ORIGINAL ARTICLE: ENVIRONMENT AND EPIDEMIOLOGY

Ovarian stimulation and risk of breast cancer in Swedish women

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Objective: To investigate whether ovarian stimulation for treating infertility is associated with the risk of breast cancer.
Design: Nationwide register-based cohort study.
Setting: Not applicable.
Patient(s): In a cohort of 1,340,211 women who gave birth 1982–2012, we investigated the relationship between assisted reproductive technology (ART) and incidence of breast cancer. Associations between any ovarian stimulation since 2005 and breast cancer incidence were studied in a separate cohort of 1,877,140 women born 1960–92. Both cohorts were followed through 2012.
Intervention(s): None.
Main Outcome Measure(s): Hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer.
Result(s): There was no increased risk of breast cancer in women who gave birth after ART compared with women who gave birth after spontaneous conception (adjusted HR, 0.84; 95% CI, 0.74–0.95). The incidence of breast cancer was not increased among women who received controlled ovarian stimulation or among women who received other hormonal fertility treatments since 2005, regardless of live birth (adjusted HR, 0.86; 95% CI, 0.69–1.07; and adjusted HR, 0.79; 95% CI, 0.60–1.05, respectively).
Conclusion(s): No increased incidence of breast cancer was found among women who had gone through ovarian stimulations, including ART. These results are consistent with other studies and reassuring given the widespread and increasing use of ART. (Fertil Steril® 2017;■:■–■. Copyright ©2017 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Key Words: Infertility, assisted reproduction, in vitro fertilization, ovarian stimulation, breast cancer

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Concerns have been expressed about the long-term safety of the hormonally potent drugs used for ovarian stimulation, in particular in relation to the increasing use of assisted reproductive technologies (ART). Clomiphene citrate or low-dose gonadotropins have commonly been used to induce ovulation in women with ovulatory disorders. For ART, high doses of gonadotropins are required to stimulate multiple follicular development in controlled ovarian stimulation (COS), while spontaneous ovulation is suppressed using GnRH agonists or antagonists.

Since ovarian stimulation influences endogenous estrogen levels, these treatments have been suspected to increase cancer risk (1). Several forms of breast cancer are estrogen sensitive, with established hormone-related risk factors such as age at menarche and menopause, oral contraceptives, and hormone therapy use (2). However, results from previous studies of breast cancer risk after ART have been inconsistent. Many studies suffer from low power due to small sample sizes or short follow-up (3). It is also debated whether observed associations have been due to COS or the underlying fertility problems.

Most previous studies have not found an increased risk of breast cancer after ovarian stimulation (4–7). In a previous Swedish study, women who had given birth after ART had a slightly lower risk of breast cancer (8). Furthermore, a systematic review and

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meta-analysis concluded that there was no clear association between ovarian stimulation and breast cancer (3).

However, a recent cohort study from Norway found an increased risk of breast cancer in women who gave birth after ART (9). In addition, some studies have shown an increased risk of breast cancer within certain subgroups of patients (10–14). In a previous study, we have shown an association between COS and mammographic breast density, a marker for breast cancer risk (15).

The objectives of the present population-based cohort study were to investigate the associations between ovarian stimulation by ovulation induction or COS and breast cancer incidence and to assess the role of the underlying infertility for the studied associations.

MATERIALS AND METHODS

The present cohort study used information on ART treatments from several Swedish registers. First, information on live births after ART treatment was recorded by the National Board of Health and Welfare during the years 1982–2006, including all ART clinics in Sweden. Since 2007, all ART treatments in Sweden, regardless of pregnancy outcome, are recorded in the National Quality Registry for Assisted Reproductive Technology (Q-IVF). In addition, the Prescribed Drug Register (PDR) contains data on all prescribed drugs dispensed in Sweden since July 2005, including those used for ovarian stimulation. Diagnoses related to infertility have been recorded in the National Inpatient Register since 1964, with complete nationwide coverage since 1987 (16), and in the National Outpatient Register since 2001.

