Annals of Surgical Oncology **15**(4):1048–1055
DOI: 10.1245/s10434-007-9800-2

The Possible Association between IVF and Breast Cancer Incidence

I. Pappo, MD,[1,2] L. Lerner-Geva, MD PhD,[3] A. Halevy, MD,[2] L. Olmer, MSc,[4] S. Friedler, MD,[5] A. Raziel, MD,[5] M. Schachter, MD,[5] and R. Ron-El, MD[5]

[1]Comprehensive Breast Care Institute, Assaf Harofeh Medical Center, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Israel, Zerifin, 70300, Israel
[2]Division of Surgery, Assaf Harofeh Medical Center, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Israel, Zerifin, 70300, Israel
[3]Women and Children's Health Research Unit, Gertner Institute for Epidemiology and Health Policy Research, Tel Hashomer, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Tel Hashomer, Israel
[4]Biostatistics Unit, Gertner Institute for Epidemiology and Health Policy Research, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Israel, Tel Hashomer, Israel
[5]IVF and Infertility Unit, Assaf Harofeh Medical Center, affiliated to the Sackler Faculty of Medicine, Tel-Aviv University, Israel, Zerifin, 70300, Israel

Background: The possible association between ovulation-inducing drugs and breast cancer development has been debated. Our aim was to evaluate the incidence of breast cancer in a cohort of women exposed to in vitro fertilization (IVF).

Methods: A retrospective cohort analysis was performed by linkage of the computerized database of all women treated at the IVF Unit at Assaf Harofeh Medical Center between 1986 and 2003, and the Israeli National Cancer Registry. The standardized incidence ratio (SIR) was computed as the ratio between the observed number of breast cancer cases and the expected cases, adjusted for age and continent of birth, in the general population. Tumor characteristics of the IVF patients were studied by reviewing original medical records.

Results: 35 breast carcinomas were diagnosed among 3,375 IVF-treated women, compared to 24.8 cases expected (SIR = 1.4; 95% CI 0.98–1.96). Age ≥40 years at IVF treatment (SIR = 1.9; 95% CI 0.97–3.30), hormonal infertility (SIR = 3.1; 95% CI 0.99–7.22), and ≥4 IVF cycles (SIR = 2.0; 95% CI 1.15–3.27) were found to be risk factors to develop breast cancer compared to the general population. Multivariate analysis revealed that women who underwent ≥4 IVF cycles compared to those with one to three cycles were at risk to develop breast cancer, although not significantly (SIR = 1.9; 95% CI 0.95–3.81). Of IVF-treated women 85% had ER(+) tumors and 29% had positive family history.

Conclusions: A possible association between IVF therapy and breast cancer development was demonstrated, especially in women ≥40 years of age. These preliminary findings need to be replicated in other cohort studies.

Key Words: Breast cancer—In-vitro fertilization—Ovulation induction.

One of the most important etiological factors for the development of breast cancer is the influence of female hormones. Early menarche and late menopause represent the connection between long exposure to endogenous hormones and an increased risk for breast cancer development.[1] The strong relationship between long exposure to hormone replacement therapy administered during and after menopause and the increased rate of breast cancer represents the

Published online January 23, 2008.
Address correspondence and reprint requests to: I. Pappo, MD; E-mail: pappo@zahav.net.il

risk that exogenous female hormones have on the development of breast cancer.[2] Therefore, in concordance with these findings, the risk of development of breast cancer in association with hormonal manipulations in infertile women should be carefully investigated.

A relatively small number of studies have addressed the potential relationship between infertility medications and the development of breast cancer, and the results from these studies vary and are inconsistent. Only sporadic series of breast cancer cases which were treated by in vitro fertilization (IVF) have been published in the past.[3] Most of them negate a direct connection between the use of infertility medications and breast cancer.[4–18] The remaining few publications have demonstrated varying degrees of increased breast cancer risk in infertile women treated medically, however, these differences were not statistically significant.[19–21] Only in a few of these cohorts of infertile treated women was IVF therapy used, and in most of them the number of breast cancer cases was small.[8,13,14,18,19]

Israel is a leading nation in the Western world with respect to the number of IVF treatment cycles per million population[22,23] and has the highest number of IVF cycles per patient.[24] This is due to the fact that infertility treatments are covered by the Israeli National Health Insurance for the first and second child in patients up to the age of 45 years. Since Israeli Jews have one of the highest incidence rates of breast cancer,[25] it seemed to us particularly important to study whether IVF treatment has any effect on the incidence of breast cancer.

