ($I^2$=96%)، وأظهر اختبار Q دلالة إحصائية. أظهر تحليل الحساسية باستخدام نموذج التأثيرات العشوائية أن التباين ظل ثابتًا، مما يشير إلى أن التباين كان يُعزى إلى الأساليب المستخدمة في الدراسات المشمولة بدلاً من كونه نتيجة للتباين الإحصائي. كان التأثير الكلي، كما تم تحديده بواسطة نسبة المخاطر، 1.01 ولم يكن ذا دلالة إحصائية ($p$=0.94).

**الخلاصة**: لم يجد هذا التحليل التلوي أي دليل على زيادة خطر الإصابة بسرطان الثدي بعد العلاج الهرموني للعقم. ومع ذلك، ينبغي توضيح النتائج بحذر، نظرًا لتباين النتائج.

**Objectives:** To comprehensively understand the relationship between infertility medications and the risk of breast cancer (BC) in females.

**Methods:** Relevant literature search using different databases (PubMed, The Cochrane Library, Embase, Scopus, and Web of Sciences) following preferred reporting items for systematic reviews and meta-analyses guidelines was carried out from 2003-2023. Population-based studies comparing the incidence of BC after hormonal fertility treatment and a control group were included. In addition, random and fixed effect models were used to carry out meta-analyses.

**Results:** A total of 15 studies involving 92,555 women were included in this review. The pooled analysis using risk ratios (RRs) showed no evidence of increased BC risk associated with hormonal fertility medications (RR=1.00, 95% confidence interval [CI]: [0.97-1.02], $p$=0.83). The level of heterogeneity, as indicated by the $I^2$ statistic, was low (32%), and the Q test was not statistically significant. Sensitivity analysis using a random-effects model yielded consistent findings, suggesting no increased BC development risk with infertility medications. Among the 4 studies reporting hazard ratios (HRs), a significant protective effect on BC risk was observed (HR=0.91, 95% CI: [0.88-0.94], $p$<0.001). The heterogeneity was substantially high ($I^2$=96%), and the Q test demonstrated statistical significance. Sensitivity analysis using a random-effects model showed that heterogeneity remained constant, suggesting that the heterogeneity was attributable to the methods utilized in the included studies rather than being a result of statistical heterogeneity. The overall effect, as determined by the HR, was 1.01 and was not statistically significant ($p$=0.94).

**Conclusion:** This meta-analysis found no evidence of increased risk of BC following hormonal infertility treatment. However, the results should be illustrated cautiously, given the heterogeneity between studies.
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**Keywords**: breast cancer, infertility, hormonal fertility treatment

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Among the malignancies in the reproductive stage of women, breast cancer (BC) is considered as the most prevalent malignancy, with significant cases detected annually.[1] The approximate estimate in 2022 was 2.3 million females identified with BC and 670,000 deaths also occurred worldwide.[2] Breast cancer is characterized by uncontrolled growth of cancerous cells within the stroma and epithelium of the mammary glands. Over the years, considerable progress has been carriedout in BC research, leading to new insights into BC diagnosis, progression, prognosis, metastasis, and treatment. Despite advancements in the understanding of BC, it remains a major public health concern and a challenging condition for management.[3]

Breast cancer development is attributed to variety of factors, with the oncogenic and proliferative activities of both endo and exogenous female hormones being significant risk factors.[4,5] Meanwhile, a subject of increasing interest is determination of potential relationship between the remedy of fertility and BC development.[6] Given the widespread use of treatments, the investigation of the association between risk of cancer and fertility drugs is at utmost importance. Moreover, it is estimated that there are one million in vitro fertilization (IVF) cycles annually, and an unknown number of ovulation induction cycles are carried out worldwide.[7,8] There are different types of medications used for the treatment of fertility (gonadotropins, clomiphene citrate, and letrozole). Gonadotropins include human chorionic gonadotropin (hCG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), and for the initiation of ovarian stimulation (OS), these gonadotropins directly bind to ovarian follicular cell receptors.[9] However, controversies still exist in terms of the impact of hCG on BC risk. Furthermore, during pregnancy, placental hCG hormone is considered with antitumor effects, whereas ectopic hCG promotes progression of tumors.[10] Meanwhile, clomiphene citrate plays a critical role in the inhibition of the negative feedback of gonadotropin release, leading to increased estrogen production and ovulation induction.[9]

