Mammographic features in infertile women as a potential risk for breast cancer: a preliminary study

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Summary

The purpose of the present study was to evaluate breast mammographic features, particularly mammographic density in a selected population of infertile women and to assess if these women should be considered at higher risk for breast cancer. The prevalence of female infertility in Western countries is approximately 10-15% and since causes affecting the female are involved in 35-40%, concerns have developed about the future health of these women, specifically whether infertility could represent a risk factor for future cancer development. Moreover, infertility is now often treated with medication and procedures that could modify the hormonal environment and be cofactors in the cellular changes towards cancer development. Mammographic breast density is a useful marker for breast cancer risk and breast density is considered one of the strongest risk factors for breast cancer. Breast density is associated with known breast cancer risk factors such as reproductive and menstrual factors including serum estrogen and progesterone concentrations. In Italy the National Federation for Breast Cancer (FONCAM) guidelines suggest the usefulness of mammography from 35 years of age for women who undergo infertility hormone therapy (FONCAM Guidelines, 2005). According to this recommendation 294 women aged ≥ 35, with primary infertility, sent to our breast service before joining an IVF program were recruited and then underwent clinical examination and X-ray mammography. Women were divided into two groups: dense breast (DB) and non-dense breast (NDB). Univariate analysis was employed to evaluate if there was an association between mammographic density and other risk factors. Evaluation of mammographic features showed the presence of BI-RADs C and D in the sample of 200 (68%) patients with DB and in 94 (32%) patients with NDB BI-RADS A and B. Univariate analysis showed that there were no statistically significant differences between the groups BD and NDB as regards age at mammography, age at menarche, BMI and family history for breast cancer, while ovulatory etiology of infertility was found to be associated with high mammographic density ($p < 0.05$). In conclusion, bearing in mind that 68% of our study sample had high breast density, we can assume that patients with primary infertility might represent a group at high risk for breast cancer, particularly if infertility is due to an ovulatory factor. We suggest breast screening from the age of 35 in infertile patients who undergo treatment with fertility drugs in accordance with FONCAM recommendations. This might allow the identification of higher risk patients who need more closely monitored breast examinations.

Key words: Infertility; Fertility drugs; Breast density; Breast cancer risk.

Introduction

Infertility is defined as the failure to conceive after one year of regular unprotected intercourse. Its prevalence in Western countries is approximately 10-15% [1] and since causes affecting the female are involved in 35-40%, concerns have developed about the future health of these women - specifically whether infertility could represent a risk factor for future cancer development. Moreover, infertility is now often treated with medication and procedures that could by themselves modify the hormonal environment and be cofactors in the cellular changes towards cancer development [2].

In recent years in Western countries the demand for infertility services has increased; in the USA prescription of fertility drugs increased almost 2-fold between 1975 and 1991 [3]. In Europe the number of reported assisted reproductive therapy (ART) cycles reached 418,111 in 2005 compared with 367,966 in 2004, equivalent to an increase of 13.6% [4]. Hormonal therapy results in the proliferation of ovarian cells and up to 5-fold increases in serum estrogen and progesterone concentrations [5-7]. These effects have raised concerns about the potential role of fertility drugs as a breast cancer risk. A number of studies have examined fertility drug use in relation to breast cancer risk [8-21]. A few studies have suggested possible risk increase [9, 10] or decrease [14, 15], whereas other studies have reported no association with risk of breast cancer [8, 11-13, 16-22].

Mammographic breast density is a useful marker for breast cancer risk and breast density is considered one of the strongest risk factors for breast cancer [23]. Breast density is associated with known breast cancer risk factors such as reproductive and menstrual factors [24] including serum estrogen and progesterone concentrations.

In Italy the National Federation for Breast Cancer guidelines suggest the usefulness of mammography starting at age 35 years for women who undergo hormone therapy (FONCAM Guidelines, 2005) [25].

According to this recommendation all women aged over 35 that undergo fertility treatment at our department have a breast examination performed.

Purpose of the present study is to evaluate breast mam-

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mographic feature, particularly mammographic density in a selected population of infertile women and to assess if these women can be considered as at higher risk for breast cancer.