We present here the results of a study in which we investigated the incidence of breast cancer among infertile women with IVF treatment as compared with the general population.

PATIENTS AND METHODS

Study Cohort

The study cohort included all women who underwent treatment for infertility at the IVF Unit at Assaf Harofeh Medical Center between April 1986 and December 2003. These women were identified from the computerized database of the IVF unit. All patients who received at least one treatment cycle were included. The information retrieved included demographic data (age, place of birth), cause of infertility, number of treatment cycles, type of medical therapy given, and the results of therapy (pregnancy: yes/no). Women with normal ovulatory cycles (including women with mechanical, male factor and unexplained infertility) were defined as having nonhormonal infertility, while anovulatory women were defined as having hormonal infertility.

This study was approved by the Institutional Helsinki Committee (permit number: 72/05).

Cancer Identification

The study cohort computerized file was linked to the Israel National Cancer Registry to identify cancer cases through December 2004. The registry was established in 1960 and maintains data on all cases of malignant disease and borderline malignancies in Israel. It receives notification of cases of cancer noted on hospital discharge reports from all hospitals, and noted on cytological and histological reports from all Departments of Pathology and Oncology in the country. This notification has been mandatory since 1982. The coverage of cases by the registry has been found to be 90–95%.[26]

For all patients who were found to have a diagnosis of breast cancer, including invasive breast cancer and ductal carcinoma in situ (DCIS), the cancer registry provided the breast cancer diagnosis code according to the International Classification of Diseases 9th edition, and the date and place of diagnosis. Diagnoses were verified by reviewing the original cytological or histological report for each case. In cases where only needle biopsy reports were provided by the registry, we reviewed the individual medical chart and the final histological report to validate the diagnosis of breast cancer.

Five cases of ductal carcinoma in situ in the registry were included in the study, but one case of lobular carcinoma in situ was excluded, as it was considered a nonmalignant condition.

Two additional cases which were reported as malignant tumors were excluded, as the histopathological report demonstrated a benign disease. The exclusion of these two cases was verified following a personal interview with the patients.

Data Analysis

Comparison with the general population: The observed numbers of breast cancer cases in the cohort were compared to the expected numbers, calculated by applying the national breast cancer age-period-specific incidence rates to the cohort, stratified by continent of birth. Standardized incidence ratios (SIR's) were computed as the ratio of observed to

TABLE 1. *Numbers of observed and expected breast cancer cases according to demographic and infertility characteristics in the in vitro fertilization (IVF) cohort (n = 3375)*

Characteristic	n	Observed	Expected	SIR	95% CI
Age, years					
40+	423	12	6.4	1.9	0.97–3.30
35–39	704	11	8.7	1.3	0.63–2.27
30–34	996	9	6.7	1.3	0.61–2.55
<30	1252	3	3.2	0.9	0.19–2.75
Type of infertility					
Primary	1792	12	9.4	1.3	0.66–2.24
Secondary	1471	23	13.6	1.7	1.07–2.54
Diagnosis of infertility					
Hormonal	355	5	1.6	3.1	0.99–7.22
Nonhormonal	2905	30	21.3	1.4	0.95–2.01
Number of IVF cycles					
1–3	2258	19	17.0	1.1	0.67–1.75
4+	1117	16	8.0	2.0	1.15–3.27
Pregnancy					
Ever	1774	13	10.1	1.3	0.68–2.20
Never	1601	22	14.8	1.5	0.93–2.25

IVF, in vitro fertilization.

expected breast cancer cases with estimated 95% confidence intervals (95% CI).[27] The SIR calculations took into account person years, which were calculated from the date of first fertility treatment until the end of follow up (31 December 2004, the last update of the National Cancer Registry), or until the date of breast cancer diagnosis, whichever came first. SIR values were also computed by categories of age, type of infertility (primary/secondary), diagnosis of infertility (nonhormonal/hormonal), number of treatment cycles and outcome of the infertility treatment (pregnancy: yes/no) when available.

