Effects of fertility drugs on cancers other than breast and gynecologic malignancies

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Objective: To examine the relationship of ovulation-stimulating drugs to risk of cancers other than breast and gynecologic malignancies.
Design: Retrospective cohort study, with additional follow-up since initial report.
Setting: Reproductive endocrinology practices.
Patient(s): Among a cohort of 12,193 women evaluated for infertility between 1965 and 1988, a total of 9,892 women (81.1% of the eligible population) were followed through 2010, via passive and active (questionnaire) approaches.
Intervention(s): None.
Main Outcome Measure(s): Hazard ratios (HRs) and 95% confidence intervals (CIs) for various fertility treatment parameters for select cancers.
Result(s): During 30.0 median years of follow-up (285,332 person-years), 91 colorectal cancers, 84 lung cancers, 55 thyroid cancers, and 70 melanomas were diagnosed among study subjects. Clomiphene citrate (CC), used by 38.1% of patients, was not associated with colorectal or lung cancer risks, but was related significantly to melanoma (HR = 1.95; 95% CI: 1.18–3.22), and non-significantly to thyroid cancer risks (HR = 1.57; 95% CI: 0.89–2.75). The highest melanoma risks were seen among those with the lowest drug exposure levels, but thyroid cancer risk was greatest among the heavily exposed patients (HR = 1.96; 95% CI: 0.92–4.17 for those receiving >2,250 mg). Clomiphene citrate–associated risks for thyroid cancer were somewhat higher among nulligravid, compared with gravid, women, but did not differ according to distinct causes of infertility. Gonadotropins, used by only 9.7% of subjects, were not related to risk of any of the assessed cancers.
Conclusion(s): Our results provide support for continued monitoring of both melanoma and thyroid cancer risk among patients receiving fertility drugs. (Fertil Steril® 2015;104:980–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Cancer, risk, infertility, clomiphene citrate, gonadotropins

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Much attention has been focused on whether use of ovulation-stimulating drugs can have an effect on malignancies of the breast, endometrium, ovary, or cervix (1), but little attention has centered on whether these drugs have relationships with other cancers. Several other cancers have been indicated to be influenced by hormonal factors, including colorectal, lung, and thyroid cancers, and melanomas (2–5). However, only a few studies have attempted to assess whether fertility drugs are related to these tumors, with imprecise results, most likely reflecting incomplete information regarding exposures of interest, or relatively small numbers of appropriate study subjects.

Although several case series have suggested potential links of fertility drugs with development of melanomas (6, 7), epidemiologic studies have

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produced conflicting results. Further, in most studies that have reported positive associations, risks have been limited to subgroups defined by reproductive history (8–12), raising questions as to whether indications for drug usage may have contributed. Several investigations have suggested that fertility drugs may increase the risk of thyroid cancers (8,13–15), again, possibly among only select subgroups defined by parity status (8, 13). Fertility drug use has not been related to either colorectal (8, 16, 17) or lung (16, 18) cancers, although the number of relevant investigations for both cancer sites has been limited. Thus, results regarding fertility drug associations with this collection of tumors are not consistent, and may vary by indications for drug usage, including reproductive characteristics of the participants.

In a large follow-up study of women evaluated and treated for infertility beginning in the early 1960s, we had the opportunity to assess drug relationships, capitalizing on an extensive collection of data on various treatments, indications for use (i.e., causes of infertility), and other cancer risk factors. In initial analyses, with 20 years of average follow-up, we previously addressed the relationship of fertility drugs to the risk of developing some of these rarely studied cancers, although with limited power to detect drug effects (8). In an extended follow-up, to an average of 30 years, we were better able to assess these relationships. We have recently evaluated associations of fertility drugs with cancer of the breast (19), endometrium (20), and ovary (21). Herein, we address updated data on associations of these drugs with some of the rarer cancers, including colorectal, lung, and thyroid cancers and melanomas. These types of cancer are of particular interest given the suggestion that they may be influenced by hormonal exposures.

MATERIALS AND METHODS

Study Subject Eligibility

Study subjects were women who had sought infertility advice at some point between 1965 and 1988, at any of 5 reproductive endocrinology practices in Boston, MA; Chicago, IL; Detroit, MI; Palo Alto, CA; and New York City, NY. These practices were chosen because they retained all records and evaluated large numbers of infertility patients, many of whom received high doses of ovulation-stimulating drugs. This study was approved by institutional review boards at the National Cancer Institute and the participating institutions.

Patients were eligible for study if they had a US address at first evaluation and were seen more than once or had been referred by another physician who provided relevant medical information. Patients with either primary or secondary infertility were eligible, but those evaluated for reversal of a tubal ligation were not. A total of 12,193 patients met the eligibility criteria.

Trained personnel abstracted data regarding the infertility workup (all procedures and tests), medications prescribed, menstrual and reproductive histories, and other factors that might affect health (e.g., weight). Information on the clinical workup was used to define causes of infertility, as previously described (22).

Follow-Up of Patients

An initial attempt at follow-up was pursued during the period 1998–2001 (8). Because of the relatively young age of the patients at that time, a second follow-up attempt was initiated in 2010. Follow-up procedures included searches for deaths and updated addresses through several publically available and proprietary databases (Social Security Administration Death Master File; MaxCOA, a change of address service; LexisNexis, a legal database service; US Postal Service National Change of Address, and the Centers for Disease Control and Prevention National Death Index). Attempts were made to mail a short questionnaire to located subjects who did not expressly indicate that they wanted no further follow-up. This questionnaire focused on the development of cancers and cancer-risk factors that might have changed over time (e.g., reproductive and menopause status).

In addition to information on cancers identified through death records and completed questionnaires, we completed linkages by using cancer registries in the 14 states in which the majority of patients resided (AZ, CA, CT, FL, IL, IN, MA, MI, NH, NJ, NY, OH, PA, and TX). For the 12.4% of patients who resided outside of these states, outcome information was dependent on completed questionnaires, with attempts to validate any self-reports of cancers by requesting records from the patients' treating physicians. Another Social Security Administration Death Master File search was completed at the end of the study in 2010 to identify new deaths.

The flowchart for inclusion and exclusion of study subjects is shown in Figure 1. Excluded were the 1,319 patients who requested no additional follow-up; 8 who were enrolled twice; 6 who were found to be aged <18 years; 1 who requested removal from the study; and 1 with a missing date of birth. We were able to obtain information related to death, development of cancer, or date last known to be alive and free of cancer for 10,018 patients—all but 840 subjects (7.7%) of the remaining 10,858. Information on last-known vital status and the development of incident cancers through 2010 was available from completed questionnaires or cancer registry linkages for 9,404 patients, from earlier follow-up efforts for 469 patients, and from original clinic records available ≥ 1 year after the first infertility evaluation for 145 patients.

Analytic Approaches

Person-years were accrued beginning 1 year after the date of the first infertility evaluation at study clinics and continued through the earliest date of any occurrence of a primary cancer, death, date last known alive and free of cancer, or if vital status depended on cancer-registry linkage, a variable ending date, depending on when each registry had complete information (time range: 2008–2010). We excluded from analysis 15 patients who had missing information on a cancer diagnosis date, and 111 with <1 year of follow-up, leaving 9,892 analytic study subjects and 285,332 person-years of follow-up.

Information on clomiphene citrate (CC) and gonadotropins that was abstracted from medical records included age at first use, treatment cycles, and total cumulative dosage. Race, gravidity and/or parity at study entry, causes of infertility, and body mass index (BMI) at study entry were defined through