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ARTICLE

Breast cancer diagnosis following ovarian stimulation: Are the tumours different?

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Abstract Demographic data and tumour characteristics of 18 patients (study group) diagnosed with breast cancer within 24 months of undergoing ovarian stimulation with either gonadotrophins or clomiphene citrate were evaluated and compared with similar 102 age-matched women diagnosed with breast cancer without prior infertility treatment (control group). Eight out of 17 (47.1%) patients in the study group and 35/95 (36.8%) patients in the control group had positive family history for breast cancer. Median tumour size was similar in the study and control groups (both 1.3 cm). Both groups were comparable regarding tumour histological types and oestrogen receptor, progesterone receptor and *Her2/Neu* expression status. Albeit not significant, stage 0 tumours were more prevalent in the study group compared with the control group (22.2% versus 10.5%), and there were no stage III tumours in the study group as opposed to 7/95 in the control group. In conclusion, breast cancer diagnosed within the first 2 years following infertility treatment is similar in tumour characteristics compared with those occurring in patients without prior infertility treatment.
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KEYWORDS: breast cancer, family history, *Her2/Neu*, oestrogen receptor, ovulation induction, progesterone receptor

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Introduction

Breast cancer is the most frequent invasive cancer seen in reproductive age women. Epidemiological, experimental and clinical evidence suggest that breast tumours are hormone sensitive (Santen et al., 2009). Among the most highly debated issues in reproductive medicine is whether there is an association between ovarian stimulation and breast cancer risk. Some epidemiological and case-control studies reported an increased risk with ovarian stimulation, while others did not demonstrate an association (Brinton et al., 2004; Dor et al., 2002; Doyle et al., 2002; Modan et al., 1998; Potashnik et al., 1999; Ron et al., 1987; Rossing et al., 1996; Venn et al., 1999). In further analysis of some studies, an increased breast cancer risk was observed in only those with a positive family history of breast cancer (Gauthier et al., 2004; Braga et al., 1996; Grabrick et al., 2002). However, in most of these epidemiological studies, the number of breast cancer cases reported was not large enough to make a clear-cut conclusion.

As the number of women treated for infertility has been increasing, the possibility that ovulation induction may increase breast cancer risk assumes greater importance. Although the mechanism is not clear, infertility may also confer an increased risk for breast cancer, especially when associated with ovulation disorders (Brinton et al., 2004; Gammon and Thompson, 1990; Venn et al., 1995). Yet there have been no data on the histopathological characteristics of breast malignancies that develop subsequent to ovarian stimulation. It is expected that, if ovulation induction *per se* causes breast cancer, such tumours may have distinct characteristics such as strong oestrogen receptor expression. Thus, the current case-control study evaluated the demographic and histopathological characteristics of breast tumours diagnosed within 24 months of ovarian simulation and compared with breast tumours diagnosed in an age-matched control group without prior ovulation induction.

Materials and methods

Patients diagnosed with breast cancer within 24 months of ovarian stimulation for IVF or intrauterine insemination (IUI) were identified from a secondary review of an anonymized database in a tertiary academic assisted reproduction centre and the records were reviewed. Ovarian stimulation protocols for IVF included gonadotrophins (225–375 IU/day) with gonadotrophin-releasing hormone agonist or antagonist down-regulation, whereas ovarian stimulation for IUI was performed with either clomiphene citrate (50–100 mg/day) or gonadotrophins (75 IU/day). Pituitary down-regulation was achieved by leuprolide acetate (Lupron/Lucrin; Abbott Laboratories) or cetrorelix (Antagon/Cetrotide; Merck-Serono). For ovarian stimulation, recombinant FSH (Gonal F; Merck-Serono; or Puregon; Schering Plough) or human menopausal gonadotrophins (Repronex/Menogon; Ferring Pharmaceuticals) were utilized. Ovulation was triggered by 10,000 IU urinary human chorionic gonadotrophin (Pregnyl; Schering Plough) or 250 μg recombinant human chorionic gonadotrophin (Ovidrel/Ovitrelle; Merck-Serono).