Letrozole is an aromatase inhibitor, which limits estrogen production and triggers ovulation to inhibit the negative feedback of FSH and is considered the first-line remedy for hormone receptor-positive BC.[9,11] However, it is still unclear that the letrozole, when combined with other fertility medications, has a risk for the development of BC. Meanwhile, female reproductive disorders, including infertility have increased, which made it a significant public health concern. Consequently, the safety of hormone-related medications, particularly OS drugs, which are mainly used medications to treat infertility.[12] Therefore, this review aims to comprehensively understand the relationship between infertility medications and the risk of BC in females. The results of this study conclusively demonstrate the absence of an increased risk of BC associated with fertility treatment, which is a significant contribution to the fields of women's health policy, clinical decision-making, cancer research, and patient education and empowerment.

**Disclosure**. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

**Methods.** Updated guidelines of preferred reporting items for systematic reviews and meta-analysis (PRISMA) and Cochrane handbook were followed for transparency and reproducibility of the studies.[13,14]

***Literature search and data collection.*** The literature was searched using different electronic databases, such as PubMed, Scopus, Embase, The Cochrane Library, and Web of Sciences utilizing the following search terms: hormonal therapy, infertility, hormonal fertility treatments, and BC.

***Eligibility criteria and selection of studies.*** For the selection of the studies, PICO guidelines were followed, P (population): the population consisted of females with fertility issues; I (intervention): the intervention involved hormonal fertility treatments; C (control/comparator): the comparator was a control group; and O (outcomes): the incidence of BC and impact of medication on fertility. In addition, randomized controlled trials (RCTs) and non-RCTs (including cross-sectional, retrospective, and cohort studies) published in peer-reviewed journals during 2003-2023 were included. Likewise, certain exclusion criteria were also considered before the selection of the studies. For instance, non-PICO studies, reviews, editorials, commentaries, letters, and studies published in non-peer-reviewed journals published before 2003 were excluded.

Duplicate studies were removed using the EndNote software. The screening process was carried out using PRISMA flowchart and initially involved reviewing the titles and abstracts, followed by full-texts, which were carried out by 2 independent authors. Any discrepancies between authors were resolved by a third senior author.

***Data extraction.*** The data comprised the following components: I) summary characteristics, which encompassed women experiencing fertility issues and undergoing hormonal fertility treatments; II) baseline data, including the location of the study, study design,

publication year, primary outcomes, and conclusions; and III) outcomes that featured the incidence of BC among females receiving hormonal fertility treatments, along with the odds ratio (OR) or risk ratio (RR) or hazard ratio (HR) and confidence interval (CI).

*Data analysis.* To analyze the extracted data from the included studies, RevMan software (Version 6.0) was employed along with the Generic Inverse Variance method, which is suitable for studies with varying sample sizes and standard errors across multiple studies. Most studies employed the RR or OR to gauge the impact of infertility medications on the incidence of BC (8 studies). However, 4 studies used HR as their estimation method, as they employed person-time years and carried out a time-to-event analysis. The analysis was based on 2 measures: RR and OR. As the conversion of OR to RR is relatively simple, particularly when the prevalence of the outcome is less than 10%, the 2 were analyzed together. However, the conversion of HR to RR was more complex and required information on the shape of the survival function, which was not available in the included studies. As a result, studies that used HR were analyzed separately (4 studies). A forest plot was constructed for all included studies using both random and fixed models to carry out sensitivity analysis and compare the findings. The $I^2$ values and Chi-square statistics were used to evaluate heterogeneity at the significance level of <0.05.

