American Journal of Epidemiology Advance Access published November 26, 2008

American Journal of Epidemiology

DOI:10.1093/aje/kwn318

Original Contribution

Cancer Risk After Exposure to Treatments for Ovulation Induction

R. Calderon-Margalit, Y. Friedlander, R. Yanetz, K. Kleinhaus, M. C. Perrin, O. Manor, S. Harlap, and O. Paltiel

Initially submitted January 23, 2008; accepted for publication September 11, 2008.

Uncertainty continues as to whether treatments for ovulation induction are associated with increased risk of cancer. The authors conducted a long-term population-based historical cohort study of parous women. A total of 15,030 women in the Jerusalem Perinatal Study who gave birth in 1974–1976 participated in a postpartum survey. Cancer incidence through 2004 was analyzed using Cox's proportional hazards models, controlling for age and other covariates. Women who used drugs to induce ovulation ($n = 567$) had increased risks of cancer at any site (multivariate hazard ratio (HR) = 1.36, 95% confidence interval (CI): 1.06, 1.74). An increased risk of uterine cancer was found among women treated with ovulation-inducing agents (HR = 3.39, 95% CI: 1.28, 8.97), specifically clomiphene (HR = 4.56, 95% CI: 1.56, 13.34). No association was noted between use of ovulation-inducing agents and ovarian cancer (age-adjusted HR = 0.61, 95% CI: 0.08, 4.42). Ovulation induction was associated with a borderline-significant increased risk of breast cancer (multivariate HR = 1.42, 95% CI: 0.99, 2.05). Increased risks were also observed for malignant melanoma and non-Hodgkin lymphoma. These associations appeared stronger among women who waited more than 1 year to conceive. Additional follow-up studies assessing these associations by drug type, dosage, and duration are needed.

breast neoplasms; cohort studies; incidence; lymphoma, non-Hodgkin; melanoma; ovarian neoplasms; ovulation induction; uterine neoplasms

Abbreviations: CI, confidence interval; HR, hazard ratio; ICDO-3, *International Classification of Diseases for Oncology*, Third Edition.

Approximately 10% of couples in developed countries seek health care for infertility (1, 2). The use of fertility treatment has grown substantially in recent decades, as can be inferred from the increasing utilization of assisted reproductive technologies (3). It has been estimated that approximately 1% of US infants born in 2004 were conceived through assisted reproductive technologies (4).

Ovulation-inducing drugs are widely used for ovarian follicle stimulation, either as independent therapies or during in vitro fertilization cycles. Clomiphene citrate, in use since the 1960s, is still considered the best initial treatment for the majority of women with anovulatory infertility (4). Clomiphene has also been widely used among couples with unexplained infertility (4). Similarly, human menopausal gonadotropins (nowadays partly replaced by recombinant follicle-stimulating hormone) have been used to promote ovulation since the early 1960s (5), and human chorionic gonadotropins have been used since 1932 (6).

Despite this long-term use, the scientific literature provides inconsistent information on the association between ovulation induction treatment and cancer incidence. An increased risk of ovarian cancer following treatment has been suggested in previous studies (7, 8), while more recent studies suggest no association (9, 10) (Table 1). Some studies have suggested an increased risk of breast cancer following treatment with clomiphene (11, 12); however, in others, investigators have reported a reduced risk among treated women (13, 14) or no effect on risk (15, 16). A few studies have assessed the association between ovulation induction and cancer at other sites, such as the uterus, thyroid, and

Correspondence to Dr. Ronit Calderon-Margalit, Braun School of Public Health and Community Medicine, Hadassah-Hebrew University, P.O. Box 12272, 91120 Jerusalem, Israel (e-mail: ronitc@ekmd.huji.ac.il).

Table 1. Findings From Published Studies on the Association Between Fertility Treatment and Incidence of Ovarian and Breast Cancer