Demographic data and tumour characteristics of 18 patients diagnosed with breast cancer within 24 months of the ovarian stimulation (study group) were evaluated and compared with 102 age-matched women with breast cancer without prior infertility treatment (control group). All of the patients allocated in the study group were diagnosed with breast cancer within 24 months of ovarian stimulation; this time point was chosen based on the knowledge regarding the progression of breast neoplasms following ovarian stimulation (Venn et al., 1999). Data for the study group was retrieved either from patients' registry records during routine office visits or via phone contacts between May 2003 and December 2007 when required data was not complete in patients' charts. Likewise, the control group was selected from age-matched patients who were diagnosed with breast cancer and referred for fertility preservation between October 2003 and December 2007. Age, body mass index, infertility history, gravida, full-term pregnancies, smoking history, oral contraceptive (OCP) use and duration, family history of breast cancer and age at year of menarche were compared between the groups. Family history of breast cancer included first- and second-degree relatives. Tumour size, tumour histological type, tumour stage, oestrogen receptor and progesterone receptor and *Her2/Neu* expression status were compared between the groups. Institutional review board approval was not needed because data were obtained by retrospective analysis of the previously established anonymized database without patient identifiers.

Statistical analysis

Comparisons were performed after excluding incomplete data in patient's charts for each variable. As the data were not normally distributed, nonparametric Mann–Whitney *U*-test was used for comparison of continuous variables. For comparison of percentages, Fisher's exact or chi-squared tests were used where appropriate. Data are given as median (range) and mean ± SD. $P < 0.05$ was considered significant.

Results

The median ages of the study group (40 years, range 36–46) and the control group (39.0 years, range 36–45) were comparable. No differences were found in median body mass index, menarche age, gravida, history of OCP use or smoking between the groups (Table 1). Infertility causes for the study group were: decreased ovarian reserve in six (33.3%), unexplained infertility in five (27.8%), endometriosis in four (22.2%), tubal factor in two patients (11.1%) and male factor in one patient (5.6%). Nine patients undergoing IVF received gonadotrophins for ovarian stimulation along with GnRH analogues or antagonists. Seven patients used clomiphene citrate (one–six cycles), whereas two patients used clomiphene citrate in combination with gonadotrophins for ovarian stimulation of IUI cycles. Number of cycles ranged from one to six for patients who underwent IUI with a mean number of 2.89 ± 2.20 cycles, whereas IVF patients had a maximum of two cycles with a mean number of 1.44 ± 0.53.

After excluding incomplete charts, eight patients (8/16) in the study group and 39 patients (39/54) in the control group reported OCP use. Two out of 17 patients (11.8%) in the study

Table 1 Demographic data of the study and control group.

Parameter	*Study*	*Control*
Age (years)	40.17 ± 2.98; 40 (36–46)	38.96 ± 2.32; 39 (36–45)
Menarche age (years)	12.50 ± 0.41; 13 (9–17)	12.56 ± 0.15; 13 (7–17)
BMI (kg/m^2)	23.85 ± 4.14; 22.90 (18.30–34.20)	23.08 ± 4.10; 21.90 (17.50–41.10)
Breast cancer family history	8/17 (47.1)	35/95 (36.8)
Family history for other cancers	4/17 (23.5)	37/95 (38.9)
OCP use	8/16 (50.0)	39/54 (72.2)
Smoking history	2/17 (11.8)	11/84 (13.1)
Gravida	1.22 ± 0.20; 1 (0–3)	0.96 ± 0.10; 1 (0–5)
Nulliparity	6/18 (33.3)	49/102 (48.0)
Full-term pregnancy	6/18 (33.3)	20/102 (19.6)

Values for continuous variables are mean ± SD; median (range). Values for categorical variables are number/total number of cases (%), where the total excludes incomplete charts. Comparison of medians was conducted by Mann–Whitney *U*-test. Percentages were compared with the chi-squared or Fisher's exact test. Statistics were conducted after exclusion of the unknown data. There were no statistically significant differences between the two groups. BMI = body mass index and OCP = oral contraceptive pill.