**Results.** Figure 1 depicts the process of identification and selection of studies for this systematic review. Initially, 3,539 records were identified from the following databases: PubMed (n=1,160), Scopus (n=613), The Cochrane Library (n=243), EMBASE (n=529), and Web of Science (n=994). After removing duplicates (n=1,862) and 924 records were found ineligible by automation tools (n=924), 753 records were screened. Of these, 631 reports were excluded, leaving 122 records for retrieval. An additional 95 records were not retrieved, leaving 27 assessed for eligibility. After excluding 12 records that did not meet the eligibility criteria, 15 records were ultimately selected in the review for further qualitative and quantitative analysis.

*Summary study characteristics.* Table 1 summarizes the studies, which evaluated the association between fertility treatment and BC risk in various populations across different countries. A study from Taheripanah et al[15] used ovulation drugs for the treatment of infertility and observed no association with BC risk, except for a rise in risk with use exceeding 6 months. Likewise, Orgéas et al[16] found no evidence for increased overall BC risk with infertility

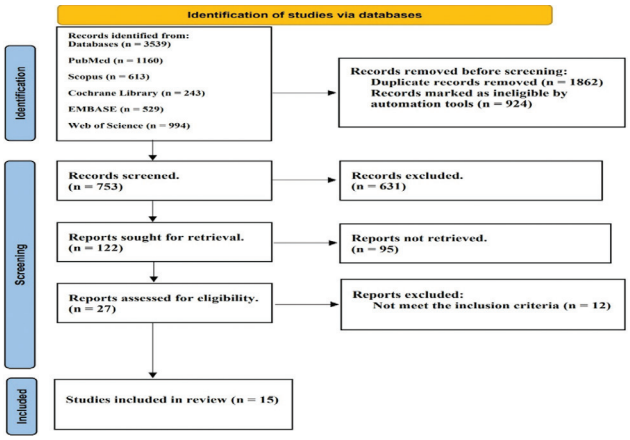


**Figure 1 -** Preferred reporting items for systematic reviews and meta-analyses flow diagram. Process study selections through databases.

treatment, however, increased risk of BC was linked with high-dose of clomiphene citrate for nonovulatory causes. Furthermore, Calderon-Margalit et al[17] observed a significant association between overall risk for cancer with ovulation induction, however, lacked understanding of treatment details. Furthermore, Lerner-Geva et al[18] found no increased ovarian cancer risk with infertility treatment and attributed higher borderline ovarian tumor risk to inherent tumor traits or surveillance bias. Bildircin et al[19] found no BC risk from controlled OS and advocated for anti-estrogen agents, GnRH antagonists, and awareness of lower ovarian reserves in patients with cancer.

A study from Basudan et al[20] attributed the rising BC incidence to lifestyle changes and called for preventive measures, such as addressing tobacco use and improving screening. In France, Gauthier et al[21] found the effect of fertility treatment on the incidence of BC unclear, but observed a potential role played by family history. Moreover, Kotsopoulos et al[22] found no increase in BC risk from fertility treatment in carriers of BRCA mutations. Likewise, Jensen et al[23] found no link between fertility drug use, cycles, or years since first use and BC overall, but possibly an effect in nulliparous women. While, Reigstad et al[24] demonstrated higher BC risk after assisted reproduction versus no treatment. However, Burkman et al[25] suggested prolonged medication use may increase risk. Meanwhile, Terry et al[26] found a lower risk of ovulatory disorders versus other infertility causes. Similarly, Stewart et al[6] associated younger IVF age with a greater risk of BC. While, Doyle et al[27] demonstrated that ovarian stimulation had no risk of cancer development, and Cooley[28] suggested estrogen treatment had an indirect effect on BC cells (Table 1).

