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Cancer incidence in a cohort of infertile women who underwent in vitro fertilization

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Objective: To assess whether ovarian hyperstimulation and IVF increase the risk for cancer.

Design: Historical cohort analysis.

Setting: IVF units of two medical centers in Israel.

Patient(s): Five thousand twenty-six women who underwent IVF between 1981 and 1992.

Intervention: Cancer incidence rates were determined through linkage to the National Cancer Registry and were compared with expected rates with respect to age, sex, and place of birth.

Main Outcome Measure(s): Development of cancer.

Result(s): Twenty-seven cases of cancer were observed, and 35.6 were expected (standardized incidence ratio, 0.76 [95% CI, 0.50–1.10]). Eleven cases of breast cancer were observed, whereas 15.86 were expected (standardized incidence ratio, 0.69 [95% CI, 0.46–1.66]). One case of ovarian cancer and 1 case of cervical cancer were observed, compared with 1.74 and 1.73 cases expected, respectively. The type of infertility, number of IVF cycles, and treatment outcome did not significantly affect risk for cancer.

Conclusion(s): In a cohort of women treated with IVF, no excess risk for cancer was noted. (Fertil Steril® 2002;77:324–7. ©2002 by American Society for Reproductive Medicine.)

Key Words: Cancer, infertility, in vitro fertilization, ovulation induction

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In the past 3 decades, follow-up studies and multiple case reports have discussed the safety of ovulation-inducing drugs and the risks associated with their use (1–6). Some complications of ovulation-inducing therapies and their incidence are well established, such as the ovarian hyperstimulation syndrome (7) and multiple pregnancies (8). Ovulation-inducing drugs are widely used for ovarian follicular stimulation during IVF cycles. In vitro fertilization treatment programs were initially designed to treat women with mechanical infertility and no evidence of ovulation disturbances. Currently, IVF treatment programs are used to treat all types of infertility.

A series of articles that suggested an association between use of ovulation-inducing drugs and ovarian cancer led to renewed interest in the potential carcinogenic risks of these drugs (9–12). Although the authors of those articles have been appropriately cautious in interpreting their results, the public perception of ovarian cancer and the risk associated with ovulation-inducing drugs caused widespread apprehension. Only a few cases of individual ovarian cancer have been described in women who participated in IVF programs (13–16). In most of these cases, the tumor was diagnosed shortly after the IVF treatment and developed very rapidly (17, 18). Even though these individual reports do not prove a relationship between IVF treatment and development of ovarian cancer, they raise the possibility that ovarian stimulation or other factors, such as oocyte aspiration, accelerate the growth of an existing tumor. In addition, in two studies of the incidence of cancer in women who were referred to IVF units, no overall increased risk for ovarian and breast cancer was found (19, 20).

We sought to evaluate the incidence of cancer in a cohort of infertile women treated with IVF.

MATERIALS AND METHODS

Study Cohort

The study cohort consisted of women who were treated for infertility from 1981 to 1992 at the IVF units of Chaim Sheba Medical Center, Tel Hashomer, and Assuta Medical Center, Tel Aviv, Israel. These two units are operated by the same physicians, who use similar treatment protocols.

Patients were identified by meticulous review of the medical records of the units since their foundation. Patients attending the IVF unit who received at least one treatment cycle were included. We obtained data on demographic characteristics (age and place of birth) in all patients. In addition, information on the type of infertility, number of treatment cycles, and treatment outcome was obtained for patients attending the Chaim Sheba Medical Center.

The study was approved by the institutional review board (permit number 5909/845, December 1995).

IVF Treatment

During the study period, three main ovarian hyperstimulation protocols were used: [1] combined treatment with clomiphene citrate, 100 mg/d on days 5–9 of the cycle, followed by hMG (Pergonal; Teva Pharmaceutical Industries Ltd., Kfar Sava, Israel), 150 IU/d of FSH and LH starting on day 8 of the cycle; [2] hMG, 225 IU/d, starting on day 3 of the cycle; and [3] GnRH analogue (D-Trip-6-LHRH microcapsules; Decapeptyl Depot, 3.2 mg microcapsules; Ferring Ltd., Malmö, Sweden), given for ovarian down-regulation, followed by hMG, 150 IU/d 15 days later after verification of complete ovarian suppression. Follicular development was monitored by measuring serum estradiol and progesterone concentrations and by ultrasonography. Human chorionic gonadotropin, 10,000 IU, was administered when appropriate ovarian response was achieved. Oocyte retrieval, culture, fertilization, embryo culture, and transfer were carried out as described elsewhere (21).