A multivariate Poisson regression model was used to evaluate the possible effects of number of IVF cycles, age group, and diagnosis of infertility on the risk of breast cancer in the cohort of infertile women treated with IVF.

In addition, the Cox proportional hazard model was used to evaluate within-cohort comparisons between women who did and did not develop breast cancer.

RESULTS

The IVF cohort consisted of 3,375 patients who were treated at the IVF Unit at Assaf Harofeh Medical Center during the period 9 April 1986 to 31 December 2003.

These women underwent 3.15 ± 2.39 (1–18 cycles) treatment cycles. One third of the women ($n = 1170$) underwent 4 or more cycles, of which 801 underwent 4–6 cycles and 316 underwent 7 or more cycles. Mean age at first treatment was 32.1 ± 5.7 years (18–45 years).

The mean length of follow-up was 8.1 ± 4.3 years (1.0–18.7 years) with a total 27,327 person-years of follow-up.

During the follow-up period, 35 women were diagnosed with breast cancer, compared to 24.8 cases expected in the general population (SIR = 1.4; 95% CI 0.98–1.95). Table 1 presents the observed and expected numbers of breast cancer cases according to demographic and infertility characteristics. Women who were 40 years or older at their first IVF treatments (SIR = 1.9; 95% CI 0.97–3.30), those with secondary infertility (SIR = 1.7; 95% CI 1.07–2.54), anovulatory women (SIR = 3.1; 95% CI 0.99–7.22) and those who underwent four or more IVF cycles (SIR = 2.0; 95% CI 1.15–3.27) were at a higher risk of breast cancer than the general population. The risk for developing breast cancer among women with hormonal infertility who were at the age of 40 or older and who underwent four or more IVF cycles was calculated to be 8.6 (95% CI 1.44–51.1).

In multivariate analysis of this cohort (Table 2), women who underwent four or more IVF cycles as compared to one to three cycles (SIR = 1.9; 95% CI 0.95–3.81) were at insignificant increased risk to develop breast cancer. Similar results were observed with the Cox proportional hazard model (Table 2) for the effect of exposure to IVF cycles. Although the effect of exposure to more than four IVF cycles as not significant, the effect of hormonal infertility and age were more significant.

TABLE 2. *Multivariate analysis for breast cancer development in the in vitro fertilization (IVF) cohort (n = 3375)*

	Poisson model			Cox model		
Variable	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age at IVF treatment						
40+ years	1.9	0.60–8.68	0.31	11.2	3.1–40.0	0.002
35–39 years	1.4	0.44–6.36	0.59	5.0	1.4–18.2	0.01
30–34 years	1.5	0.44–6.71	0.55	3.1	0.8–11.4	0.09
<30 years	1.0					
Diagnosis of infertility						
Hormonal	2.3	0.79–5.56	0.18	3.6	1.3–9.9	0.01
Nonhormonal	1.0					
Number of IVF cycles						
≥4	1.9	0.95–3.81	0.07	1.8	0.9–3.6	0.07
1–3	1.0					

IVF, in vitro fertilization.

TABLE 3. *The characteristics of 35 breast cancer patients who underwent in vitro fertilization (IVF) treatment [mean age at diagnosis (years ± SD) 44.5 ± 4.8]*

Tumor characteristics		
Histological type:	n	Percentage
IDC	23	(66%)
ILC	3	(9%)
DCIS	5	(14%)
Tubular	2	(5.5%)
Mucinous	2	(5.5%)
Stage		
0	5	(14.5%)
1	12	(34%)
2	10	(28.5%)
3	7	(20%)
4	1	(3%)
Grade		
1	1	(5%)
2	12	(63%)
3	6	(32%)
Number of patients with positive lymph nodes	10	(28.6%)
Mean size of tumors (cm)	1.87	(range: 0.2–3.2 cm)
ER (+)	22	(85%)
PR (+)	15	(58%)
Her 2neu (+)	4	(22%)
Number of patients with positive family history (%)	10	(29.6%)
Type of surgery:		
Mastectomy	10	
Lumpectomy	23	
Bilateral mastectomy	1	
Not operated	1	

IDC, infiltrative ductal carcinoma; ILC, infiltrative lobular carcinoma; DCIS, ductal carcinoma in situ.