First Author (Ref. No.) and Country	Study Design	Participants	No. of Women Exposed to Ovulation Induction	Duration of Follow-up, years	Age at End of Follow-up, years	No. of Cancer Cases	Treatment and Main Results
			Ovarian Cancer				
Rossing (7), United States	Case-cohort	11 cases vs. 135 women in infertile subcohort (1974–1985)	Clomiphene: 96; hCG: 38	Mean, 11.3	79% <45	11	Clomiphene >1 year: SIR = 11.1 (95% CI: 1.5, 82.3); clomiphene <1 year: no association
Whittemore (8), United States	3 case-control studies, pooled	844 cases, 977 controls	31 treated; of those—clomiphene: 2; hMG: 0 (46)	NA	NA	844	Nulligravid women: OR = 27.0 (95% CI: 2.3, 316); gravid women: OR = 1.4 (95% CI: 0.52, 3.6)
Modan (18), Israel	Historical prospective	2,496 infertile women vs. general population	Clomiphene: 908; hMG: 159; clomiphene + hMG: 242	Mean, 21.4	Mean = 50	120	Clomiphene: SIR = 2.7 (95% CI: 0.97, 5.8); not significantly higher than SIR for untreated infertile women (SIR = 1.6, 95% CI: 0.6, 3.5)
Brinton (9), United States	Historical prospective	Infertile women vs. general population; treated vs. nontreated	Clomiphene: 3,277; gonadotropins: 866	Median, 18.8	NA	45	Ever use of clomiphene (vs. never): RR = 0.82 (95% CI: 0.4, 1.5); gonadotropins: 1.09 (95% CI: 0.4, 2.8)
Venn (16), Australia	Historical prospective	In vitro fertilization patients: 20,656 exposed to ovulation induction vs. general population and vs. 9,044 unexposed	20,656; clomiphene: ≥6,543; hMG: ≥11,153	Exposed: 7; unexposed: 10	Median, 39	13	Ovulation induction: SIR = 0.88 (95% CI: 0.42, 1.84)
Rossing (10), United States	Case-control	378 cases diagnosed in 1994–1998 and 1,637 population controls	102; clomiphene: 98			378	No association with ovulation induction or clomiphene
			Breast Cancer				
Lerner-Geva (11), Israel	Historical prospective	3,076 treated women vs. general population	3,076; clomiphene: 2,751	Mean, 20.9	Mean at diagnosis = 47	131	Clomiphene only: SIR = 1.40 (95% CI: 1.05, 1.83); hMG only: SIR = 0.66 (95% CI: 0.21, 1.54); clomiphene, then hMG: 1.06 (95% CI: 0.59, 1.75)
Potashnik (13), Israel	Historical prospective	1,197 infertile women vs. general population	780 (clomiphene and/or hMG)	Mean, 18	Median, 48	20	Ovulation induction: SIR = 1.65 (95% CI: 0.94, 2.68)
Brinton (12), United States	Historical prospective	1) 8,431 infertile women vs. general population; 2) women exposed to a certain drug vs. nonexposed	Clomiphene: 3,280; gonadotropins: 867	Median, 18.8	Median at diagnosis, 48	292	Infertility: SIR = 1.29 (95% CI: 1.1, 1.4); clomiphene: SIR = 1.29 (95% CI: 1.1, 1.5); gonadotropins: SIR = 1.40 (95% CI: 0.9, 2.0). RR for invasive cancers—ever use of clomiphene (vs. never) and ≥20 years of follow-up: RR = 1.6 (95% CI: 1.0, 2.5); high dose of gonadotropins: RR = 1.79 (95% CI: 1.0, 3.3)
Venn (16), Australia	Historical prospective	See above		NA	Median at end of follow-up, 39	143	Ovulation induction (yes/no): SIR = 0.93 (95% CI: 0.79, 1.09); <12 months of exposure: SIR = 1.96 (95% CI: 1.22, 3.15)
Lerner-Geva (11), Israel	Nested case-control	61 cases vs. 120 controls				61	Clomiphene: OR = 2.1 (95% CI: 0.99, 4.3); hMG: OR = 0.6 (95% CI: 0.1, 2.2); clomiphene, then hMG: OR = 0.8 (95% CI: 0.3, 2.2)
Jensen (15), Denmark	Case-cohort	331 breast cancer patients vs. 1,221 women in infertile subcohort	739; clomiphene: ~33%	Median, 8.8	Median, 40	331	No association for clomiphene, hCG, or gonadotropin-releasing hormone. Progestins: RR = 3.36 (95% CI: 1.3, 8.6); hMG, 5–9 years from exposure: hazard ratio = 1.96 (95% CI: 1.06, 3.64)
Rossing (14), United States	Case-cohort	27 cases vs. subcohort of 135 infertile women	Clomiphene: 102	Mean, 11.3	NA	27	Clomiphene: RR = 0.5 (95% CI: 0.2, 1.2); hCG: RR = 0.5 (95% CI: 0.2, 1.8)

Abbreviations: CI, confidence interval; hCG, human chorionic gonadoptropins; hMG, human menopausal gonadotropins; NA, not available; OR, odds ratio; RR, rate ratio; SIR, standardized incidence ratio.

colon, and malignant melanoma; results have been inconsistent (17). Overall, most investigators studying the association between fertility treatment and cancer have reported on outcomes occurring before the age at which women are at substantial risk of cancer and/or have used the general population as the comparison group, precluding control for major confounders and risk factors (17). Some of these studies compared exposures within cohorts of infertile women (Table 1); however, it is likely that infertile women who were not assigned to fertility treatment had different causes of infertility than those who underwent ovulation induction. Those causes may be associated with a different risk of cancer (16, 18), calling into question the comparability of these groups.

We aimed to study the association between ovulation-inducing treatments and the incidence of cancer in a unique population-based cohort of parous women.

MATERIALS AND METHODS

Study participants and design

The Jerusalem Perinatal Study is a population-based cohort study of all births to residents of West Jerusalem, Israel, and its surroundings in 1964–1976 (19). The database includes demographic, obstetric, and neonatal information on 92,408 births to 41,206 mothers collected from birth notifications and maternity ward log books. Between November 1974 and December 1976, 15,426 mothers were interviewed in the hospital on the first or second day after giving birth. This postpartum subcohort included 98% of births occurring in the 3 major obstetric units in West Jerusalem and covered 91% of all births in the area at the time. The questionnaire collected information on obstetric and gynecologic history, time to conception, and whether the couple had sought advice for infertility, including mechanical treatments such as tubal insufflation. Women were asked whether they had received medical treatment for induction of ovulation prior to the index pregnancy.

Linkage of the cohort with the Israel Population Registry using mothers' identity numbers permitted tracing and ascertainment of vital status for 97.5% ($n = 15{,}047$) of mothers. Information on cancer incidence as of December 31, 2004, was obtained by linking the ascertained cohort with the Israel Cancer Registry, which receives notification of all malignancies diagnosed throughout the country. Since 1981, reporting of cases to the Registry has been mandatory by law, but reporting was considered relatively complete even before this. We excluded from this study 17 mothers who were diagnosed with cancer prior to their first birth in the postpartum subcohort.

The study was approved by the institutional review boards of Hadassah-Hebrew University (Jerusalem, Israel) and Columbia University (New York, New York).

Study variables

Cancer diagnoses were coded according to the *International Classification of Diseases for Oncology*, Third Edition (ICDO-3). We analyzed the incidence of all cancer as well as site-specific cancer at sites for which the total number of events exceeded 30. These included non-Hodgkin lymphoma (morphologic codes 95903–96502, 96674–97143, and 97273; $n = 50$), malignant melanoma (morphologic codes 87202–87743; $n = 78$), and solid tumors of the breast (ICDO-3 codes 50.0–50.9; $n = 530$), colon and rectum (ICDO-3 codes 18.0–20.9; $n = 102$), ovary (ICDO-3 codes 56.0–56.9; $n = 43$), uterus (ICDO-3 codes 54.0–55.9; $n = 44$), thyroid (ICDO-3 codes 73.0–73.9; $n = 68$), uterine cervix (ICDO-3 codes 53.0–53.9; $n = 43$), and brain (ICDO-3 codes 70.0, 71.0–72.9, 75.1, and 75.2; ICDO-3 code 30.0 with morphologic code 95223; and ICDO-3 code 75.3 with morphologic code 93611; $n = 58$).