**Table 1 -** Study characteristics (N=15).

| Study ID | Sites | Study designs | Inclusion criterias | Conclusion |
|---|---|---|---|---|
| Taheripanah et al[15] | Iran | Case control | Patients who had been referred to the radio-oncotherapy clinic of Shahid Beheshti University of Medical Sciences with a diagnosis of BC in either teaching or general hospitals were analyzed. Only histopathologically confirmed female BC patients, diagnosed within one year prior to the interview, were included in the study. | No apparent association was observed between BC risk and ovulation induction drugs, however rise in BC patients using fertility medications over six months was also observed. |
| Orgéas et al[16] | Sweden | Cohort | During the period between 1961 and 1976, women who were receiving treatment for subfertility-related issues at major obstetrics and gynecology clinics (Gothenburg, Stockholm, and Uppsala, Sweden), were the focus of a study. | Increased overall risk of BC associated with infertility treatment was not observed. However, patients received clomiphene citrate therapy for non-ovulatory with high dose heightened risk for developing BC. |
| Calderon-Margalit et al[17] | Israel | Cohort | The study involved 567 women who utilized drugs to stimulate ovulation. | This study was performed for the assessment of association of infertility treatment using ovulation induction with risk of developing cancer (uterine cancer). However, still lacking the understanding regarding the dose and durations of clomiphene and its association with cancer. |
| Lerner-Geva et al[18] | Israel | Cohort | Women were identified from medical records of the infertility clinic of Sheba Medical Center situated in Tel Hashomer, Israel. These women were diagnosed with primary or secondary infertility between January 1, 1964, and December 31, 1974. | The findings pertaining to the potential connection between infertility, drugs like ovulation induction, and invasive ovarian cancer suggest a lack of increased risk, which is comforting. The higher risk of borderline ovarian tumors might be attributed to inherent traits of these tumors or surveillance bias. |
| Bildircin et al[19] | Turkey | Cohort | Women who used drugs to induce ovulation. | The use of controlled OS does not present a risk for the development of BC. The employment of anti-estrogen agents in stimulation protocols has demonstrated effectiveness, with a correspondingly low increase in estradiol levels. The utilization of Gonadotrophin Releasing Hormone antagonists can be utilized to initiate baseline ovarian conditions, thereby circumventing the delay typically associated with the initiation of OS. Importantly, ovarian reserves and responses are often lower in women who have been diagnosed with BC. |
| Basudan et al[20] | Saudi Arabia | Retrospective analysis | Among the patients diagnosed with BC in Saudi Arabia, those of all age groups and residing in all administrative regions have been identified. | The findings suggest that there has been arise in incidence of BC in Saudi Arabian population, which can be attributed to the changing their lifestyle and followed more westernized lifestyle. For the prevention of BC incidence, following measures should be considered. For instance, prevent the use of tobacco in any form, management of body weight and awareness for the benefits of physical activity, and establishment of an effective programs BC screening. |

RCT: randomized controlled trial, BC: breast cancer, IVF: in vitro fertilization, MBRN: the Medical Birth Registry of Norway, OS: ovarian stimulation, ER: estrogen receptor, hCG: human chorionic gonadotropin

*Meta-analysis using the risk ratio.* **Figure 2** shows a pooled effect size of 8 studies and revealing an overall RR=1.00, $p$=0.83. The RR for the association between infertility medications and BC in women was (RR=1.0, 95% CI: [0.97-1.02]), according to the fixed effect model. This suggests that there is no evidence to support the notion that infertility medications increase risk of BC in women.

*Meta-analysis (random effects model).* The level of heterogeneity, as indicated by the I2 statistic, was low (32%) and the Q test was not statistically significant. Sensitivity analysis was carried out via random-effects model for the assessment of the heterogeneity, which has an impact on our findings (**Figure 3**). The findings of this analysis were consistent with those of fixed-effects model, suggesting that there is currently no evidence to underpin and establish the notion that infertility medications increase the risk of BC.

*Meta-analysis using hazard ratio.* The degree of heterogeneity was substantially high, as indicated by the I2 value (96%), and the Q test demonstrated statistical significance. This suggests the presence of heterogeneity, which may be attributed to the following factors, such as differences in patient clinical characteristics or variations in statistical methodologies among the studies. A sensitivity analysis was carried out by employing either fixed- or random-effects models. **Figure 4** illustrates a forest plot depicting all assessed studies utilizing the model (fixed-effects) to determine the effect size. The HR for the overall analysis is indicated by the black diamonds in the figure. The HR estimated at 0.91 (95% CI: [0.88-0.94]) revealed significant reduction in BC risk in women, who used infertility medications than those with no medications ($p$<0.001). This analysis employs time-to-event data, accounting for the risk among women during non-follow-up periods.