Materials and Methods

Ethical approval for this single-center observational study was granted by the Medical Research Ethics Committee of our institution, and written informed consent was obtained from all patients.

The study was carried out from January 2007 to November 2009 at the Department of Gynecology and Obstetrics, University of Rome "Sapienza" among women with primary infertility sent to our centre for breast advice prior to entering an assisted fertilization program.

According to the protocol we selected only women aged ≥ 35 with primary infertility who had never undergone fertility drug treatments. After recruitment the women were interviewed by a physician (trained in medical research) and collected information included: age, etiology of infertility (if known), family history of breast cancer (two or more cases), previous administration of hormonal contraceptive therapy (yes/no), and age at menarche (years). Height without shoes (m) and weight in light clothes (kg) were registered by a trained nurse for the calculation of body mass index (BMI).

All recruited women, according to FONCAM recommendations, underwent clinical examination and X-ray mammography (XRM). In all cases conventional XRM was performed at our Department of Radiological Sciences using digital image formation and computed radiography. At least two views per breast were obtained. Mammograms were interpreted in accordance with the guidelines of the American College of Radiology (ACR) Breast Imaging Reporting and Data system (BI-RADS) by three physicians (two radiologists and a breast specialist) blinded to the clinical data.

The diagnostic quality of mammograms was assessed according to the British criteria "PGMI" [25].

Based on the BI-RADS lexicon, patients were then assigned to one of the four categories of breast parenchymal density distribution [26]: type A, the breast is almost entirely fat (glandular parenchyma < 25% of the total area of both breasts); type B, scattered fibroglandular densities (25-50%); type C, heterogeneously dense breast tissue (51-75%); type D extremely dense (> 75% glandular). It is a well known fact that sensitivity of mammography is reduced in type 3 and 4 [39-41], and the patients participating in our study were therefore divided into two groups: dense breast (DB) which included BI-RADS type C and D and nondense breast (NDB) which included BI-RADS type A and B. In case of contradictory judgments, the classification assigned by at least two readers out of three was considered correct.

The presence of focal disease at mammography or request for further diagnostic tests such as breast ultrasound, breast magnetic resonance imaging or needle biopsy were reasons for exclusion from the study.

To assess whether classification of DB and NDB was consistent, agreement between the three referents was evaluated using Cohen's kappa coefficient before further statistical analysis.

Univariate analysis, involving examination of each of the considered variables was carried out; particularly percentages, mean values and standard deviations of quantitative and qualitative variables (age, BMI, age at menarche, family history of breast cancer and previous administration of hormonal contraceptive therapy) were calculated. To assess the association or dependent relation between categorical variables, Pearson's chi-square test was employed. Group mean values were compared using the Student's t-test. Significance level was set at 0.05.

Results

A total of 306 women were assessed for eligibility; 12 of these were excluded according to exclusion criteria (i.e., presence of focal disease at mammography or request for further diagnostic tests). This selection produced a final sample of 294 women.

All mammographic examinations were considered as class P (perfect) or G (good) according to the British "PGMI" criteria.

Table 1 lists the data collected at the anamnestic interview: demographic information, reproductive history, family medical history and anthropometric measurements.

Evaluation of mammographic features showed the presence of BI-RADS C and D in the sample of 200 (68%) patients with DB and in 94 (32%) patients with NDB BI-RADS A and B (Table 2). Assessment of inter-operator variability did not show any statistically significant differences; Cohen's kappa values ranged from 0.85 to 0.89 ($p = 0.001$) thus indicating a high level of agreement.

Univariate analysis to assess the association between qualitative and quantitative variables and mammographic breast density showed that there were no statistical significant differences between the two groups of BD and NDB (Table 3) regarding age at mammography, age at menarche, BMI and family history of breast cancer while ovulatory etiology of infertility was found to be associated with high mammographic density ($p < 0.05$).