Study Populations

The Swedish Multi-Generation Register (MGR) links all persons who were born after 1932 and residing in Sweden 1961 or later to their parents. Using the personal identity number assigned to all Swedish residents, we linked these registers and several other Swedish national population registers to establish two cohorts: [1] a parous population of women who had their first live birth between 1982 and 2012 (n = 1,535,678) and [2] women born 1960–92 (ages 20–45 between 2005 and 2012; n = 2,338,869). From the parous population (Supplemental Fig. 1), we excluded women who had invalid personal identification numbers (n = 1,876), did not reside in Sweden at the start of pregnancy (n = 189,110), or had a previous diagnosis of malignant disease (n = 4,481), leaving a cohort of 1,340,211 women. The cohort of women born 1960–92 (Supplemental Fig. 2) included 1,877,140 women after excluding those with invalid personal identification numbers (n = 2,592) and those who had died (n = 28,484), emigrated (n = 356,111), been diagnosed with malignant diseases (n = 14,718), or given birth to four or more children (n = 59,824) before start of follow-up. Due to overlap, 1,061,510 women were included in both cohorts.

Exposure Information

For each woman, diagnoses related to infertility were identified using the National Patient Registers. In addition to the diagnosis "female infertility," we included the following diagnoses commonly associated with impaired female fertility: ovarian dysfunction (including polycystic ovary syndrome and premature ovarian insufficiency); absent, scanty, or rare menstruation; and endometriosis (diagnosis codes in Supplemental Table 1).

In the cohort of parous women, ART births were identified using information from the National Board of Health and Welfare for the years 1982–2006 and the Q-IVF for 2007–12. Both fresh and frozen ETs from standard IVF and intracytoplasmic sperm injection (ICSI) were included. Women with no ART births were subdivided into two groups, those with and without an infertility-related diagnosis.

In the cohort born 1960–92, we used the PDR to identify all ovarian stimulation treatments 2005–12. COS was defined as dispensations of gonadotropins (either hMG or FSH) and down-regulation (using either GnRH-agonist or antagonist) in the PDR with a maximum of 90 days between dispensations, or stimulation for ART recorded in Q-IVF. Ovulation induction was defined as dispensations of either clomiphene citrate or gonadotropins without down-regulation in the PDR. Women with no ovarian stimulation were further divided into two groups, those with and without an infertility-related diagnosis.

Breast Cancer

Since 1958, the Swedish Cancer Register (SCR) records occurrences of cancer in all Swedish residents with an estimated completeness of >95% for solid tumors (16). Recorded information includes date of diagnosis, tumor site and morphology, with diagnoses coded using the current version of the International Classification of Diseases (ICD) and also translated to version 7 (ICD-7).

In the present study, breast cancers were defined according to ICD-7 code 170 and pathoanatomical diagnosis code 096. Women with a first diagnosis of breast cancer during follow-up were considered cases. Women with any diagnosis of malignant diseases (ICD-7, codes 140–205) before start of follow-up were excluded, and those with a malignancy other than breast during the study period were censored at date of diagnosis. By combining information in the MGR with the SCR, family history of breast cancer was defined as having a biological mother or sister with breast cancer.

Covariates

Date of childbirth and the woman's parity were obtained from the MGR. Gestational length was obtained from the Medical Birth Register (MBR). Where this information was missing, 280 days was used. Start of pregnancy was calculated by subtracting the gestational length from the birthdate of each child. Body mass index (BMI, kg/m^2) was calculated from height and weight at start of pregnancy, available from the MBR (missing for the years 1990–91).

The woman's date and country of birth were obtained from the Total Population Register, highest achieved level of education from the Education Register, date of death from the Cause of Death Register, and any migrations in or out of Sweden from the Total Population Register.