Cancer Identification

The study cohort computer file was linked to the Israel National Cancer Registry to identify cancer cases through December 1996. The registry was established in 1960 and maintains data on all cases of malignant diseases in Israel, including borderline and some benign tumors (primarily central nervous system). The registry receives notification of all cases of cancer from hospital discharge reports and oncology and pathology departments. Depending on the cancer site, cancer ascertainment during internal verifications was found to be 90% to 95% complete (22).

The records were linked by computer matching of patients' identification numbers, names, and demographic variables with the data file in the cancer registry. For all patient matches, the cancer registry provided cancer diagnosis, coded according to the *International Classification of Diseases, Ninth Revision,* and the date and place of diagnosis. Diagnoses were verified by reviewing the original histopathologic report for each case.

Cases of cancer that were diagnosed within 1 year of initiation of IVF treatment were excluded from analysis to allow a minimal latency period between exposure and development of cancer.

TABLE 1

Observed and expected cases of cancer among infertile women treated with IVF (n = 5,026).

Site	No. of observed cases	No. of expected cases	Standardized incidence ratio[a] (95% CI)[b]
All	27	35.6	0.76 (0.50–1.10)
Breast	11	15.86	0.69 (0.46–1.66)
Ovary	1	1.74	0.57 (0.01–3.20)
Cervix	1	1.73	0.58 (0.01–3.22)
Endometrium	2	0.89	2.25 (0.25–8.11)
Other	12	15.38	0.78 (0.40–1.36)

Colon cancer (3 cases); melanoma (3 cases); and 1 case each of tongue cancer, thyroid cancer, stomach cancer, leukemia, lymphoma, and cancer of the peritoneum.

[a] SIR = Standardized Incidence Ratio.

[b] 95% CI = 95% Confidence Interval.

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Statistical Analyses

Standardized incidence ratios (SIRs) were computed as a ratio of observed to expected cases of cancer, along with estimated 95% CIs (23). Woman-years at risk were calculated from the date of first treatment until date of last follow-up (December 31, 1996, the last update of the cancer registry) or until date of diagnosis of cancer.

Expected cases of cancer were computed on the basis of age, sex, place of birth, and year-specific national cancer incidence rates. Power calculations to detect excess risk for cancer in the cohort were performed by using the EpiInfo statistics program (24).

RESULTS

The study cohort consisted of 5,026 women and 18,291 woman-years of follow-up (mean follow-up, 3.6 ± 3.4). The mean age at first IVF treatment was 34.0 ± 6.4 years, and the mean age at the end of follow-up was 37.5 ± 7.1 years.

When the study cohort was linked to the cancer registry data from 1996, we observed 27 cases of cancer diagnosed at least 1 year after IVF treatment; although 35.6 cases were expected (SIR, 0.76 [95% CI, 0.50–1.10]) (Table 1). Eleven cases of breast cancer were observed compared with 15.86 expected cases (SIR, 0.69 [95% CI, 0.46–1.66]). One case of ovarian cancer and one case of cervical cancer were observed, whereas 1.74 and 1.73 cases, respectively, were

TABLE 2

Observed and expected cases of cancer, by continent of birth.

Place of birth	No. of women	No. of observed cases	No. of expected cases	Standardized incidence ratio (95% CI)
Israel	3,632	15	24.0	0.63 (0.35–1.03)
Asia-Africa	703	7	5.8	1.21 (0.48–2.49)
Europe-United States	691	5	5.8	0.86 (0.28–2.01)

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expected. No excess risk of cancer was evident when we compared the observed and expected number of cases of cancer by continent of birth (Table 2).