Ovulation induction treatments were coded in the questionnaires as clomiphene citrate ($n = 312$), human menopausal gonadotropins ($n = 61$), other ($n = 54$), unknown ($n = 87$), and combinations of some or all of the above. Treatments were further categorized into any treatment versus none and treatments that included clomiphene versus no ovulation induction.

Maternal demographic and social variables included age at earliest birth in the subcohort as a continuous variable; mother's geographic origin, defined according to her father's country of birth (categorized as Israeli, North African, West Asian, European (including North America, Europe, Australia/New Zealand, and South Africa), and non-Jewish); maternal education ($\leq$12 and $>$12 years); and social class (socioeconomic status), defined according to occupation of the child's father (categorized into 3 levels).

Body mass index was calculated as the ratio between self-reported prepregnancy weight (kg) and squared height (m^2) and was subdivided into the categories <25 and ≥ 25.

First birth in the Jerusalem Perinatal Study cohort was considered a proxy for the first birth in a woman's life, and family size in the cohort was considered a surrogate for parity, divided into 1, 2–3, and $\geq$4 offspring. Ovulatory disorders were defined as either irregular menstrual periods or regular menstrual periods with cycle lengths of less than 21 days or more than 35 days. Other reproductive variables included use of oral contraceptives (ever vs. never), mechanical assessments and treatments for infertility (combination of the codes for tubal insufflation, dilation and curettage, and other vs. none), and time to conception.

Statistical analysis

For every woman, follow-up time was counted from the earliest birth in the subcohort (i.e., births that took place after November 1974) until the diagnosis of cancer, death, or December 31, 2004. Bivariate and multivariate Cox proportional hazards models were used to calculate hazard ratios for the development of cancer among women who received any ovulation induction or clomiphene in particular in comparison with women who received no ovulation induction.

Data were virtually complete for all variables except body mass index, where missing values were present for 8% of the study population. Missing values were replaced by the reference category (body mass index < 25) after examination of the data and sensitivity analysis.

Age 50 years was used as the cutoff point for estimation of pre- or postmenopausal status. A time-dependent survival analysis was performed for the association between fertility treatment and cancer incidence, testing for interaction between menopausal status and fertility treatment.

In order to estimate possible misclassification of exposure, we conducted sensitivity analyses in which we restricted the exposure either to women who were treated with clomiphene and human menopausal gonadotropins or women who were treated with clomiphene and/or an unknown regimen.

In the tables we present hazard ratios, 95% confidence intervals, and 2-sided *P* values.

RESULTS

Table 2 shows the characteristics of the study population by type of treatment. Compared with untreated women, those who received treatment to induce ovulation were more affluent, more educated, and more likely to have fathers born in Israel or Europe. Treated women were older at the time of their first birth, had lower parity than untreated women, and were more likely to have waited more than 12 months for conception.

Overall incidence of cancer

During 424,193 person-years of follow-up (median, 29), 1,215 women developed cancer (median age at diagnosis, 49.4 years). Women who received ovulation induction treatment had an age-adjusted 50% increased risk of developing cancer at any site (Table 3). Adjustment for socioeconomic status, mother's geographic origin, and body mass index did not materially change the association. Additional adjustment for parity yielded a hazard ratio of 1.36 (95% confidence interval (CI): 1.06, 1.74) (Table 4). Further adjustments either for ovulation disorders or for mechanical treatments or assessments for infertility did not alter the results (not shown). There was no interaction of menopausal status with the association between fertility treatment and cancer.

Analyses restricted to primiparous women or to women who received clomiphene yielded virtually unchanged results (Tables 3 and 4).

When results were stratified by time to conception (Table 5), treated women who waited more than 12 months to conceive had double the risk of cancer compared with untreated women (age-adjusted hazard ratio (HR) = 2.03, 95% CI: 1.36, 3.01), whereas exposed women who had a shorter time to conception did not experience an increased risk of cancer (HR = 1.23, 95% CI: 0.80, 1.89; *P* for interaction = 0.153).

When results were stratified by time since birth, significantly increased risks were observed during the first 20 years following birth (Table 6).

The sensitivity analysis of exposure yielded similar results (Table 7). Similarly, exclusion of women with unknown treatment had a minimal effect on the association (for all cancer, adjusted HR = 1.38, 95% CI: 1.05, 1.82; $P = 0.022$).

Cancer at specific sites

No association was found between fertility treatment and cancers of the colon (age-adjusted HR = 1.05, 95% CI: 0.39, 2.86), thyroid (HR = 1.60, 95% CI: 0.58, 4.40), or cervix (HR = 1.68, 95% CI: 0.40, 7.04) (Table 3). No brain cancer events were diagnosed among treated women, but the small numbers precluded any further analysis.

Ovarian cancer. Of 43 women diagnosed with ovarian tumors, 1 had been treated with clomiphene and was diagnosed with a germ-cell tumor (morphologic code 90603). No association was found between clomiphene exposure and cancer of the ovaries (age-adjusted HR = 0.98, 95% CI: 0.14, 7.11) (Table 3).

Breast cancer. Women who underwent ovulation induction treatment had a significantly increased risk of developing breast cancer (age-adjusted HR = 1.65, 95% CI: 1.15, 2.36). Controlling for geographic origin, socioeconomic status, body mass index, and parity weakened this association (HR = 1.42, 95% CI: 0.99, 2.05) (Table 4). The results were minimally altered with further adjustment for history of oral contraceptive use (HR = 1.47, 95% CI: 1.02, 2.11) or age at first birth (HR = 1.42, 95% CI: 0.99, 2.05), and there was no interaction of the association with either age at first birth ($\leq$30 years vs. >30 years) or menopausal status. No association was found between ovulation induction and breast cancer among primiparous women (Table 3).

Women who were exposed to ovulation induction in general or clomiphene in particular had twice the risk of breast cancer as untreated women, but only among women who waited more than 12 months to conceive (Table 5). Analysis by time from birth showed significantly increased risks of breast cancer in the first 20 years (Table 6).