Characteristics of the Tumors

The demographics of the patients with breast cancer and the characteristics of their tumors are shown in Table 3. The mean age of the patients at time of diagnosis was 44.5 ± 4.8 years (range: 32–51 years).

The number of patients with stage 0, I, II, III and IV was 5, 12, 10, 7, and 1, respectively.

The mean size of the tumors was 1.87 cm (range: 0.2–3.2 cm). Two additional patients had diffuse DCIS, one patient presented with metastatic disease and her tumor was not measured. In two patients, the size of tumor was not available. Ten patients out of 34 who underwent surgery, had axillary lymph node involvement.

Twelve out of 19 patients with infiltrating duct carcinoma (IDC) in which the grade of tumor was available had grade 2 disease.

About two thirds of the patients had IDC, five patients had DCIS, three had ILC, and two each had tubular and mucinous infiltrating carcinoma.

Data on estrogen receptors (ER) and progesterone receptors (PR) was available in 24 out of 30 tumors with infiltrating carcinomas. Twenty-two out of 26 patients were positive for ER (85%) and the rate of PR positive tumors was 58%.

Four out of 18 patients (22%) in which HER 2neu was studied had a positive result.

Four women in our cohort of 35 breast cancer patients developed the disease during the four-year interval following term pregnancy. Age at first-term pregnancy among these four women was 33.4 years as compared to 28.7 years in the general population.

Nine out of 31 patients in which family history was available were found to have at least one first-degree relative with breast cancer (29%; 95% CI 14.6%–46.3%).

DISCUSSION

Infertility in General, and Breast Cancer

In the present study, we investigated the possible association between IVF therapy and breast cancer development. A significantly higher risk to develop

breast cancer was reported in the past for nulliparous married women who tried and failed to become pregnant.[28] Weiss et al.[29] found that, among women with a first full-term birth at age 35 years or older, fertility problems were associated with a twofold risk of breast cancer.

Two other studies observed an increased risk of breast cancer in infertile women, but a possible influence of infertility drugs in these cohorts was not obvious. Modan et al.[17] found a 40% risk for breast cancer development in infertile women as compared to the general population. However, it is not known whether all of these patients were treated with ovulation induction. Brinton et al.[19] found that infertile women had an approximately 30% higher risk to develop breast cancer, while the contribution of infertility drugs to the increased risk was again not obvious in his study. The same author earlier conducted a retrospective cohort study of 2,335 women who were evaluated for infertility at the Mayo Clinic between 1935 and 1964.[4] They examined this relatively large cohort of women over an extended follow-up period for the incidence of all kinds of hormone-related cancers, and found no increased rate of breast cancer. The strength of this study comes from the fact that the women examined were diagnosed in an era in which no hormonal therapy whatsoever was administered and, therefore, they represent a pure infertile population.

Others who studied various subgroups of infertile women failed to identify an increased risk to develop breast malignancies.[29–31] Klip et al.[32] and Venn et al.[33] summarized the association between infertility and breast cancer and concluded that infertile women appear to be at no higher risk for breast cancer.

However, the possible influence of infertility itself on the risk of breast cancer occurrence, without exposure to infertility drugs, should be taken into consideration whenever one studies the effect of infertility drugs on breast cancer risk. In the present study, breast cancer incidence was evaluated in comparison only to the general population rates. Infertile women who have never used fertility medications would be the ideal comparison group. However, due to the liberal policy regarding infertility treatments in Israel, such a group is very difficult to assemble.