and 11/84 patients in the control group (13.1%) were current or past smokers. Six patients (33.3%) in the study and 49 patients (48.0%) in the control group were nulliparous. There was no significant difference between the study (6/18) and the control (20/102) groups regarding full-term pregnancies. In the study group, mean time to breast cancer diagnosis from the last ovarian stimulation was 9.72 ± 8.34 months. With regard to the family history, 8/17 (47.1%) patients in the study group and 35/95 (36.8%) patients in the control group had a first- and/or second-degree relative who had breast cancer. Four of the 17 patients (23.5%) in the study group and 37/95 patients in the control group (38.9%) had positive family history for other cancers.

Median tumour size was 1.3 cm (0.2–3.0) and 1.3 cm (0.1–6.0) in the study and group control groups, respectively. The histological types of the breast cancers for the study group were ductal carcinoma *in situ* (DCIS) in four patients and infiltrating ductal carcinoma (ID) in 14 patients. In the control group, 10 and 85 patients had DCIS and infiltrating ductal carcinoma, respectively, while seven patients had other histological subtypes (tubular cancer ($n = 1$), lobular cancer ($n = 1$), metastatic cancer ($n = 1$) and DCIS/ID with lobular cancer ($n = 4$)). The distribution of tumour histological types and tumour stages were similar between the groups. Although not statistically significant, there were no stage III tumours in the study group as opposed to 7/95 in the control group. Thus, stage 0 tumours tended to be more prevalent in the study group compared with the control group (22% versus 10.5%, respectively; Table 2). No statistical difference was found regarding oestrogen receptor, progesterone receptor and *Her2/Neu* expression status between the groups (Table 2).

Comparing demographic and tumour characteristics of breast cancer patients who underwent ovarian stimulation for IVF and IUI could not find any significant difference regarding demographic data, obstetric history and tumour characteristics (Table 3). Mean time interval between breast cancer diagnosis and last ovarian stimulation was similar between patients undergoing IVF and IUI (10.0 months versus 9.44 months, respectively).

In the study group, the time to breast cancer diagnosis after last ovarian stimulation and tumour size were compared between patients with ($n = 8$) and without ($n = 10$) a family history of breast cancer. The time to breast cancer diagnosis after the last ovarian stimulation was significantly longer for patients with a family history for breast cancer compared with those without (15.5 ± 3.23 months, range 1–24 versus 5.1 ± 1.14 months, range 1–13; $P = 0.004$).

Discussion

It is well known that the majority of breast tumours are hormone dependent. Endogenous or exogenous exposure to high concentrations of oestrogen is thought to play a significant role in the tumorigenesis of breast cancer (Chen, 2008). The reproductive factors that can modify the risk of breast cancer include parity, age at full-term birth, age of menarche, menopause and family history. During ovarian stimulation, peak oestradiol concentrations can increase up to 10-fold or higher compared with a normal ovulatory cycle (Sonmezer and Oktay, 2004). It is presumed that this supraphysiological increase in serum oestradiol may stimulate the growth of pre-existing tumour cells (Oktay et al., 2005). Epidemiological and case-control studies have produced equivocal findings, and it is not known whether there is a subgroup of patients with increased breast cancer risk associated with ovarian stimulation, especially in those with a family history of breast cancer (Gauthier et al., 2004; Grabrick et al., 2002).

Studies on hormone replacement therapy (HRT) have provided important data regarding the association of breast cancer and exogenous oestrogen use. Data from the Women's Health Initiative Randomized Trial suggested a significantly increased breast cancer incidence in women using conjugated equine oestrogen plus medroxyprogesterone acetate (MPA) (Rossouw et al., 2002). However, further analysis of the data on the use of conjugated equine oestrogen alone revealed no significant increase in breast cancer incidence in post-menopausal women. The trial documented

Table 2 Tumour characteristics of the study and the control group.