Women who were treated *only* with clomiphene (n = 312) had an age-adjusted hazard ratio of 1.74 (95% CI: 1.09, 2.79; $P = 0.02$), irrespective of time to conception, and a multivariate hazard ratio of 1.51 (95% CI: 0.94, 2.42; $P = 0.092$). Women who were treated only with clomiphene and waited more than 12 months to conceive had an age-adjusted hazard ratio of 2.82 (95% CI: 1.40, 5.65; $P = 0.004$) (not shown).

Uterine cancer. Women who received ovulation induction treatment had a 3-fold increased risk of uterine cancer (age-adjusted HR = 3.32, 95% CI: 1.31, 8.42) compared with unexposed women. Controlling for age, socioeconomic status, geographic origin, body mass index, family size, and ovulatory disorders did not materially change this association (HR = 3.39, 95% CI: 1.28, 8.97) (Table 4).

Clomiphene treatment was associated with an age-adjusted hazard ratio of 4.33 (95% CI: 1.55, 12.13) for the development of uterine cancer. In the multivariate model, the adjusted hazard ratio for cancer of the uterus among women who were treated with clomiphene was 4.56 (95% CI: 1.56, 13.34; $P = 0.006$). Mothers treated with clomiphene who waited more than 12 months to conceive had an 8-fold increased risk of uterine cancer (age-adjusted HR = 8.26, 95% CI: 1.24, 55.0; $P = 0.029$) (Table 5).

Of 5,814 primiparous mothers, uterine cancer was diagnosed among 9 untreated women and 4 treated women,

Table 2. Distribution of Participants According to Type of Ovulation Induction Treatment and Selected Characteristics, Jerusalem Perinatal Study, 1974–2004

	No Treatment (n = 14,463)		Type of Ovulation Induction Treatment			
			Any Type (n = 567)		Clomiphene (n = 362)	
	No.	%	No.	%	No.	%
Mean age at subcohort entry, years	27.5 (5.4)[a]		28.1 (4.8)		27.9 (4.6)	
Age at first birth, years						
<20	2,020	14	31	5	13	4
20–24	7,657	53	231	41	159	44
25–29	3,605	25	216	38	142	39
≥30	1,181	8	89	16	48	13
Mean age at first birth, years	24.0 (4.1)		26.0 (4.4)		25.9 (4.0)	
Geographic origin (country/region of birth of mother's father)						
Israel	2,148	15	116	21	79	22
West Asia	3,751	26	122	22	66	18
North Africa	3,043	21	69	12	39	11
Europe	5,320	37	258	45	178	49
Non-Jewish	201	1	2	0	0	0
Social class (socioeconomic status)						
1–2 (high)	7,160	50	331	58	232	64
3–4	5,343	37	184	32	102	28
5–6 (low)	1,960	14	52	9	28	8
Education, years						
≤12	8,719	60	286	50	168	46
>12	5,447	38	267	47	187	52
Missing data	297	2	14	3	7	2
Parity[b]						
1	3,958	27	256	45	169	47
2–3	6,397	44	264	47	169	47
≥4	4,108	28	47	8	24	7
Mean body mass index[c]	22.09 (3.1)		22.47 (3.5)		22.04 (3.5)	
<25	11,363	79	436	77	274	76
≥25	1,926	13	104	18	70	19
Missing data	1,174	8	27	5	18	5
Time to conception, months						
≤12	13,758	95	222	39	140	39
>12	705	5	345	61	222	61
Ovulatory disorders[d]	1,377	10	151	27	106	29
Mechanical treatment/assessment (tubal insufflation, dilation and curettage, other)	238	2	263	46	158	44

[a] Numbers in parentheses, standard deviation.
[b] Number of children at the end of data collection.
[c] Weight (kg)/height $(m)^2$.
[d] Defined as irregular menstrual periods or menstrual cycles with lengths of <21 days or >35 days.

yielding a 6-fold increased risk (after adjustment for age, body mass index, and ovulatory disorders, HR = 6.69, 95% CI: 2.05, 21.8; $P = 0.002$). Clomiphene treatment in primiparous women was associated with a similarly adjusted hazard ratio of 8.33 (95% CI: 2.25, 30.85; $P = 0.002$) (not shown).

Table 3. Age-Adjusted Hazard Ratio for Incident Cancer According to Type of Ovulation Induction Treatment, Overall and by Cancer Site, Jerusalem Perinatal Study, 1974–2004

Cancer Site	No. of Cases With No Treatment	Type of Ovulation Induction Treatment					
		Any Type of Treatment			Clomiphene		
		No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI
All women	(n = 14,463)		(n = 567)			(n = 362)	
All sites	1,148	67	1.50	1.17, 1.91	42	1.50	1.10, 2.04
Breast	498	32	1.65	1.15, 2.36	18	1.48	0.93, 2.37
Uterus	39	5	3.32	1.31, 8.42	4	4.33	1.55, 12.13
Ovary	42	1	0.61	0.08, 4.42	1	0.98	0.14, 7.11
Cervix	31	2	1.68	0.40, 7.04	2	2.65	0.63, 11.08
Non-Hodgkin lymphoma	45	5	2.86	1.14, 7.20	3	2.74	0.85, 8.80
Brain	58	0	0		0		
Malignant melanoma	72	6	2.14	0.93, 4.92	6	3.39	1.47, 7.79
Thyroid	64	4	1.60	0.58, 4.40	3	1.91	0.60, 6.08
Colon	98	4	1.05	0.39, 2.86	3	1.27	0.40, 4.02
Primiparous women	(n = 5,469)		(n = 345)			(n = 225)	
All sites	361	37	1.42	1.01, 2.00	22	1.33	0.87, 2.05
Breast	162	15	1.26	0.74, 2.15	8	1.08	0.53, 2.19
Uterus	9	4	5.36	1.63, 17.61	3	6.58	1.78, 24.35
Ovary	15	1	0.88	0.12, 6.74	1	1.41	0.18, 10.72
Cervix	12	2	2.34	0.52, 10.61	2	3.68	0.82, 16.62
Non-Hodgkin lymphoma	12	4	5.24	1.64, 16.69	2	3.86	0.85, 17.50
Brain	17	0	0		0	0	
Malignant melanoma	32	2	0.82	0.20, 3.45	2	1.37	0.33, 5.72
Thyroid	20	3	2.43	0.71, 8.36	2	2.49	0.57, 10.79
Colon	23	1	0.56	0.08, 4.13	1	0.90	0.12, 6.68

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Age-adjusted HR for comparison of treated mothers with untreated mothers.