Statistical Analyses

Parous women who had their first live birth between 1982 and 2012 were followed from the start of the first pregnancy resulting in a live birth. Women born 1960–92 were followed from July 2005 or age 20, whichever occurred last. All women were followed until the date of their first breast cancer diagnosis, or censored at date of other cancer diagnosis, death, emigration, start of pregnancy with fourth child, or the end of follow-up in December 2012, whichever occurred first. Follow-up time in the parous cohort was also censored at the 60th birthday, since no ART exposed case occurred after age 60 (Supplemental Table 2).

Cox proportional hazard models were used to estimate hazard ratios (HRs) for breast cancer with 95% confidence intervals (CIs), with attained age as the timescale. For both cohorts, the main models compared breast cancer incidence rates among women exposed to ovarian stimulation and among women with infertility-related diagnoses but no ovarian stimulation/ART treatment to that of women with neither infertility-related diagnosis nor ovarian stimulation/ART treatment. In a second step, the models were also estimated using women with an infertility-related diagnosis with no ovarian stimulation/ART treatment as the reference category. All analyses were performed on complete cases.

In the parous cohort, having an ART birth was entered into the models as a time-dependent exposure, that is, women changed exposure category from the date of conception of an ART birth and were considered exposed to ART thereafter. Women who had a spontaneous birth before ART treatment contributed person-time to the unexposed group until date of conception of the ART birth. In the cohort born 1960–92, COS and ovulation induction were entered as time-dependent exposures in a similar way. Women who received ovulation induction before COS contributed person-time to the ovulation induction exposure group and later to the COS exposure group.

The proportional hazards assumption was assessed using tests based on Schoenfeld residuals, and calendar time, parity, and time since latest pregnancy were included as time-dependent covariates in the models. Calendar time was split into 5-year intervals. Highest attained education level, country of birth, family history of breast cancer, and age at first birth were included as fixed covariates.

The following sensitivity analyses were performed: First, in the parous cohort, we excluded women for whom information on pregnancy length was missing for any pregnancy during follow-up. Second, separate effects were estimated for pre- and postmenopausal breast cancer by splitting the risk-time into two age groups (<50, ≥ 50 years) in the parous cohort. Third, the main models were also estimated in the subpopulation of the parous cohort with BMI information, and a third model also included BMI as a fixed covariate. In the cohort born 1960–92, we estimated separate effects among nulliparous and parous women. The effect modifications by age and parity were tested using the likelihood-ratio test comparing models with and without interaction terms. Finally, we excluded women who had received gonadotropins for ovulation induction from the cohort born 1960–92, leaving women treated only with clomiphene citrate in the ovulation induction group.

The significance level was 5%, and all tests were two-sided.

SAS software (ver. 9.4, SAS Institute) was used to prepare the data and Stata software version 13 IC (*Stata Statistical Software: Release 13*, StataCorp) was used for the statistical analyses.

The study was approved by the Ethical Review Board in Stockholm, Sweden (ethical approval 2013/1849-31/2, amendment 2014/118-32).

RESULTS

Of the 1,340,211 women in the parous cohort, 38,047 gave birth after ART treatment. During the follow-up period, 13,414 women were diagnosed with breast cancer, of which 262 were exposed to ART. The mean length of follow-up was 9.6 (SD, 6.4) years for women with ART birth and 14.6 (SD, 8.8) years for women with no ART birth.

Of the 1,877,140 women born 1960–92, 39,469 had gone through COS and 26,232 had received ovulation induction since July 2005. In the ovulation induction group, 25,303 women had been treated with clomiphene citrate and 3,093 women had been given gonadotropins (2,164 of the women had used both types of drugs). In this cohort, 7,229 women developed breast cancer during follow-up, of which 84 had received COS and 50 ovulation induction. The mean length of follow-up was 7.4 (SD, 0.7) years for COS women, 7.2 (SD, 1.1) years for women with ovulation induction, and 6.3 (SD, 2.2) years for women who did not receive any ovarian stimulation.

Population Characteristics

Population characteristics, by exposure status, are described in Table 1. In the parous cohort, 69.7% of women with ART births and 6.7% of women with no ART birth had diagnoses related to infertility. Women with ART births were more likely to be born in the 1970s compared with women giving birth without ART. Women who had gone through ART were more highly educated, older at their first birth, and had higher BMI at the start of pregnancy, while there were no major differences regarding country of birth or family history of breast cancer.