Specific Types of Infertility and Breast Cancer

Although, as demonstrated above, an increased risk of breast cancer cannot be attributed to infertility alone, several diagnoses of infertility were demonstrated to harbor a higher risk for breast cancer development. Cowan et al.[34] traced 81% of 1083 infertile women at John Hopkins from 1945 to 1965 and identified 17 breast cancers. It was found that women with ''progesterone deficiency'' had a 5.4 higher chance to develop premenopausal breast cancer compared with women with nonhormonal infertility. A minor excessive number (12 versus 8.25 expected) of postmenopausal breast cancer in women with chronic anovulation was found by Coulam.[35] On the other hand, Garland and colleagues,[36] who studied 116,678 women in the Nurses' Health Study II, found that the relative risk associated with a history of anovulatory infertility, compared with no such history, was 0.41 (95% CI 0.18–0.93). In the current study, the findings are in concordance with the results of Cowan et al.[34] and Coulam et al.[35] as they demonstrate an increased risk for breast cancer in women with hormonal infertility. In contrast to Garland's findings, the risk to develop breast cancer in treated women with anovulatory type of infertility compared to other types was elevated (SIR = 3.1; 95% CI 0.99–7.22).

The Influence of Infertility Drugs on Breast Cancer Development

Only a few studies found some evidence that infertility drugs may, in some situations, increase the risk for breast cancer. Brinton et al.[19] found a slight but nonsignificant elevation in risk for both clomiphene and gonadotropins after ≥20 years of follow-up (1.39 and 1.54, respectively). This risk became significant for clomiphene when examined for invasive breast cancer development (1.6). A similar increase in the risk of breast cancer was also identified in a cohort of 5,788 patients who were studied retrospectively and a 1.4 hazard rate to develop breast cancer in women treated by clomiphene –citrate was found.[21]

Burkman et al.[20] in a multicenter study, compared patients with breast cancer to healthy controls and found that a history of using infertility drugs was not associated with an increased risk to develop breast cancer. In general, they did not find an overall increased risk to develop breast cancer in association with the use of ovulation induction drugs. However, he identified a subgroup of patients, treated by clomiphene, who were followed for more than 20 years and had a relative risk of 1.39 to develop breast cancer.

Therefore, these studies hint at the possible role played by extensive exposure to infertility drugs in the

increased risk of breast cancer development. Yet, the question remains open as to whether the long exposure to infertility drugs contributes to a higher risk for breast cancer, or whether it is the long exposure to unopposed estrogen that exists in anovulatory women that tends to increase their risk to develop breast cancer.

Contrary to the aforementioned results, Braga et al.,[6] who conducted a case-control study, reported an odds ratio of 1.43 to develop breast cancer in treated infertile women, compared to an odds ratio of 0.85 in infertile women who were not treated with ovulation induction. Although different subgroups of patients demonstrated various risks, no specific drug was identified to harbor a significant increased risk of inducing breast malignancy.

IVF and Breast Cancer

Only a few studies with a specific emphasis on infertile women treated by IVF techniques have been performed aiming to investigate the risk to develop breast cancer. As the overall dosage of drugs to stimulate the ovary in each treatment cycle may be significantly higher in IVF therapy, and they are administered during a relatively short time period, the long-term effects and breast cancer risk in these patients should be carefully considered. Two studies from two other IVF units in Israel[13,14] did not demonstrate any increased rate of breast cancer. However the mean follow-up time in these groups was relatively short (6.5 and 3.6 years), with few cases of breast cancer in each (4 and 11, respectively).

Venn and coworkers[8] examined the incidence of breast and ovarian cancer in a cohort of 10,358 women referred to IVF units in Australia between 1978 and 1992. They studied all women who attended the units and compared those treated by IVF to non-treated women. No increased risk for breast cancer was demonstrated in those exposed to IVF therapy. However, in this study, the number of IVF cycles was relatively low: 77% of all patients received three or fewer cycles of therapy. Among 16 patients who actually developed breast cancer and who were treated by IVF, 11 received one or two cycles, 2 patients received three cycles, 2 four cycles, and 1 six cycles of fertility drugs. Although the incidence ratio for breast cancer was not significantly different with increasing number of cycles, the overall low number of treatment cycles may reflect low amounts of fertility drugs administered to the exposed patients. Evidence for the possible importance of the number of treatment cycles is provided by Brzezinski et al.,[18] who demonstrated a twofold increase in the rate of breast cancer in women who used infertility drugs compared to the general population. Most of the women who developed breast cancer received more than six cycles of hMG. The association between the number of cycles and the increased rate of breast cancer may be supported by the results of the current study, as women who were treated with four or more IVF cycles had twice the risk to develop breast cancer as compared to those who had one to three cycles, although not significantly. In general, there was a 40% increase in the incidence of breast cancer in IVF-treated women (although without statistical significance).