Malignant melanoma. Treatment for ovulation induction in general was not associated with the development of malignant melanoma (multivariate HR = 1.68, 95% CI: 0.72, 3.92). However, women treated with clomiphene experienced a significantly increased risk of malignant melanoma, with a multivariate-adjusted hazard ratio of 2.56 (95% CI: 1.10, 5.97; $P = 0.030$) (Table 4).

Non-Hodgkin lymphoma. For non-Hodgkin lymphoma, treatment for ovulation induction was associated with a multivariate-adjusted hazard ratio of 2.63 (95% CI: 1.02, 6.82) (Table 4). The increased risks were evident especially among primiparous women (Table 3) and in the first 5 years following birth (Table 7). Clomiphene treatment was not associated with a significantly increased risk of non-Hodgkin lymphoma (multivariate HR = 2.46, 95% CI: 0.74, 8.13) (Table 4).

DISCUSSION

In this study, women who were treated for ovulation induction experienced a significantly higher overall risk of cancer. This increased risk was especially evident for cancer of the uterus following treatment with clomiphene citrate. Furthermore, this study's results suggest increased risks of breast cancer, malignant melanoma, and non-Hodgkin lymphoma following ovulation induction treatment that were more pronounced among women who waited more than 1 year to conceive, perhaps representing a dose-response relation. The results of the current study do not support an increased risk of ovarian cancer following ovulation induction in parous women.

Possible limitations of this study include the absence of detailed information regarding type of infertility, type of treatment, dosage, and number of cycles and lack of information regarding treatment in other pregnancies. While introduction of family size into our multivariate models reduced the magnitude of all associations studied, suggesting that family size is a confounder, parity might also be a surrogate for treatment in previous pregnancies; therefore, controlling for family size might partially mask the effects of ovulation induction. While treatments were self-reported in this study, the proportion of women reporting exposure to clomiphene treatment (64% of all treated women) was similar to that reported in other studies with data from the 1970s (7, 15). Moreover, according to the sensitivity analysis,

Table 4. Hazard Ratio for Incident Cancer (Multivariate Analysis) According to Type of Ovulation Induction Treatment, Overall and by Cancer Site, Jerusalem Perinatal Study, 1974–2004

Ovulation Induction Treatment and Cancer Site	Model 1[a]		Model 2[b]		*P* Value
	Adjusted HR	95% CI	Adjusted HR	95% CI	
Any type of treatment					
All sites	1.47	1.15, 1.89	1.36	1.06, 1.74	0.017
Breast	1.63	1.14, 2.33	1.42	0.99, 2.05	0.058
Uterus	3.36	1.32, 8.60	3.39[c]	1.28, 8.97	0.014
Melanoma	1.94	0.84, 4.48	1.68	0.72, 3.92	0.228
Non-Hodgkin lymphoma	2.68	1.06, 6.79	2.63	1.02, 6.82	0.046
Clomiphene					
All sites	1.47	1.08, 2.00	1.35	0.99, 1.84	0.060
Breast	1.46	0.91, 2.33	1.27	0.79, 2.04	0.331
Uterus	4.46	1.58, 12.63	4.56[c]	1.56, 13.34	0.006
Melanoma	2.97	1.29, 6.85	2.56	1.10, 5.97	0.030
Non-Hodgkin lymphoma	2.49	0.77, 8.04	2.46	0.74, 8.13	0.140

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Results were adjusted for age, socioeconomic status, country of birth, and body mass index.
[b] Results were adjusted for family size in addition to the variables included in model 1.
[c] Results were additionally adjusted for ovulatory disorders.

misclassification of treatment, if any existed, did not materially bias the results.

The current study included only parous women; thus, its results cannot be generalized to women who were treated but failed to conceive. However, since the success rates for clomiphene and gonadotropins among women with an intact hypothalamic-hypophysic-ovarian axis are approximately 40% (4) and 80%–90% (20), respectively, this study is relevant for a major subset of women who were treated and conceived. While investigators in most other cohort studies

Table 5. Age-Adjusted Hazard Ratio for Incident Cancer According to Type of Ovulation Induction Treatment and Time to Conception, Jerusalem Perinatal Study, 1974–2004

Ovulation Induction Treatment and Cancer Site	Time to Conception, months								*P* Value
	≤12				>12				
	No. of Untreated Cases	No. of Treated Cases	HR	95% CI	No. of Untreated Cases	No. of Treated Cases	HR	95% CI	
Any type of treatment	($n = 13{,}758$)	($n = 222$)			($n = 705$)	($n = 345$)			
All sites	1,091	21	1.23	0.80, 1.89	57	46	2.03	1.36, 3.01	<0.001
Breast	475	10	1.35	0.72, 2.52	23	22	2.36	1.30, 4.27	0.005
Uterus	37	2	3.53	0.85, 14.67	2	3	4.47	0.71, 28.23	0.11
Melanoma	70	1	0.90	0.12, 6.48	2	5	6.31	1.19, 33.53	0.03
Non-Hodgkin lymphoma	43	1	1.47	0.20, 10.70	2	4	4.42	0.80, 24.52	0.089
Clomiphene	($n = 13{,}758$)	($n = 140$)			($n = 705$)	($n = 222$)			
All sites	1,091	10	0.94	0.50, 1.75	57	32	2.33*	1.49, 3.63	<0.001
Breast	475	5	1.08	0.45, 2.60	23	13	2.17	1.08, 4.35	0.03
Uterus	37	1	2.84	0.39, 20.72	2	3	8.26	1.24, 55.0	0.03
Melanoma	70	1	1.44	0.20, 10.34	2	5	10.65	1.96, 57.97	0.006
Non-Hodgkin lymphoma	43	0	0		2	3	5.53	0.89, 34.45	0.067

Abbreviations: CI, confidence interval; HR, hazard ratio.
* *P* for interaction = 0.038.