Discussion

We hypothesized that women with primary infertility might have denser breasts than the general population. In the literature there is no information about the characteristics of these women because mammography screening programs for breast cancer are offered after age 50 years and mammographic examinations are not routinely recommended for women under the age of 40 or for those undergoing fertility treatments [27, 28]. In Italy, FONCAM guidelines suggest the usefulness of mammography starting at 35 years of age for women undergoing fertility drug treatment.

Mammographic breast density (MD) has consistently been one of the strongest risk factors for breast cancer, with risk estimates that are three-to five-fold greater for women in the highest quartile of density than for women of similar age in the lowest quartile [29]; 16% to 32% of breast cancers may be attributed to this trait [30, 31] with an even larger estimated proportion among premenopausal women [32]. The relationship between MD and breast cancer is thought to be multifactorial, and in

Table 1. — *Main characteristics of the study population: percentage of qualitative variables, mean value and standard deviation for the quantitative variables.*

Variables	
Age at mammography (years)	38.9 ± 3.0
Age at menarche (years)	12.4 ± 1.4
BMI (kg/m^2)	22.7 ± 2.5
Family history for breast cancer	
No	275 (93.5%)
Yes	19 (6.5%)
Previous administration of hormonal contraceptive therapy	
No	117 (58.5%)
Yes	122 (41.5%)
Infertility etiology	
Ovulatory factor	140 (47.6%)
Tubal disease	100 (34%)
Male infertility	45 (15.3%)
Endometriosis	9 (3.1%)

Table 2. — *Mammogram classification according to the BI-RADS system and categorization into two groups: dense breast (DB) which included BI-RADS type C and D, and non breast dense (NDB) which included BI-RADS type A and B.*

BI-RADS category	Frequency	Percent (%)
A	63	21.6
B	31	10.4
C	127	43.3
D	73	24.7
A-B (non breast dense; NDB)	94	32
C-D (dense breast; BD)	200	68.0

Table 3. — *Main characteristics of the patients versus mammographic features: percentage of qualitative variables, mean value and standard deviation for the quantitative variables in the two groups of non-dense breast (NDB) and dense breast (DB). To assess the association between mammographic density and qualitative variables Pearson's chi-square was employed, whereas for quantitative variables Student's t-test was used. Significant level was $\alpha = 0.05$.*

Variables	Non-dense breast (NDB) (n = 94; 32%)	Dense breast (DB) (n = 200; 68%)	*p* value
Age at mammography (years)	39.1 ± 2.8	38.9 ± 3.1	NS
Age at menarche (years)	12.3 ± 1.4	12.4 ± 1.4	NS
BMI (kg/m^2)	22.4 ± 2.5	22.9 ± 4	NS
Ovulatory etiology of infertility	32 (10.8%)	108 (36.8%)	< 0.05
Family history of breast cancer (yes)	5 (1.8%)	14 (4.7%)	NS
Previous administration of hormonal contraceptive therapy (yes)	36 (12.3%)	86 (29.2%)	NS

NS: not significant.

early studies the main explanation was thought to be due to 'masking bias' [33] but Boyd and colleagues [32] found that compared with women with density in less than 10% of the mammogram, women with more than 75% density had an increased risk of breast cancer (odds ratio [OR] = 4.7; 95% confidence interval [CI]: 3.0, 7.4), whether detected by screening (OR = 3.5; 95% CI: 2.0, 6.2) or detected within 12 months of a negative screening examination (OR = 17.8; 95% CI: 4.8, 65.9).

A recent meta-analysis [29] illustrates a high prevalence of increased density in the general population (31% to 43% had a BI-RADS of 3 or 4). Importantly, a larger proportion of premenopausal women have dense breasts, with estimates of 37% among premenopausal women [34] compared with 12% among postmenopausal women. Even without significant differences in association by menopausal status, the attributable risk is much higher in younger women (26%) than in older women (7%) [23, 24, 32, 33]. This underscores the importance of MD for potential risk prediction in younger women.

In our study population 68% of women were classified as DB according to BI-RADS score. This value is significantly higher than the 37% reported by Celine *et al*. [34].

This difference could be attributed to the fact that we have considered a select sample of women with primary infertility and therefore nulliparous.