The possible increased rate of breast cancer due to excessive exposure to high levels of fertility drugs during IVF therapy may be the result either of the triggering of de novo breast tumors, or the promotion of preexisting undetected breast malignancies or premalignant conditions in the treated women.

Other possible risk factors for the development of breast cancer should not be overlooked. Women are at a higher risk to develop breast cancer during the first three to four years following a term pregnancy.[37] One could assume that the proximity to pregnancy explains the slightly increased risk for breast cancer development. However, the fertility rate in our cohort was 1.15 $\pm$ 1.09 compared to 2.77 in the general population. Therefore, the proximity of the term pregnancy as a risk factor for breast cancer should be higher in the general population as compared to our cohort. Despite this fact, we observed a possible risk in our cohort.

The theory that IVF therapy promotes preexisting tumors may be supported by the relatively high percentage of treated women with breast cancer in the current cohort who had a positive family history (29%). This group of high-risk women most likely had small tumors, or premalignant breast changes that became detectable following the exposure to ovarian hyperstimulation. The possible vulnerability of women with a positive family history to develop breast cancer following infertility therapy was demonstrated by other studies. Although Burkman et al.[20] demonstrated lower numbers of first-degree relatives with breast cancer overall, he found that 17.1% of treated patients had a positive family history compared to only 10% of the controls. Braga et al.[6] reported even lower numbers of positive family history: 11.6% in treated patients, but only 5.2% in the controls. A similar enhanced risk to develop breast cancer in women with a positive family history was demonstrated in a third study by Gauthier and colleagues.[15]

Eliassin and colleagues[38] suggested the same possible association in a different setting. In a prospective nested case-control study within the Nurses' Health Study, they tried to examine whether the associations of endogenous estrogens and testosterone with breast cancer risk differ between high- and low-risk women, with respect to a family history of breast cancer. They found that estradiol appeared to be more strongly associated with breast cancer in women with a higher predicted risk [relative risk (RR) = 4.5] compared with women with a lower risk (RR = 2.1).

Information regarding a positive family history of breast cancer among the IVF-treated women was not available in the present study, except for those who had breast cancer. However, from another study carried out at our institute, where 21.8% of the patients with breast cancer under the age of 70 had first-degree family members with breast cancer,[39] we can determine that the rate of a positive family history among breast cancer patients is lower (significance could not have been evaluated) than the rate observed in patients treated by IVF and presented in the current study.

The study of Eliassin et al.[38] may also support the notion that new breast cancer may result from the increased exposure to female hormones, and a clue for this theory may be found in the rate of tumors with ER(+) status, which was higher than the expected rate in this age group. However, the small number of patients is not sufficient to evaluate the significance of this finding. Similar higher rates of ER(+) tumors in treated women were also reported earlier in another center in Israel, the Beer-Sheva University.[11] This relative high rate of ER(+) breast tumor in the population of breast cancer patients may also point at a possible role of fertility drugs on the development of breast cancers.