Table 6. Age-Adjusted Hazard Ratio for Incident Cancer According to Any Type of Ovulation Induction Treatment Among All Women and Primiparous Mothers, by Cancer Site and Time Since Birth, Jerusalem Perinatal Study, 1974–2004

Cancer Site and Time Since Birth, years	All Women			Primiparous Mothers		
	No.	HR	95% CI	No.	HR	95% CI
All sites						
<5	51	3.32	1.42, 7.79	22	2.86	0.96, 8.54
5–<10	113	1.91	0.93, 3.92	36	2.02	0.78, 5.23
10–<20	376	1.58	1.03, 2.43	114	1.52	0.83, 2.77
20–<30	675	1.25	0.87, 1.79	226	1.13	0.68, 1.88
Breast cancer						
<5	21	4.16	1.22, 14.11	8	1.58	0.19, 12.92
5–<10	43	2.58	0.92, 7.22	10	1.27	0.16, 10.10
10–<20	176	2.20	1.27, 3.79	56	2.18	1.02, 4.63
20–<30	290	1.02	0.56, 1.87	103	0.75	0.31, 1.86
Uterine cancer						
<5	0			0		
5–<10	2	25.43	1.59, 407.66	2	12.51	0.75, 209.03
10–<20	10	2.91	0.37, 22.97	1		
20–<30	32	2.69	0.82, 8.84	10	2.98	0.63, 14.14
Malignant melanoma						
<5	3	0		2	0	
5–<10	15	3.94	0.89, 17.48	9	3.75	0.76, 18.44
10–<20	25	4.88	1.68, 14.23	8	0	
20–<30	35	0		15	0	
Non-Hodgkin lymphoma						
<5	2	26.15	1.62, 422.47	2	13.8	0.81, 235.69
5–<10	5	0		2	0	
10–<20	15	1.81	0.24, 13.76	2	17.06	0.96, 302.30
20–<30	28	3.12	0.94, 10.33	10	3.89	0.80, 18.87

Abbreviations: CI, confidence interval; HR, hazard ratio.

either did not control for parity or controlled for parity at the time treatment was initiated, considering women who subsequently gave birth as nulliparous, this study had no residual confounding by nulliparity.

We did not observe an association between ovulation induction and ovarian cancer, a finding supported by the results of other studies (9, 10, 18, 21); it is possible that the association found in previous studies (7, 8) between ovulation induction in general and clomiphene in particular and ovarian cancer was restricted to nulliparous women, since nulliparity is a major risk factor for ovarian cancer (22). This suggestion could also be implied from a meta-analysis (23) in which a 1.5-fold increased risk of ovarian cancer was evident when treated women were compared with the general population but no excess in risk was shown when treated women were compared with untreated infertile women.

The increased risk of uterine cancer observed in this study was prominent among women treated with clomiphene. Modan et al. (18) demonstrated standardized incidence ratios of 5.7–11.5 for uterine cancer among women treated with clomiphene; however, these standardized incidence ratios were not significantly different from those obtained for untreated infertile women. Althuis et al. (24) suggested a dose-response relation for clomiphene with standardized incidence ratios of 1.63 (95% CI: 0.8, 3.4) and 2.16 (95% CI: 0.9, 5.2) among women treated for fewer than 6 cycles and 6 or more cycles, respectively. Two small case-control studies showed no significant associations, representing perhaps lack of statistical power (25, 26). Among women who underwent in vitro fertilization (16), women treated with fertility drugs had a 5-fold increased risk of uterine cancer within the first year only, suggesting surveillance bias. However, in this latter study, very few were treated for more than 6 cycles, and the follow-up period was relatively short. Our findings cannot be explained by other risk factors for uterine cancer, such as nulliparity, since all women in our cohort gave birth; nor can they be explained by ovulation disorders or obesity, for which we controlled in our multivariate analysis. Like tamoxifen, clomiphene is a selective estrogen

Table 7. Results From Sensitivity Analysis of Multivariate-Adjusted Hazard Ratios for Incident Cancer Among Women Exposed to Ovulation Induction Treatment, Overall and by Cancer Site, Jerusalem Perinatal Study, 1974–2004[a]

Cancer Site	Results Presented in Table 4 (Model 2)			Sensitivity Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
	Any Type of Treatment			*Clomiphene and/or Human Menopausal Gonadotropins*		
All sites	1.36	1.06, 1.74	0.017	1.35	1.01, 1.80	0.042
Uterus	3.39[b]	1.28, 8.97	0.014	3.82[b]	1.30, 11.19	0.014
Non-Hodgkin lymphoma	2.63	1.02, 6.82	0.046	2.76	0.96, 7.92	0.058
Breast	1.42	0.99, 2.05	0.058	1.30	0.84, 2.00	0.242
Melanoma	1.68	0.72, 3.92	0.228	2.14	0.92, 5.00	0.078
	Clomiphene			*Clomiphene and/or Unknown*		
All sites	1.35	0.99, 1.84	0.060	1.42	1.08, 1.86	0.013
Uterus	4.56[b]	1.56, 13.34	0.006	4.32[b]	1.63, 11.45	0.003
Non-Hodgkin lymphoma	2.46	0.74, 8.13	0.140	2.69	0.94, 7.68	0.065
Breast	1.27	0.79, 2.04	0.331	1.36	0.90, 2.05	0.115
Melanoma	2.56	1.10, 5.97	0.030	2.15	0.92, 5.02	0.076

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] In all models, results were adjusted for age, geographic origin, socioeconomic status, body mass index, and parity.

[b] Results were also adjusted for ovulation disorders.

receptor modulator. While tamoxifen has been proven to reduce recurrence rates of breast cancer and improve survival, it is well established that it increases the risk of endometrial cancer 2- to 7-fold (27, 28). The structural similarities as well as the similarities in ovulation induction properties (29) raise the possibility of clomiphene as a carcinogen in endometrial cancer.