**Table 1 -** Study characteristics (N=15, continuation).

| Study ID | Sites | Study designs | Inclusion criterias | Conclusion |
|---|---|---|---|---|
| Gauthier et al[21] | French | Cohort | The study population comprised of 98,997 French women (40-65 years) and health expenditures covered by the MGEN insurance agency. A total of 4,567 and 239 women with a history of cancer other than basal cell carcinoma at the baseline and whom the date of diagnosis was unavailable, respectively were excluded. Additionally, 1636 women never engaged in sexual intercourse were also excluded. Ultimately, 92,555 women were selected. | The impact of infertility treatment on the risk of developing BC is unclear, and more research is required to draw definitive conclusions. However, it is worth noting that family history of BC had utmost role in the development of the disease, and further investigation into this potential interaction is warranted. |
| Kotsopoulos et al[22] | Canada | Non-RCT | Individuals possessing a BRCA1 or BRCA2 mutation and utilizing fertility medications or undergoing IVF | According to the findings, the employment of fertility treatments appears to have no detrimental impact on the likelihood of developing BC in individuals who have inherited BRCA gene mutations. |
| Jensen et al[23] | Denmark | Non-RCT | In the timeframe of 1965 to 1998, all women were identified through medical records, who experienced infertility (primary and secondary) and mentioned to either Danish hospitals or private fertility clinics. | The analysis of all fertility drug groups revealed no associations between duration or number of cycles used since first use and the risk of BC. However, among nulliparous women, gonadotrophins may have a more pronounced impact on BC risk. |
| Reigstad et al[24] | Norway | Non-RCT | MBRN recorded all female residents of Norway who gave birth to a child (gestation >22 weeks) between January 1, 1984, and December 31, 2010. While, women diagnosed with BC prior to the commencement of study were excluded from the analysis. | All Norwegian women who had given birth and were followed for 27 years demonstrated a higher risk of developing BC underwent ART than no ART. |
| Burkman et al[25] | Metropolitan Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle. | Non-RCT | Histologically confirmed women (35-64 years), primary invasive BC and had no prior history for invasive or in situ BC. Ability to understand the English language. | The prolonged administration of specific infertility medications may possibly increase the risk of developing BC. |
| Terry et al[26] | Boston | Non-RCT | Female participants aged between 25 and 42 years who reported having cancer at the time of enrollment (excluding non-melanoma skin cancer) were not eligible for inclusion in the study. | The data imply a negative correlation between BC and infertility resulting from ovulatory disorders, but not from other sources of infertility. |
| Stewart et al[29] | Australia | Non-RCT | The demographic of focus for this study is all women aged 20 to 44 from Western Australia, who were investigated and treated for infertility during 1983 and 2002. | The commencement of IVF at a youthful age has been found to be correlated with a higher incidence of BC. |
| Doyle et al[27] | UK | Non-RCT | Ladies who were permanent residents of United Kingdom and received treatment at the clinic between beginning of 1975 and the end of 1989, and had undergone infertility treatment for at least one cycle and at least 20 years old at the time of treatment. | No correlation was observed between treatment for infertility by using OS and the development of breast, uterine, or ovarian cancer during the follow-up period investigated. |
| Cooley et al[28] | USA | Non-RCT | Infertile women treated for infertility and outcomes were followed for 30 years and now, the mean age was 62.7 years at te end of follow-up. | The findings from the preclinical study suggest that ER-positve BC cells can be impacted indirectly by the estrogenic effects of infertility treatments and validate the potential protective effect of exposure to hCG during pregnancy. |

RCT: randomized controlled trial, BC: breast cancer, IVF: in vitro fertilization, MBRN: the Medical Birth Registry of Norway, OS: ovarian stimulation, ER: estrogen receptor, hCG: human chorionic gonadotropin

***Meta-analysis using random effects model and hazard ratio.*** By employing the random-effects model in Figure 5, it was observed that heterogeneity remained constant, suggesting that source of heterogeneity was attributable to the methods utilized in the included studies rather than being a result of statistical heterogeneity. The overall effect, as determined by the HR, was 1.01 with non-significant difference ($p$=0.94). Consequently, the use of the random-effects model in this instance was not beneficial as it led to the loss of statistical significance, while the heterogeneity remained unchanged.