In the cohort born 1960–92, 75.2% of women with COS, 53.9% of women with ovulation induction, and 5.8% of those who had not received any ovarian stimulation had infertility-related diagnoses. The majority of women who received COS or ovulation induction since 2005 were born in the 1970s. They were also more highly educated, older at first birth, and less likely to be nulliparous at the end of follow-up compared with women who had not received any ovarian stimulation. Women who received ovulation induction were more likely to be born in non-Nordic countries.

TABLE 1

Characteristics of the study populations.

	Parous women		Women born 1960–92		
Parameter	**ART birth (n = 38,047)**	**No ART birth (n = 1,302,164)**	**COS (n = 39,469)**	**Ovulation induction (n = 26,232)**	**No ovarian stimulation (n = 1,811,439)**
Birth year					
<1960	2,818 (7.4)	182,094 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)
1960–69	12,911 (33.9)	468,415 (36.0)	7,242 (18.3)	4,379 (16.7)	553,098 (30.5)
1970–79	18,729 (49.2)	431,587 (33.1)	25,342 (64.2)	13,447 (51.3)	523,115 (28.9)
≥1980	3,589 (9.4)	220,068 (16.9)	6,885 (17.4)	8,406 (32.0)	735,226 (40.6)
Infertility-related diagnosis					
No	11,547 (30.3)	1,214,642 (93.3)	9,756 (24.7)	12,105 (46.1)	1,706,603 (94.2)
Yes	26,500 (69.7)	87,522 (6.7)	29,713 (75.3)	14,127 (53.9)	104,836 (5.8)
Highest education					
9-year compulsory school	1,765 (4.6)	112,479 (8.6)	1,854 (4.7)	2,099 (8.0)	212,281 (11.7)
Secondary school 1–2 years	6,033 (15.9)	282,632 (21.7)	3,938 (10.0)	2,797 (10.7)	275,791 (15.2)
Secondary school 3 years	8,175 (21.5)	305,432 (23.5)	9,291 (23.5)	7,088 (27.0)	538,523 (29.7)
Higher education <3 years	6,112 (16.1)	196,349 (15.1)	5,691 (14.4)	3,566 (13.6)	277,474 (15.3)
Higher education ≥3 years	15,846 (41.6)	381,215 (29.3)	18,621 (47.2)	10,531 (40.1)	451,512 (24.9)
Missing	116 (0.3)	24,057 (1.8)	74 (0.2)	151 (0.6)	55,858 (3.1)
Country of birth					
Nordic country	33,186 (87.2)	1,149,233 (88.3)	33,557 (85.0)	21,147 (80.6)	1,552,158 (85.7)
Non-Nordic country	4,861 (12.8)	152,855 (11.7)	5,912 (15.0)	5,085 (19.4)	259,088 (14.3)
Missing	0 (0.0)	76 (0.0)	0 (0.0)	0 (0.0)	193 (0.0)
Family history of breast cancer					
No	35,949 (94.5)	1,239,131 (95.2)	37,515 (95.0)	25,136 (95.8)	1,736,532 (95.9)
Yes	2,098 (5.5)	63,033 (4.8)	1,954 (5.0)	1,096 (4.2)	74,907 (4.1)
Parity at end of follow-up					
Nulliparous	0 (0.0)	0 (0.0)	9,309 (23.6)	4,813 (18.3)	696,174 (38.4)
One child	14,740 (38.7)	318,569 (24.5)	14,727 (37.3)	7,827 (29.8)	272,055 (15.0)
Two children	17,574 (46.2)	662,684 (50.9)	12,210 (30.9)	9,797 (37.3)	582,685 (32.2)
Three children	5,733 (15.1)	320,911 (24.6)	3,223 (8.2)	3,795 (14.5)	260,525 (14.4)
Age at first birth (among parous women)					
<25	2,230 (5.9)	428,486 (32.9)	2,840 (7.2)	4,366 (16.6)	418,727 (23.1)
25–29	7,503 (19.7)	490,576 (37.7)	5,951 (15.1)	7,122 (27.2)	410,520 (22.7)
30–34	15,600 (41.0)	287,443 (22.1)	11,198 (28.4)	6,762 (25.8)	224,619 (12.4)
35–39	10,923 (28.7)	81,521 (6.3)	8,102 (20.5)	2,581 (9.8)	54,488 (3.0)
≥40	1,791 (4.7)	14,138 (1.1)	2,069 (5.2)	588 (2.2)	6,911 (0.4)
BMI at start of first pregnancy, kg/m^2					
<18.5	678 (1.8)	43,281 (3.3)			
18.5–24.9	20,877 (54.9)	677,142 (52.0)			
25–29.9	7,695 (20.2)	178,610 (13.7)			
≥30	2,782 (7.3)	64,979 (5.0)			
Missing	6,015 (15.8)	338,152 (26.0)			