Characteristic	*Study*	*Control*
Tumour size (cm)	1.4 ± 0.7; 1.3 (0.2—3.0)	1.5 ± 1.0; 1.3 (0.1—6.0)
Tumour stage		
0	4/18 (22.2)	10/95 (10.5)
I	9/18 (50.0)	50/95 (52.6)
II	5/18 (27.8)	28/95 (29.5)
III	0/18	7/95 (7.4)
Tumour histology		
DCIS	4/18 (22.2)	10/102 (9.8)
ID	14/18 (77.8)	85/102 (83.3)
Other types	NA	7/102 (6.9)
Oestrogen receptor positive	13/15 (86.7)	79/93 (84.9)
Progesterone receptor positive	12/15 (80.0)	50/77 (64.9)
Her2/Neu positive	7/14 (50.0)	25/72 (34.7)

Values for continuous variables are mean ± SD; median (range) for continuous variables. Values for categorical variables are number/total number of cases (%), where the total excludes incomplete charts. Comparison of medians was conducted by Mann—Whitney *U*-test. Percentages were compared with the chi-squared or Fisher's exact test. Statistics are conducted after exclusion of the unknown data. There were no statistically significant differences between the two groups. DCIS = ductal carcinoma *in situ*; ID = infiltrating ductal carcinoma; other types = lobular, tubular, metastatic; and NA = not applicable.

Table 3 Comparison of demographic data and tumour characteristics between patients who underwent ovarian stimulation for IVF and intrauterine insemination (IUI).

Parameter	*IVF*	*IUI*
Age (years)	40.6 ± 2.7; 40 (38—46)	39.8 ± 3.4; 40 (36—45)
Menarche age (years)	12.6 ± 2.3; 13 (9—17)	12.4 ± 1.0; 13 (11—14)
BMI (kg/m^2)	24.1 ± 5.1; 22.9 (18.3—34.2)	23.5 ± 2.9; 23.2 (20.4—27.2)
Time to breast cancer diagnosis (months)[a]	10.0 ± 8.2; 6 (1—24)	9.4 ± 9.0; 6 (1—24)
Breast cancer family history	5/9 (55.6)	3/8 (37.5)
OCP use	3/9 (33.3)	5/7 (71.4)
Smoking	2/8 (25.0)	—
Full-term pregnancy	2/9 (22.2)	4/9 (44.4)
Tumour size (cm)	1.4 ± 0.5; 1.4 (0.8—2.5)	1.4 ± 0.9; 1.2 (0.2—3.0)
Tumour stage		
0	3/9 (33.3)	1/9 (11.1)
I	3/9 (33.3)	6/9 (66.7)
II	3/9 (33.3)	2/9 (22.2)
Tumour histology		
Oestrogen receptor positive	7/7 (100.0)	6/8 (75.0)
Progesterone receptor positive	7/7 (100.0)	5/8 (62.5)
Her2/Neu positive	3/6 (50.0)	4/8 (50.0)

Values for continuous variables are mean ± SD; median (range) for continuous variables. Values for categorical variables are number/total number of cases (%), where the total excludes incomplete charts. Comparison of medians is conducted by Mann—Whitney *U*-test. Percentages are compared with Chi-square or Fisher's exact test. Statistics are conducted after exclusion of the unknown data. There were no statistically significant differences between the two groups.
[a]Time to breast cancer diagnosis from last ovulation induction. BMI = body mass index and OCP = oral contraceptive pill.

that breast cancers were larger and diagnosed at a more advanced stage in women who used oestrogen plus progestin than in those who did not use HRT. In the Million Women Study, breast cancer hazard ratio was observed to increase by 2.0 for oestrogen plus progesterone use and 1.3 for current oestrogen only use (Beral et al., 2003). Notably, some studies found an inverse association with breast cancer risk and the use of oestrogen only regimens in *BRCA1*-positive patients; on the other hand the association with the use of oestrogen plus progesterone was not significant (Eisen

et al., 2008). In the Million Women Study, the risk disappeared rapidly after stopping HRT suggesting that this effect may be due to oestrogenic stimulation of the growth of existing hormone positive tumours or preneoplastic lesions. Consistent with the latter hypothesis, breast cancer incidence declined in the USA in parallel to a decrease in HRT use during 2001—2003 and this decline was most pronounced for oestrogen receptor-positive tumours (Santen et al., 2009).