The role of nulliparity as risk factor for breast density has been discussed in several studies.

De Waard *et al*. [35] postulated that breast density could be the biological relationship between parity and breast cancer risk because women who have had several pregnancies show lower MD than nulliparous women. Similarly Boyd *et al*. [23, 24] found that DB is less extensive in women who are parous and less extensive in those with a larger number of live births.

The breasts of nulliparous women often show a large quality of undifferentiated epithelial breast tissue more susceptible to carcinogenic stimuli such as endonenous and exogenous female hormones [36]. Other studies provided evidence of independent effects of breast density and parity [37]. Finally, Van Gils *et al*. [38] in their case control study found that breast density was not simply an explanatory factor in the relationship between parity and breast cancer. They postulated that parity and MD may interact and nulliparous women with high breast density could possibly represent a high-risk group for breast cancer.

In addition, infertility itself may be a risk factor for breast density as 35-40% of cases have pathologies of the female reproductive organs including ovulatory dysfunction, the most common cause of female infertility [39].

In our series ovulatory etiology of infertility was found to be associated with high mammographic density. This result underlines the role of sexual hormones in the pathogenesis of MD.

In addition, our sample consisted of women who wanted to undergo treatment with fertility drugs.

The role of these drugs in the pathogenesis of breast cancer has not been demonstrated, but is still widely debated.

In a recent meta-analysis [8] the relationship between fertility drugs used in ART procedures and the risk of breast cancer were examined: combining the result of several studies [8-21], the authors found that the risk of

breast cancer was not significantly associated with fertility drug treatment (RR 0.99; CI 0.89-1.11).

Analysis of the relationship between number of fertility treatment cycles and cancer risk has shown that there was no statistically significant trend in risk of breast cancer across the number of cycles of therapy (RR 1.04; 95% CI 0.88-1.22).

Regarding age, the distribution of MD changes with increasing age reflected a reduction in glandular tissue and increase in fat. The decline in density with age may seem paradoxical, as breast cancer incidence increases with age, but this apparent paradox may be resolved by reference to a model of breast cancer incidence that is based on the concept that breast tissue age, or breast tissue exposure rather than chronological age, is the relevant measure for describing the incidence of breast cancer. Breast tissue "age" is closely associated with exposure of breast tissue to hormones and growth factors, and to the effects that menarche, pregnancy and menopause have on these exposures and on susceptibility to carcinogens [23, 24, 34].

Breast tissue exposure is greatest at the time of menarche, falls with pregnancy, is further reduced in the perimenopausal period and is least after menopause.

Thus, women with DB would have an increased risk of breast cancer that persists over time even when, due to age-related involution of fat, the breast does not appear dense on mammography.

This study has some limitations. One concerns the reliability of mammographic classification which was performed qualitatively and not by a computer-assisted method. Furthermore, the BI-RADS system was developed to alert the referring clinician that the ability to detect small cancers in dense breast is reduced and is not related to the risk *per se* [26]. In contrast, another method of classification, i.e. Boyd's rating system, showed a large gradient for breast cancer risk after adjustment for the effect of all other generally recognized risk factors for breast cancer [40].

The lack of a control group, randomization in the selection of patients and lack of follow-up makes it impossible to evaluate if women with infertility really represent a group at higher risk for breast cancer. In fact the higher prevalence of MD observed in our population study compared to data reported in the literature might be due to age. Finally, in this study MD was not adjusted for any potential confounding factors [41-43].

In conclusion, bearing in mind that 68% of our study sample had a high breast density, we can assume that patients with primary infertility might represent a group at high risk for breast cancer, particularly if infertility is due to ovulatory factor.

We suggest breast screening from the age of 35 in infertile patients who undergo or want to undergo treatment with fertility drugs in accordance with FONCAM recommendations.

This might allow the identification of higher risk patient who need more closely monitored breast examinations.

On the other hand this recommendation could increase the number of tests required and therefore costs benefits.

Careful prospective randomized trials are required to determine whether there is an association between infertility, mammographic density and breast cancer risk together with cost benefits of mammography screening from age 35 in a subgroup of potential higher risk women.

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