Note: Values presented as n (%).

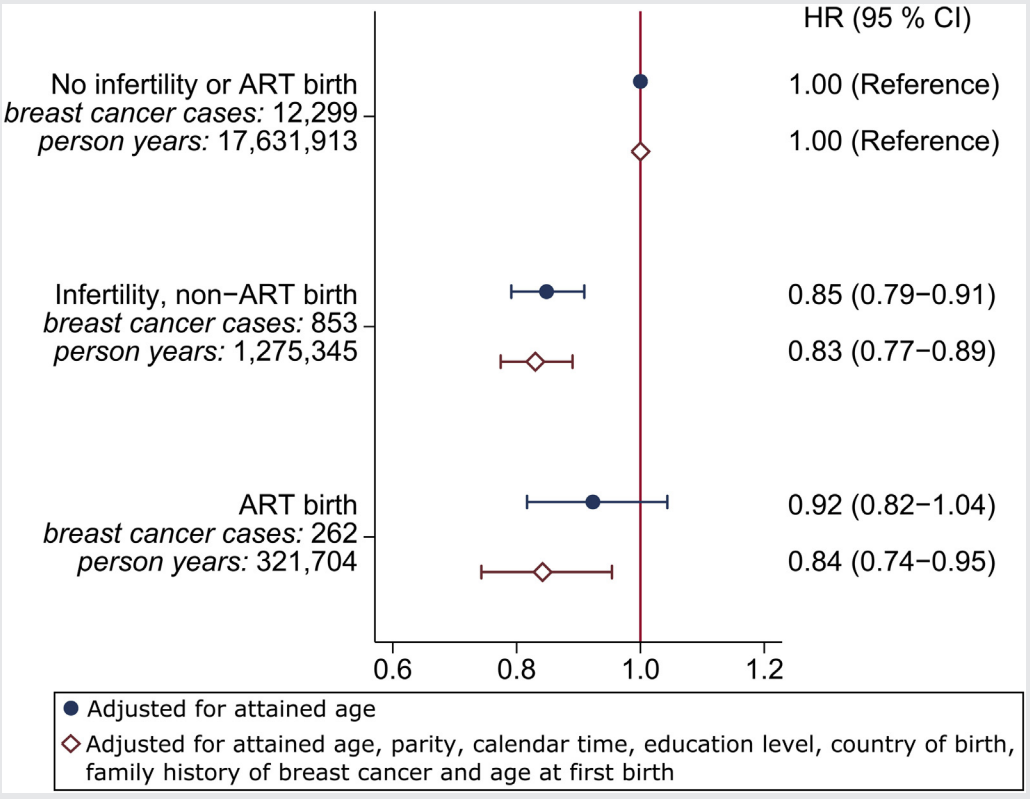
Lundberg. Ovarian stimulation and breast cancer risk. Fertil Steril 2017.