Histological patterns of breast cancer in the present study demonstrated slightly lower rates of infiltrating duct disease compared to other infiltrating types of cancer, as was reported in the general population of breast cancer in a previous study from our center, a population which may represent accurately the general population of breast cancer patients in our referral area, although this difference does not seem to be of importance due to the relatively small number of patients in the present study.[39] Intraductal carcinoma of the breast was also found to be similar to the rate of patients younger than 70 years in our previous study: 14% compared to 16% in the general population. This relatively smaller percentage can be attributed to the low screening rate of patients at the age of breast cancer patients of the present cohort, or may result from a lower screening rate in general at the time period in which the follow-up was started, the end of the 1980s and the beginning of the 1990s. When we compared other characteristics of the tumors to the findings of the previous study from our center, we found that they were quite similar (involved lymph nodes, stage of the disease, and the rate of tumors positive to HER-2neu). A possible difference was found in the grades of tumors, which was higher in the women treated by IVF: grade II tumors were found in 63% compared to 54% in the previous study.

This study succeeded in identifying subgroups of women who were treated by IVF and had a tendency to be more vulnerable to develop breast cancer. These subgroups include women older than 40 years of age at first treatment, those who received more than four cycles of therapy, and women with hormonal infertility.

A limitation of the present study, as well as other studies on the subject, is that so many infertility medications are used and they may be very different. Unfortunately, over 40% of the women in our cohort received more than one treatment protocol. Therefore, individual analysis per protocol could not be performed.

The possible short-term risk that was observed in our study may have less clinical significance. However, the establishment of this cohort of infertile women will enable us to conduct longer follow-up, since the effects of therapy may be more evident later on.

In summary, our results raise the possibility of an association between long exposure to fertility drugs during IVF therapy and the development of breast cancer. These preliminary findings need to be replicated in other cohort studies, preferably with more information regarding other possible contributing factors such as a family history of breast cancer.

ACKNOWLEDGMENT

The authors gratefully acknowledge support for this study from The Israel Cancer Association.

REFERENCES

1. Lipworth L. Epidemiology of breast cancer. *Eur J Cancer Prev* 1995; 4:7–30.
2. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002; 288:872–81.

