



## Original Contribution

# Cancer Risk After Exposure to Treatments for Ovulation Induction

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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

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**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  |
|-------------------------------------|--------------------------------|---|--|------------------------------|--------------------------------|---------------------|---|
| <i>Ovarian Cancer</i>               |                                |   |  |                              |                                |                     |   |
| 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   |
| <i>Breast Cancer</i>                |                                |   |  |                              |                                |                     |   |
| 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 gonadotropins; 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  $\geq 25$ .

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<br>(n = 14,463) |    | Type of Ovulation Induction Treatment |    |                         |    |
|---|------------------------------|----|---------------------------------------|----|-------------------------|----|
|   |                              |    | Any Type<br>(n = 567)                 |    | Clomiphene<br>(n = 362) |    |
|   | No.                          | %  | No.                                   | %  | No.                     | %  |
| Mean age at subcohort entry, years  | 27.5 (5.4) <sup>a</sup>      |    | 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 <sup>b</sup>   |                              |    |                                       |    |                         |    |
| 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 <sup>c</sup>   | 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 <sup>d</sup>  | 1,377                        | 10 | 151                                   | 27 | 106                     | 29 |
| Mechanical treatment/assessment (tubal insufflation, dilation and curettage, other) | 238                          | 2  | 263                                   | 46 | 158                     | 44 |

<sup>a</sup> Numbers in parentheses, standard deviation.

<sup>b</sup> Number of children at the end of data collection.

<sup>c</sup> Weight (kg)/height (m)<sup>2</sup>.

<sup>d</sup> 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 <sup>a</sup> | 95% CI      | No. of Cases | HR <sup>a</sup> | 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.

<sup>a</sup> 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 <sup>a</sup> |             | Model 2 <sup>b</sup> |             | 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 <sup>c</sup>    | 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 <sup>c</sup>    | 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.

<sup>a</sup> Results were adjusted for age, socioeconomic status, country of birth, and body mass index.

<sup>b</sup> Results were adjusted for family size in addition to the variables included in model 1.

<sup>c</sup> 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 ra-

tios 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<sup>a</sup>

| Cancer Site          | Results Presented in Table 4<br>(Model 2) |             |         | Sensitivity Analysis                                    |             |         |
|----------------------|---|-------------|---------|---|-------------|---------|
|                      | HR  | 95% CI      | P Value | HR  | 95% CI      | P Value |
|                      | <i>Any Type of Treatment</i>              |             |         | <i>Clomiphene and/or Human Menopausal Gonadotropins</i> |             |         |
| All sites            | 1.36                                      | 1.06, 1.74  | 0.017   | 1.35  | 1.01, 1.80  | 0.042   |
| Uterus               | 3.39 <sup>b</sup>                         | 1.28, 8.97  | 0.014   | 3.82 <sup>b</sup>                                       | 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   |
|                      | <i>Clomiphene</i>                         |             |         | <i>Clomiphene and/or Unknown</i>                        |             |         |
| All sites            | 1.35                                      | 0.99, 1.84  | 0.060   | 1.42  | 1.08, 1.86  | 0.013   |
| Uterus               | 4.56 <sup>b</sup>                         | 1.56, 13.34 | 0.006   | 4.32 <sup>b</sup>                                       | 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.

<sup>a</sup> In all models, results were adjusted for age, geographic origin, socioeconomic status, body mass index, and parity.

<sup>b</sup> 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 gonadotropins, 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.

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