Association among ART, Ovarian Stimulation, and Incidence of Breast Cancer

In the crude analysis of the parous cohort, compared with women with no infertility-related diagnosis or ART birth, women with infertility-related diagnoses had a decreased incidence of breast cancer (HR, 0.85; 95% CI, 0.79–0.91; Fig. 1), while women with ART births had no significant difference in incidence (HR, 0.92; 95% CI, 0.82–1.04). After adjustments for confounders, the incidence of breast cancer was lower in women with infertility-related diagnoses (HR, 0.83; 95% CI, 0.77–0.89) as well as in women with ART births (HR, 0.84; 95% CI, 0.74–0.95), compared with women with no infertility-related diagnosis or ART birth. When the reference group was changed to women with infertility-related diagnoses but no ART birth, there was no difference in breast cancer incidence between women with ART births and women with no ART birth (Supplemental Table 3).

Among women born 1960–92, those with infertility-related diagnoses but no ovarian stimulation had a lower incidence of breast cancer both in the crude (HR, 0.84; 95% CI, 0.77–0.92) and adjusted (HR, 0.83; 95% CI, 0.76–0.91) analysis (Fig. 2) compared with women with no infertility-related diagnosis or ovarian stimulation. The incidence among women who had received ovulation induction also seemed to be slightly lower, although not statistically significant (HR crude, 0.84; 95% CI, 0.63–1.11; HR adjusted, 0.79; 95% CI, 0.60–1.05). COS-treated women had no significant difference in breast cancer incidence compared with women with no infertility-related diagnosis or treatment (HR crude, 0.92; 95% CI, 0.74–1.14; HR adjusted, 0.86; 95% CI, 0.69–1.07). Compared with

FIGURE 1



Associations among infertility, ART, and breast cancer incidence in the parous cohort.

Lundberg. Ovarian stimulation and breast cancer risk. Fertil Steril 2017.

women with infertility-related diagnoses but no ovarian stimulation, the breast cancer incidence rates did not differ among women with either ovulation induction (adjusted HR, 0.95; 95% CI, 0.71–1.28) or COS (adjusted HR, 1.03; 95% CI, 0.82–1.30; Supplemental Table 4).

Sensitivity Analyses of the Parous Cohort

Excluding women with missing information on pregnancy length, that is, for whom pregnancy length had been estimated to 280 days, did not change the results in the main analysis (Supplemental Table 5).

When splitting the effects by age below and above 50 years, the association was still present for premenopausal breast cancer (below 50 years) among women with infertility-related diagnoses (adjusted HR, 0.76; 95% CI, 0.70–0.83) and women with ART births (adjusted HR, 0.81; 95% CI, 0.71–0.93), while there was no association among women with postmenopausal breast cancer (Supplemental Table 6). The likelihood-ratio test for effect modification by age was statistically significant ($P=.0005$).

Adjusting for BMI at the start of the first pregnancy did not affect the estimates among the 986,403 women with information on all covariates including BMI (Supplemental Table 7).

Sensitivity Analyses of the Cohort Born 1960–92

In analyses stratified by parity, the association between fertility treatments and breast cancer incidence was similar in parous and nulliparous women, and the likelihood-ratio test for effect modification by parity was not statistically significant ($P=.1847$; Supplemental Table 8).