**Discussion.** The incidence of BC following hormonal treatment for infertility, as with all gynecological cancers poses significant threat to the overall health of women and also considered as a leading cause of mortality among women worldwide and has serious implications for public health.[30,31] Therefore, this meta-analysis aimed to compare medications used for fertility and their role on the BC development.

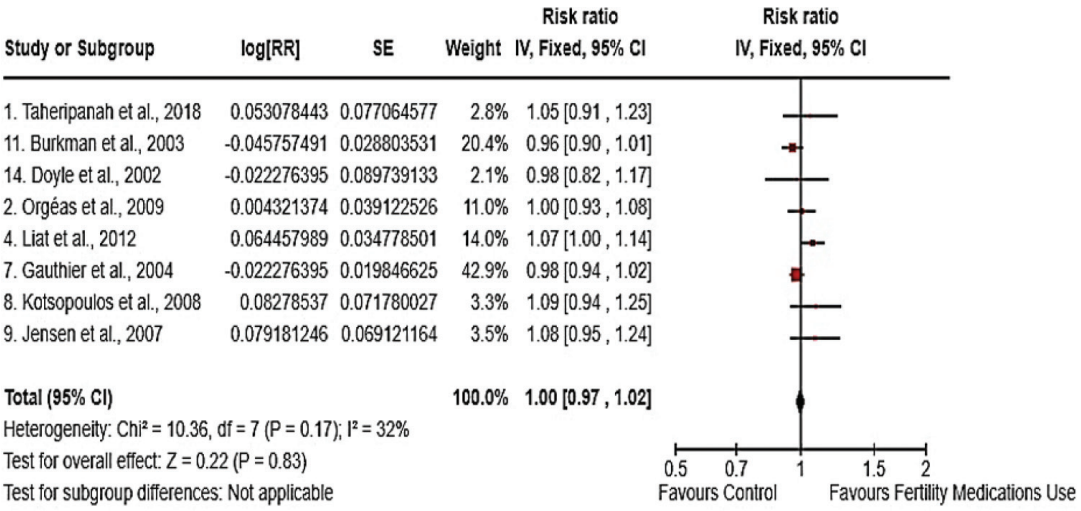


**Figure 2 -** The influence of infertility medications on breast cancer risk in women was assessed using a fixed effects model.

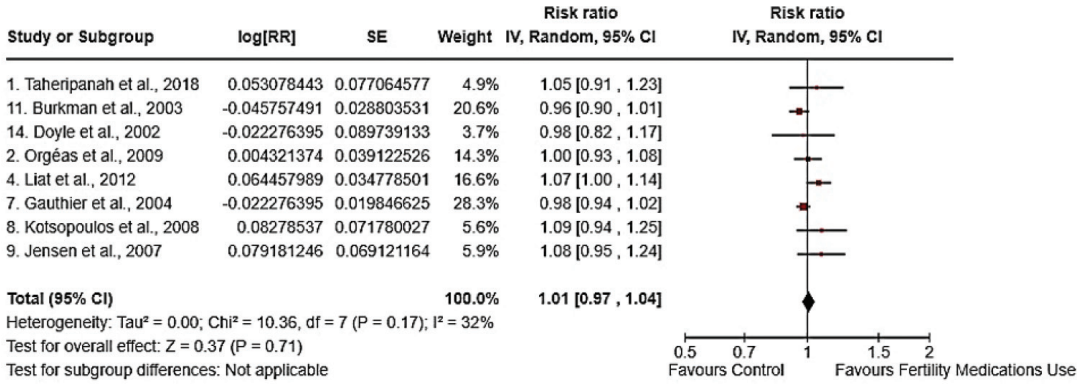


**Figure 3 -** The impact of infertility treatments on a woman's likelihood of developing breast cancer using a random effects model.