Our results might suggest that clomiphene as the only treatment is associated with an increased risk of breast cancer. Similarly to the results of Lerner-Geva et al. (11), we observed an increased risk of breast cancer of comparable magnitude for women treated only with clomiphene which disappeared when all women exposed to clomiphene were included in the analysis. Brinton et al. (12) suggested an increased breast cancer risk for clomiphene only after 20 years of follow up, irrespective of dosage or number of treatment cycles. Potashnik et al. (13) suggested an increased risk of breast cancer only among women who received short-term treatment or a low dose of clomiphene. Contradictory results include those of Terry et al. (29), who showed a significantly reduced risk of breast cancer among women with ovulatory infertility who underwent ovulation induction, with a dose-response pattern, and those of Rossing et al. (14), which suggested a nonsignificantly reduced risk following receipt of clomiphene. Jensen et al. (15) demonstrated no association between treatment with clomiphene, human chorionic gonadoptropins, or other gonadotropins and breast cancer. Similar to their results for uterine cancer, Venn et al. (16) found an increased risk of breast cancer among in-vitro-fertilization-treated women only within 12 months of treatment.

We could not find any previous publications on fertility treatments and their association with non-Hodgkin lymphoma. Reproductive factors such as age at menarche and parity have been suggested to be associated with non-Hodgkin lymphoma in a pattern quite similar to that for breast cancer (30). However, unlike the case with breast cancer, oral contraceptives have been suggested to be protective against non-Hodgkin lymphoma (31). While 1 study suggested that hormone replacement therapy increases the risk of non-Hodgkin lymphoma (32), other studies failed to demonstrate such an association (33, 34). If indeed estrogens are related to the incidence of non-Hodgkin lymphoma, an association between ovulation induction and non-Hodgkin lymphoma is plausible.

We found an increased risk of malignant melanoma only among women treated with clomiphene. Althuis et al. (35) suggested a doubled risk among clomiphene-treated women followed for more than 15 years; however, the increased risk associated with clomiphene treatment was demonstrated only among nulliparous women (35). Hannibal et al. (36) suggested an increased risk for gonadotropins (but not clomiphene) among parous women only. Other studies of the possible hormonal factors contributing to malignant melanoma include conflicting reports on the association between exogenous estrogen use and melanoma risk (37, 38) and a suggestion that older age at first birth might be associated with melanoma (38).

The strengths of this study included the design of the within-cohort comparison and the completeness of follow-up data on cancer incidence. Our study contained a small number of women who were treated in the 1970s and thus

exposed to different treatment protocols in the era preceding widespread use of in vitro fertilization. However, this is also one of the study's main strengths, allowing follow-up to the age of increasing cancer incidence in women. Our results suggest that the increased risk was most pronounced in the first 20 years following exposure. These results parallel observations in other studies of associations between other exogenous hormones and cancer, such as oral contraceptives and breast cancer, where the increased risks were evident during exposure and in the first years following exposure (39–41). Similarly, studies of tamoxifen demonstrated increased risks of uterine cancer in the first decade following exposure (42–45).

In conclusion, the present study demonstrated an association between treatment for ovulation induction and overall risk of cancer, particularly cancer of the uterus. There are still gaps in our knowledge regarding dosages and durations of various treatments and their relation to cancer, especially regarding clomiphene and uterine cancer. The disparate results in studies of ovulation induction and breast cancer underscore the possibility of selection bias and residual confounding among the studies. Ideally, extending the follow-up periods of double-blind randomized controlled trials of first-line treatment for ovulation induction could help overcome these obstacles; however, the paucity of randomized controlled trials and their small sizes make them underpowered for the study of cancer incidence. Since some of our results might be specific to women within the Jerusalem Perinatal Study cohort, there is a need for other well-conducted cohort studies with adequate data on causes of infertility, treatment modalities, hormone status, and exposures throughout the reproductive period and with prolonged follow-up, which would help confirm or refute the generalizability of our findings.

ACKNOWLEDGMENTS

Author affiliations: Braun School of Public Health and Community Medicine, Hadassah-Hebrew University, Jerusalem, Israel (R. Calderon-Margalit, Y. Friedlander, R. Yanetz, O. Manor, O. Paltiel); Department of Psychiatry, Columbia University Medical Center, New York, New York (K. Kleinhaus); Department of Psychiatry, School of Medicine, New York University, New York, New York (M. C. Perrin, S. Harlap); and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York (S. Harlap).

This study was supported by National Institutes of Health grant RO1 CA80197 (to S. H.).

Conflict of interest: none declared.

REFERENCES

1. Chandra A, Martinez GM, Mosher WD, et al. Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. *Vital Health Stat 23*. 2005:(25):1–160.
2. Juul S, Karmaus W, Olsen J. Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. The European Infertility and Subfecundity Study Group. *Hum Reprod*. 1999;14(5): 1250–1254.
3. Henne MB, Bundorf MK. Insurance mandates and trends in infertility treatments. *Fertil Steril*. 2008;89(1):66–73.
4. Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. *Fertil Steril*. 2004;82(suppl 1):S90–S96.
5. Vandewiele RL, Turksoy RN. Treatment of amenorrhea and of anovulation with human menopausal and chorionic gonadotropins. *J Clin Endocrinol Metab*. 1965;25:369–384.
6. Lunenfeld B. Historical perspectives in gonadotrophin therapy. *Hum Reprod Update*. 2004;10(6):453–467.
7. Rossing MA, Daling JR, Weiss NS, et al. Ovarian tumors in a cohort of infertile women. *N Engl J Med*. 1994;331(12):771–776.
8. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992;136(10):1184–1203.
9. Brinton LA, Lamb EJ, Moghissi KS, et al. Ovarian cancer risk after the use of ovulation-stimulating drugs. *Obstet Gynecol*. 2004;103(6):1194–1203.
10. Rossing MA, Tang MT, Flagg EW, et al. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. *Am J Epidemiol*. 2004;160(11): 1070–1078.
11. 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(2):201–212.
12. Brinton LA, Scoccia B, Moghissi KS, et al. Breast cancer risk associated with ovulation-stimulating drugs. *Hum Reprod*. 2004;19(9):2005–2013.
13. 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(5):853–859.
14. Rossing MA, Daling JR, Weiss NS, et al. Risk of breast cancer in a cohort in infertile women. *Gynecol Oncol*. 1996;60(1):3–7.
15. Jensen A, Sharif H, Svare EI, et al. Risk of breast cancer after exposure to fertility drugs: results from a large Danish cohort study. *Cancer Epidemiol Biomarkers Prev*. 2007;16(7):1400–1407.
16. Venn A, Watson L, Bruinsma F, et al. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet*. 1999; 354(9190):1586–1590.
17. Brinton LA, Moghissi KS, Scoccia B, et al. Ovulation induction and cancer risk. *Fertil Steril*. 2005;83(2):261–274.
18. Modan B, Ron E, Lerner-Geva L, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol*. 1998;147(11): 1038–1042.
19. Harlap S, Davies AM, Deutsch L, et al. The Jerusalem Perinatal Study cohort, 1964–2005: methods and a review of the main results. *Paediatr Perinat Epidemiol*. 2007;21(3):256–273.
20. Balen AH, Braat DD, West C, et al. Cumulative conception and live birth rates after the treatment of anovulatory infertility: safety and efficacy of ovulation induction in 200 patients. *Hum Reprod*. 1994;9(8):1563–1570.
21. Doyle P, Maconochie N, Beral V, et al. Cancer incidence following treatment for infertility at a clinic in the UK. *Hum Reprod*. 2002;17(8):2209–2213.
22. Zhang M, Lee AH, Binns CW. Reproductive and dietary risk factors for epithelial ovarian cancer in China. *Gynecol Oncol*. 2004;92(1):320–326.