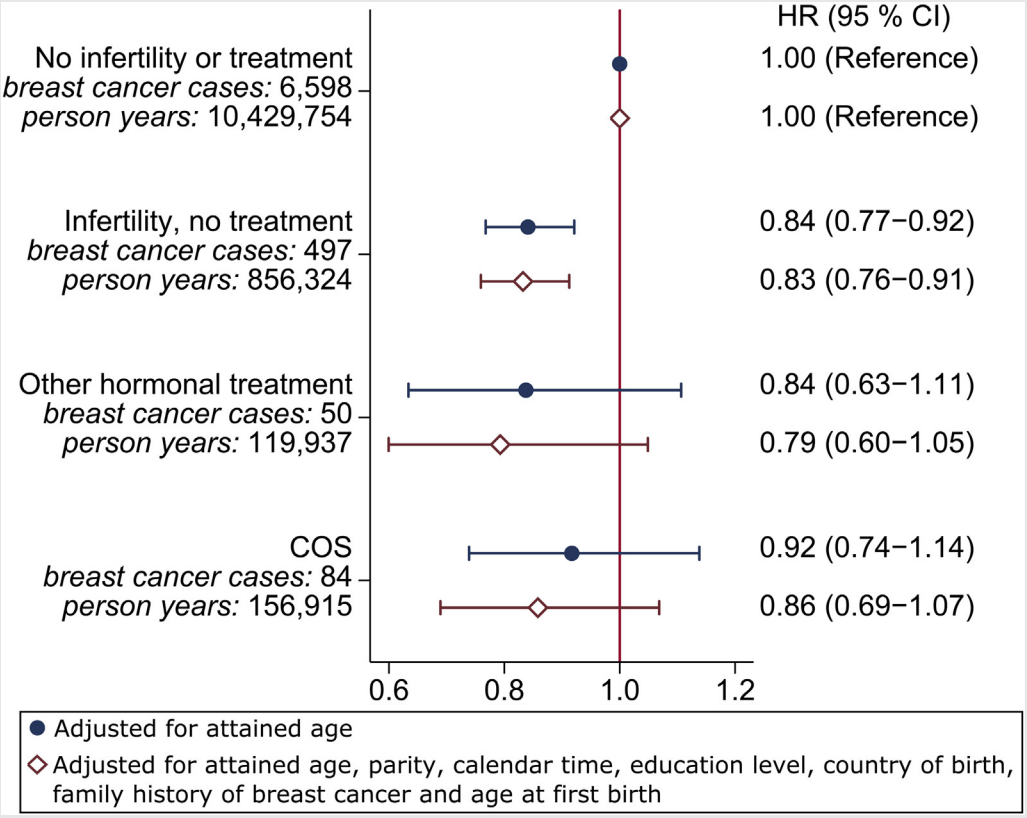
When excluding women treated with gonadotropins for ovulation induction, clomiphene citrate alone was not associated with an increased incidence of breast cancer (Supplemental Table 9).

DISCUSSION

In this large population-based cohort study, women undergoing ART treatment had no overall increased risk of breast cancer. The risk did not differ between women who had gone through ovarian stimulation, including COS, and untreated women with an infertility-related diagnosis. These results suggest that ovarian stimulation does not increase breast cancer risk.

The results are in line with previous studies (4–7). A large meta-analysis by Sergentanis et al. (2014) found no association between ART and breast cancer risk when compared with the general population and infertile women (3). Previous Swedish studies have shown similar results to ours (8, 17).

FIGURE 2



Associations among infertility, ovarian stimulation, and breast cancer incidence in the cohort born 1960–92.

Lundberg. Ovarian stimulation and breast cancer risk. Fertil Steril 2017.

A recent Dutch study found that ART treatment was not associated with an increased risk of breast cancer after a median follow-up of 21 years among women who went through fertility treatments between 1980 and 1995 (4). In an Israeli study comprising women who gave birth between 1988 and 2013, no significant association was found between fertility treatments (ovulation induction and ART) and future risk of breast cancer (5).

In contrast, some studies have reported a slightly increased risk of breast cancer among infertile women (18) and among women who gave birth after ART (9). The findings of the present study suggested that the risk of breast cancer was lower among women with infertility-related diagnoses who had not been treated with ART, compared with women with no infertility problems. Similar lower risks were observed among women with ART births. These findings indicate that the lower breast cancer risk may be associated with the underlying infertility causes and not the fertility treatments per se. Terry et al. (19) found a lower risk of breast cancer in women with ovulatory etiology of infertility. The investigators suggested that fewer lifetime ovulatory cycles might reduce breast cancer risk. Another potential explanation could be that women undergoing fertility treatments belong to a healthier group of women compared with the general population. In a previous Swedish study, women who had received ART were more highly educated, more often employed full time, and less likely to be cigarette smokers (20). Our risk estimates were adjusted for educational level, but residual confounding cannot be ruled out.