The safety of hormone-containing fertility treatments for OS has garnered significant attention; however, evidence supporting their safety remains limited.[12] Numerous studies have explored the connection between exogenous hormones and BC; however, the association between infertility treatment and BC remains unclear. Evaluating BC risk is particularly challenging for women seeking treatment for fertility in their early age of life (20s and 30s), and in the later stage of life (3-4 decades), the peak incidence of BC occurs.[32] Although the incidence of BC and its associated deaths increases with age, this association remains unclear.

One of the key difficulties in investigating the impact of the treatment for fertility on BC risk is the confounding factors, which are the underlying causes of infertility. As, infertility and nulliparity are considered as the risk factors for BC, and the effect may be unreliable when checked with the general population.[33]

Our results demonstrated a non-significant impact of treatments used for fertility on the increase risk of developing BC among women. Our findings are in consistent with the another meta-analysis, which was carried out in the general female population. Furthermore, fertility therapy did not significantly increase the BC incidence in genetically vulnerable women, or in women with BRCA mutations, and those with a family history of BC. In addition, lower mortality rate was observed in women assessed for infertility than the general population.[12,34] Furthermore, another meta-analysis also observed similar findings and revealed non-significant risk of BC development with fertility treatment and compared with subfertility or general population as a reference group. The OR was 0.97 (95% CI: [0.90-1.04]) and even women administrated with 6 or more IVF cycles did not develop or show the risk of BC development.[35] Moreover, another study also

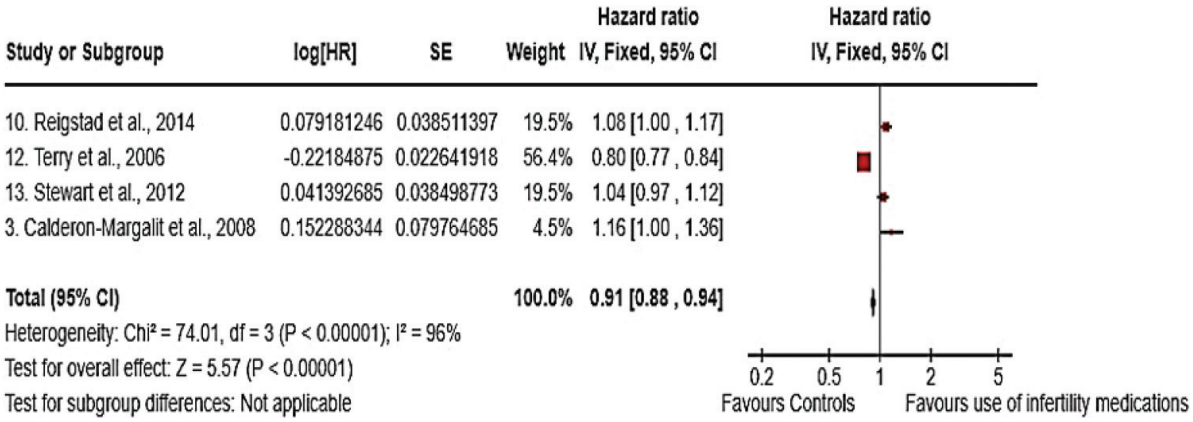


**Figure 4 -** Forest plot for hazard ratio to assess the impact of infertility treatments on women's susceptibility to breast cancer, specifically examining the fixed effects model.