23. Kashyap S, Moher D, Fung MF, et al. Assisted reproductive technology and the incidence of ovarian cancer: a meta-analysis. *Obstet Gynecol*. 2004;103(4):785–794.
24. Althuis MD, Moghissi KS, Westhoff CL, et al. Uterine cancer after use of clomiphene citrate to induce ovulation. *Am J Epidemiol*. 2005;161(7):607–615.
25. Benshushan A, Paltiel O, Brzezinski A, et al. Ovulation induction and risk of endometrial cancer: a pilot study. *Eur J Obstet Gynecol Reprod Biol.* 2001;98(1):53–57.
26. Parazzini F, Ricci E, Rosa C, et al. Risk of endometrial cancer after use of fertility drugs [letter]. *Hum Reprod*. 2001;16(1):196.
27. Rutqvist LE, Johansson H, Stockholm Breast Cancer Study Group. Long-term follow-up of the randomized Stockholm trial on adjuvant tamoxifen among postmenopausal patients with early stage breast cancer. *Acta Oncol*. 2007;46(2):133–145.
28. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet*. 1998;351(9114):1451–1467.
29. Steiner AZ, Terplan M, Paulson RJ. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. *Hum Reprod*. 2005;20(6):1511–1515.
30. Zhang Y, Holford TR, Leaderer B, et al. Menstrual and reproductive factors and risk of non-Hodgkin's lymphoma among Connecticut women. *Am J Epidemiol*. 2004;160(8):766–773.
31. Nelson RA, Levine AM, Bernstein L. Reproductive factors and risk of intermediate- or high-grade B-cell non-Hodgkin's lymphoma in women. *J Clin Oncol*. 2001;19(5):1381–1387.
32. Cerhan JR, Vachon CM, Habermann TM, et al. Hormone replacement therapy and risk of non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2002;11(11):1466–1471.
33. Nørgaard M, Poulsen AH, Pedersen L, et al. Use of postmenopausal hormone replacement therapy and risk of non-Hodgkin's lymphoma: a Danish population-based cohort study. *Br J Cancer.* 2006;94(9):1339–1341.
34. Altieri A, Gallus S, Franceschi S, et al. Hormone replacement therapy and risk of lymphomas and myelomas. *Eur J Cancer Prev.* 2004;13(4):349–351.
35. Althuis MD, Scoccia B, Lamb EJ, et al. Melanoma, thyroid, cervical, and colon cancer risk after use of fertility drugs. *Am J Obstet Gynecol*. 2005;193(3):668–674.
36. Hannibal CG, Jensen A, Sharif H, et al. Malignant melanoma risk after exposure to fertility drugs: results from a large Danish cohort study. *Cancer Causes Control*. 2008;19(7):759–765.
37. Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women: ovulatory life, menopause, and use of exogenous estrogens. *Cancer Epidemiol Biomarkers Prev.* 1994;3(8):661–668.
38. Naldi L, Altieri A, Imberti GL, et al. Cutaneous malignant melanoma in women. Phenotypic characteristics, sun exposure, and hormonal factors: a case-control study from Italy. *Ann Epidemiol*. 2005;15(7):545–550.
39. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet*. 1996;347(9017):1713–1727.
40. Lurie G, Wilkens LR, Thompson PJ, et al. Combined oral contraceptive use and epithelial ovarian cancer risk: time-related effects. *Epidemiology.* 2008;19(2):237–243.
41. La Vecchia C, Negri E, Franceschi S, et al. Oral contraceptives and breast cancer: a cooperative Italian study. *Int J Cancer.* 1995;60(2):163–167.
42. Andersson M, Jensen MB, Engholm G, et al. Risk of second primary cancer among patients with early operable breast cancer registered or randomised in Danish Breast Cancer Cooperative Group (DBCG) protocols of the 77, 82 and 89 programmes during 1977–2001. *Acta Oncol.* 2008;47(4):755–764.
43. Ferguson SE, Soslow RA, Amsterdam A, et al. Comparison of uterine malignancies that develop during and following tamoxifen therapy. *Gynecol Oncol*. 2006;101(2):322–326.
44. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst*. 1996;88(21):1529–1542.
45. Matsuyama Y, Tominaga T, Nomura Y, et al. Second cancers after adjuvant tamoxifen therapy for breast cancer in Japan. *Ann Oncol*. 2000;11(12):1537–1543.
46. Shapiro S. Risk of ovarian cancer after treatment for infertility [letter]. *N Engl J Med*. 1995;332(19):1301.