When breast cancer risk was assessed separately for parous and nulliparous women, we found no evidence of an increased risk after ART in either group. This is in line with the results from two recent studies that also investigated risks among both nulliparous and parous women (4, 6). These findings are reassuring, since several previous studies have not been able to assess risks among women who remain nulliparous after treatment (5, 7–9, 17).

The strengths of the present study include the large, population-based setting with long follow-up (up to 32 years for parous women). Using information from several national registers, with virtually complete follow-up, ensured high ascertainment of breast cancer cases and strong control for several important confounders, as well as eliminated the risk of recall bias. We were also able to compare the breast cancer risk among women with hormonal fertility treatment both to untreated women with infertility-related diagnoses and to women with no infertility-related diagnosis or treatment. Diagnoses

included in the Swedish Patient Register have been shown to have good validity (16).

There are several limitations with the current study. Despite the completeness of Swedish registers, we were not able to identify all women with infertility-related problems. The Swedish Patient Registers do not cover primary health care. Specialist outpatient care has only been included since 2001, with a nationwide coverage of 70%–80% (21). Additionally, it has been estimated that only half of couples who experience fertility problems seek medical help (22). Because of this, some women with infertility-related problems were likely classified as noninfertile. Also women with an infertility-related diagnosis may conceive spontaneously since only some women with a diagnosis of endometriosis or ovarian dysfunction will have infertility. These misclassifications would attenuate the findings toward the null. Furthermore, infertility is investigated in couples, with the results that women with an infertile partner are also diagnosed with infertility. ART, ICSI in particular, is used to treat infertility of both female and male etiology. As a result, fertile women with infertile partners were likely included in both the untreated infertile group and in the ART-treated group.

As in all epidemiological studies, it is possible that unidentified or unmeasured confounders affected the results. For instance, we did not have information on age at menarche. Late menarche has been linked to a decreased risk of breast cancer (23) and an increased risk of infertility (24). This might have contributed to the lower risk of breast cancer among infertile women in our study. BMI was available only for a subset of parous women. However, in this subset BMI did not seem to influence the relationship between ART and breast cancer risk.

While the coverage of the PDR (25) and Q-IVF (26) is essentially complete, the information on ART births 1982–2006 was collected from IVF clinics retrospectively and might have lower coverage (27).

Since only treatments leading to live birth were recorded 1982–2006, we were unable to ascertain the number of ART cycles each woman had gone through. Additionally, these records did not include type and dosage of fertility drugs or protocol (short or long) used for COS. It was therefore not possible to study breast cancer risk in relation to total gonadotropin dose or number of COS cycles. Gonadotropins have been used for COS only since the mid-1990s. Before then, both gonadotropins and clomiphene citrate were used (8). As clomiphene citrate is the first-line treatment for anovulatory infertility, some of the parous women in our study had likely been given clomiphene citrate before starting ART. It is also likely that a proportion of women with infertility-related diagnoses and non-ART birth had gone through other hormonal treatments. In the cohort born 1960–92, we were unable to identify whether women received ovarian stimulation before 2005. Consequently, women treated before 2005 and not after were classified as untreated. Although these women are likely to make up a small part of the whole comparison group, this misclassification could attenuate the risk ratio toward null.

Both ART and breast cancer are rare events that require large population samples with long follow-up to perform informative studies. Since the introduction of ART in the 1980s, the number of ART births has increased over time. However, the number of events was low in some exposure groups, despite the large population-based setting. Further, the majority of women with a history of ART have not yet reached the most common ages of developing breast cancer, which has a median age at diagnosis of around 60 years (28).

Conclusions

The findings of this study add to the growing body of evidence that ART does not increase the risk of breast cancer. These results are reassuring both for the women who go through fertility treatments and for the clinicians counseling women with fertility problems. However, since most women who have gone through ART are still young, studies with longer follow-up are needed to further investigate the risk of breast cancer.

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