3. Jourdain O, Avril A, Mauriac L, et al. Breast cancer and in vitro fertilization. About 32 cases. *Eur J Obstet Gynecol Reprod Biol* 1996; 67:47–52.
4. Brinton LA, Melton LJ 3rd, Malkasian GD Jr, et al. Cancer risk after evaluation for infertility. *Am J Epidemiol* 1989; 129:712–22.
5. Gammon MD, Thompson WD. Infertility and breast cancer: a population-based case-control study. Infertility and breast cancer: a population-based case-control study. *Am J Epidemiol* 1990; 132:708–16.
6. Braga C, Negri E, La Vecchia C, et al. Fertility treatment and risk of breast cancer. *Hum Reprod* 1996; 11:300–3.
7. Rossing MA, Daling JR, Weiss NS, et al. Risk of breast cancer in a cohort in infertile women. *Gynecol Oncol* 1996; 60:3–7.
8. Venn A, Watson L, Lumley J, et al. Breast and ovarian cancer incidence after infertility and in vitro fertilization. *Lancet* 1995; 346:995–1000.
9. Ricci E, Parazzini F, Negri E, et al. Fertility drugs and the risk of breast cancer. *Hum Reprod* 1999; 14:1653–5.
10. Venn A, Watson L, Bruinsma F, et al. Risk of cancer after use of fertility drugs with in-vitro fertilization. *Lancet* 1999; 354:1586–90.
11. Potashnik G, Lerner-Geva L, Genkin L, et al. Fertility drugs and the risk of breast and ovarian cancers: results of a long-term follow-up study. *Fertil Steril* 1999; 71:853–9.
12. Doyle P, Maconochie N, Beral V, et al. Cancer incidence following treatment for infertility at a clinic in the UK. *Hum Reprod* 2002; 17:2209–13.
13. Dor J, Lerner-Geva L, Rabinovici J, et al. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. *Fertil Steril* 2002; 77:324–7.
14. Lerner-Geva L, Geva E, Lessing JB, et al. The possible association between in vitro fertilization treatments and cancer development. *Int J Gynecol Cancer* 2003; 13:23–7.
15. Gauthier E, Paoletti X, Clavel-Chapelon FE3N group Breast cancer risk associated with being treated for infertility: results from the French E3N cohort study. *Hum Reprod* 2004; 19:2216–21.
16. Bernstein L, Hanisch R, Sullivan-Halley J, et al. Treatment with human chorionic gonadotropin and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 1995; 4:437–40.
17. Modan B, Ron E, Lerner-Geva L, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol* 1998; 147:1038–42.
18. Brzezinski A, Peretz T, Mor-Yosef S, et al. Ovarian stimulation and breast cancer: Is there a link?. *Gynecol Oncol* 1994; 52:292–5.
19. Brinton LA, Scoccia B, Moghissi KS, et al. Breast cancer risk associated with ovulation-stimulating drugs. *Hum Reprod* 2004; 19:2005–13.
20. Burkman RT, Tang MT, Malone KE, et al. Infertility drugs and the risk of breast cancer: findings from the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences Study. *Fertil Steril* 2003; 79:844–51.
21. Lerner-Geva L, Keinan-Boker L, Blumstein T, et al. Infertility, ovulation induction treatments and the incidence of breast cancer-a historical prospective cohort of Israeli women. *Breast Cancer Res Treat* 2006; 100:201–12.
22. Collins J. An international survey of the health economics of IVF and ICSI. *Hum Reprod Update* 2002; 8:265–77.
23. Mosher WD, Pratt WF. Fecundity and infertility in the United States: incidence and trends. *Fertil Steril* 1991; 56:192–8.
24. Insler V, Gonnen O, Levran D, et al. Israel National Registry of assisted reproductive technologies. Assisted reproductive technologies reported in the National Registry of Israel 1995–1996. *Harefuah* 2000; 139:421–4; 495.
25. Israel National Cancer Registry. Annual report updated 1.2005. Israeli Ministry of Health. Available: http://www.health.gov.il/.
26. Fishler Y, Chetrit A, Barchana M, et al. The completeness of the National Cancer Registry database. Methods and results. Completeness of the data in the year 1991 and its implications on the completeness of current data. Israel Center for Disease Control, Oct 2003; publication # 230 [Hebrew].
27. Rothman KJ, Boice JD, Jr. Epidemiologic analysis with a programmable calculator. Washington, DC: US GPO, 1979. (DHEW publication no. [NIH] 79-1649).
28. Sellers TA, Potter JD, Severson RK, Bostick RM, Nelson CL, Kushi LH, Folsom AR. Difficulty becoming pregnant and family history as interactive risk factors for postmenopausal breast cancer: the Iowa Women's Health Study. *Cancer Causes Control* 1993; 4:21–8.
29. Weiss HA, Troisi R, Rossing MA, et al. Fertility problems and breast cancer risk in young women: a case-control study in the United States. *Cancer Causes Control* 1998; 9:331–9.
30. Wild S, Pierpoint T, Jacobs H, et al. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)* 2000; 3:101–5.
31. Ron E, Auvinen A, Alfandary E, et al. Cancer risk following radiotherapy for infertility or menstrual disorders. *Int J Cancer* 1999; 82:795–8.
32. Klip H, Burger CW, Kenemans P, et al. Cancer risk associated with subfertility and ovulation induction: a review. *Cancer Causes Control* 2000; 11:319–44.
33. Venn A, Healy D, McLachlan R. Cancer risks associated with the diagnosis of infertility. *Best Pract Res Clin Obstet Gynaecol* 2003; 17:343–67.
34. Cowan LD, Gordis L, Tonascia JA, et al. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol* 1981; 114:209–17.
35. Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. *Obstet Gynecol* 1983; 61:403–7.
36. Garland M. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. *Am J Epidemiol* 1998; 147:636–43.
37. Liu Q, Wuu J, Lambe M, et al. Transient increase in breast cancer risk after giving birth: postpartum period with the highest risk (Sweden). *Cancer Causes Control* 2002; 13:299–305.
38. Eliassen AH, Missmer SA, Tworoger SS, et al. Endogenous steroid hormone concentrations and risk of breast cancer: Does the association vary by a woman's predicted breast cancer risk?. *J Clin Oncol* 2006; 24:1823–30.
39. Pappo I. Breast cancer in the elderly: histological, hormonal and surgical characteristics. *Breast* 2007; 16:60–7.