Likewise, the association between OCP use and breast cancer risk is still unclear. While some studies reported an increased risk of breast cancer diagnosed in recent years related to OCP use, others advocate the opposite (Brinton et al., 2004; Dor et al., 2002; Ron et al., 1987). In a recent case-control study Rosenberg et al. (2009) found that the relative odds for developing breast cancer was 1.5 for 1 year or more of OCP use, relative to less than 1 year of use, after controlling for breast cancer risk factors. Another population-based case-control study showed that high progestin potency OCP use of at least 1-year duration early in reproductive life was also associated with a moderate increase in breast cancer (Ron et al., 1987). On the contrary, results from a pooled analysis of 54 studies suggest that the use of OCP does not significantly modify the risk of breast cancer among women with a familial history of breast cancer (Gaffield et al., 2009)

It is known that the mitotic activity in the breast tissue peaks during the luteal phase of the menstrual cycle after ovulation (Pike et al., 1993). It also remains to be resolved whether extended duration of progesterone use following embryo transfer would further increase the risk of breast cancer. In some studies, numerous cancer cases were reported within the first year of ovarian stimulation, suggesting the possibility that the 'already existing cancer cells are provoked by ovarian stimulation, rather than oestrogen acting as an initiator' (Dor et al., 2002; Venn et al., 1995, 1999) In the latter study, although no association was found with ever having used various ovulation stimulating drugs, a twofold increased risk of breast cancer was observed within 1 year of last treatment (Venn et al., 1995). In contrast, others failed to find such an association neither for clomiphene citrate nor for gonadotrophins (Brinton et al., 2004).

This study evaluated the demographic data, obstetric history and tumour characteristics of 18 patients and compared with 102 age-matched control patients who were diagnosed with breast cancer without a history of infertility treatment. Since breast tumours in young patients tend to have lower oestrogen positivity and be more aggressive than that of older patients (Anders et al., 2008), 102 age-matched patients were selected as the control group. The tumour characteristics in these young patients may be independent of prior hormonal stimulation, as no significant differences in tumour characteristics were found between the groups, especially in hormone receptor expression. It is also unclear whether a specific type of ovulation induction agent is associated with higher risk of breast cancer. Some studies reported an increased risk with clomiphene citrate, while others reported a decreased risk (Burkman et al., 2003; Rossing et al., 1996). Clomiphene citrate is a selective oestrogen receptor modulator and the finding was interpreted as possible support for a chemopreventive effect, similar to what has been observed for tamoxifen (Fisher et al., 1998). Some reported increased risk only with long-term human menopausal gonadotrophin use, whereas others found no association either with clomiphene citrate or human menopausal gonadotrophin use (Brinton et al., 2004; Burkman et al., 2003). In a further analysis in the current study also compared patients undergoing ovarian stimulation for IVF and IUI with regard to demographic and obstetric data and tumour characteristics of breast cancer patients. Peak oestradiol concentrations are considerably higher in IVF cycles, but this did not make any difference for the tumour characteristics. The most important weakness of this study is the small sample size that limits further analysis of the association of tumour characteristics with respect to hormone receptor status in the study group.

Another important aspect to underline is whether or not tumours occurring following ovarian stimulation are more aggressive. Although not statistically significant, there were no stage III tumours in the study group as opposed to 7/102 in the control group. Moreover stage 0 tumours tended to be more prevalent in the study group compared with the control group (22.2% versus 10.5%, respectively) but the difference was not statistically significant. One may speculate that exogenous use of oestrogens may act differently on breast tissue during the reproductive years as opposed to during the post-menopausal period.

As far as is known, no previous study has assessed whether tumour characteristics and demographic data of the patients diagnosed with breast cancer subsequent to ovulation induction differ from those without prior history of ovulation induction. In conclusion, this retrospective cohort study found that the characteristics of breast tumours diagnosed within the first 2 years following ovarian stimulation showed no difference compared with those diagnosed in patients without prior ovarian stimulation. The novel findings of the current study could be reassuring to many patients and physicians in the field of infertility.

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