Thirteen additional cases of cancer were diagnosed within 1 year of IVF treatment: four ovarian cancers (three borderline malignancies and one ovarian carcinoma), four cervical malignancies (all CIN-III), one endometrial carcinoma, and five others (melanoma, skin, mediastinum, lung, or thyroid).

In the 1,254 women that were treated at Chaim Sheba Medical Center, type of infertility, number of IVF cycles, and treatment outcome did not significantly affect the risk for cancer (Table 3).

DISCUSSION

During IVF treatment, multiple folliculogenesis is achieved by using intensive ovulation induction. Oocytes are then retrieved through puncture of the ovarian follicles. Both ovulation induction and ovarian puncture were associated in the past with development of ovarian cancer (14, 17). In addition, infertility itself has been regarded as a risk factor for ovarian and breast cancer (25). We found no increased incidence of cancer in general and ovarian cancer in particular after IVF treatment. Although our follow-up period (18,291 woman-years) is adequate to rule out excess risk for all-site cancer (relative risk, 2.0) with power of 80%, it may not be sufficient to exclude an association between IVF and ovarian cancer (power of 60%) (24).

TABLE 3

Observed and expected cases of cancer, by type of infertility, number of IVF cycles, and treatment outcome.[a]

Characteristic	No. of women	No. of observed cases	No. of expected cases	Standardized incidence ratio (95% CI)
Type of infertility				
Mechanical	611	11	10.30	1.04 (0.53–1.91)
Ovulatory	108	3	1.45	2.07 (0.42–6.04)
Male factor	243	0	2.78	0 (0–1.32)
Unexplained	292	3	4.28	0.70 (0.14–2.05)
Number of IVF cycles				
1–2	663	9	9.17	0.98 (0.45–1.86)
3–5	417	8	6.60	1.21 (0.52–2.39)
≥6	174	0	3.06	0 (0–1.20)
Pregnancy				
Yes	398	5	6.35	0.79 (0.25–1.84)
No	856	12	12.48	0.96 (0.50–1.68)

[a] Assessed in 1,254 women.

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As expected, the most common site of cancer was the breast. Our group previously investigated the possible association between breast cancer, infertility, and ovulation induction (6, 26). Although we observed a 40% increase in the risk of breast cancer among women with anovulatory infertility as compared to the general population, we found no differences between women who were treated by ovulation-inducing drugs and those who were not.

Another study (27) reported breast cancer in 16 of 950 women who attended an infertility clinic, a rate that was calculated to be twice the estimated population rates. These women had been treated with ovulation-inducing drugs, but the authors did not note whether they had attended IVF programs.

No excess risk for breast cancer was found in a large cohort of infertile women compared with population rates (28). Moreover, treatment with clomiphene citrate appeared to reduce the risk compared with patients who did not use this drug. In the only studies that assessed cancer risk among patients attending IVF programs (19, 20), the incidence of breast and ovarian cancer was no greater than expected. Women with unexplained infertility had significantly more cases of cancer of the ovary and uterus than expected (standard incidence ratio, 2.64 [95% CI, 1.10–6.35] and standardized incidence ratio, 4.59 [95% CI, 1.91–11.0]), respectively.

We observed numerous cases of cancer that were diagnosed within the first year of IVF treatments. This finding agrees with that of another study (20) in which the incidence of breast and uterine cancer within 12 months of exposure to fertility drugs with IVF was higher than expected. Development of cancer might not be caused by the ovulation induction treatment but rather provoked by the hormonal changes enhanced by this treatment. In addition, a cohort of IVF-treated patients is unique in that every patient is closely followed before, during, and after each cycle. Close medical surveillance, including routine ultrasonography tests and Papanicolaou smears, may contribute to the early detection of gynecological cancers, especially ovarian and cervical cancer, in these women.

Moreover, IVF treatment programs were primarily designed for women with tubal infertility. Tubal infertility may be caused by pelvic adhesions or by lack of tubal patency as a result of previous pelvic infection. Cervical cancer may share the same infectious etiology.

In conclusion, we found no increased risk for cancer in women undergoing IVF treatment compared with the general population. Careful follow-up of women attending IVF may allow better and earlier diagnosis of already existing cancers, especially of the genital organs.

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