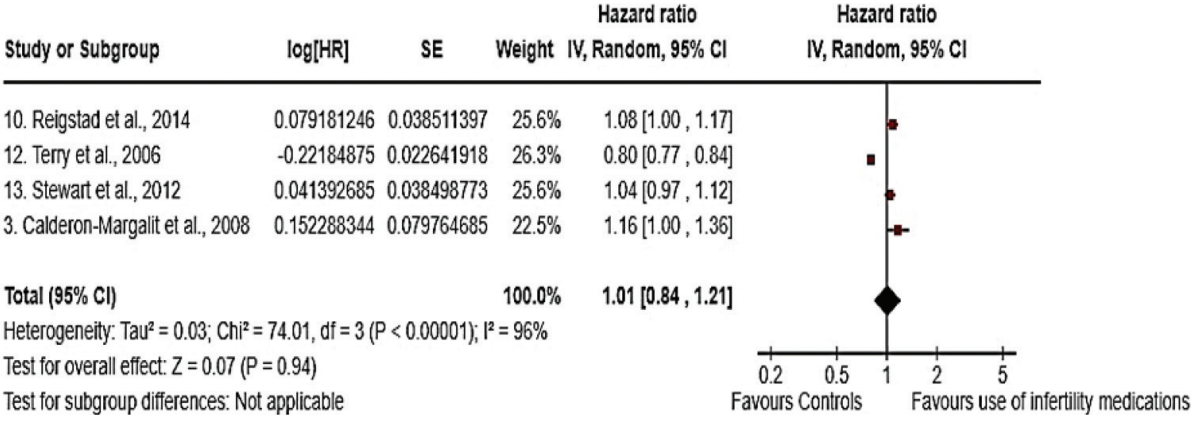


**Figure 5 -** The impact of infertility treatments on the likelihood of breast cancer in women can be analyzed using a random-effects model and hazard ratio.

demonstrated a non-significant relationship between BC and IVF in general population with 0.91 RR (95% CI: [0.74-1.11]), while in infertile women RR was 1.02 (95% CI: [0.88-1.18]).[36] Likewise, a cohort study included 25, 108 women and treated with IVF and compared with general population for the risk of development of BC. This study observed non-significant difference with 1.01 standardized incidence ration (SIR, 95% CI: [0.93-1.09]) for general population and for non-IVF group HR was 1.01 (95% CI: [0.86-1.19]).[37] In contrast, research has demonstrated that women who undergo assisted reproductive technology (ART) have a 20% higher risk of developing BC.[24] Meanwhile, a question can arise that how these fertility medications cause BC and the possible explanation can be that with the fertility medications stimulate ovarian activity, leading to elevated levels of progesterone and estrogen hormones, which play an important role in breast tissue proliferation.[38] In addition, prolonged or repeated exposure to high level of these hormones can enhance and increase cell division in breast tissue, potentially heightening the risk of tumor formation.[39] Overall, this study highlights the non-significant impact of fertility treatment on the risk of development of BC. However, clinically the outcomes of the present study should be used with caution as it is also established that with high dose or duration of these treatments can increase risk of BC.

Future studies should focus on large scale, long-term cohort studies with robust design for better comparison and further elucidate the association between fertility treatment and risk of BC. In addition, studies should incorporate treatment type, dose, cycles, and duration and most importantly confounding factors, such as age, lifestyle factors, genetic predisposition, and history.

*Study limitations.* This review was characterized by several robust features and limitations. The studies included in our review were primarily observational

and retrospective, and cohort studies were retrieved from national databases. These databases are prone to information and recall bias, which may affect the accuracy of the collected data. Additionally, the data often lacked key variables, such as HRT exposure, BMI, family history for cancer or BC, smoking, alcohol consumption, and age at menarche, which are considered utmost and significant risk factors and potential confounders for developing BC.

In conclusion, this review did not provide concrete evidence to support a connection between the hormonal medications use for infertility treatment and an BC development risk in women. Although this systematic review indicates that fertility medications did not appear to increase the risk of BC, however, it is challenging to definitively prove the absence of any association because of the variety of existing studies and the need for thorough, long-term registry studies that account for confounding factors. Therefore, the results of this study are useful for guiding clinical practice and patient counseling. However, further research is necessary to monitor BC incidence after infertility treatment.

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