Effects of Fertility Drugs on Cancers

Other than Breast and Gynecologic Malignancies

Running Title: *Fertility Drugs and Rarely Studied Cancers*

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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: Five U.S. reproductive endocrinology practices.

Patients: Among a cohort of 12,193 women evaluated for infertility between 1965 and 1988, 9,892 women (81.1% of the eligible population) were followed through 2010 via passive and active (questionnaires) approaches.

Intervention(s): None

Main Outcome Measure(s): Hazard ratios (HR) and 95% confidence intervals (CI) for different fertility treatment parameters for select cancers.

Results: 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, used by 38.1% of patients, was not associated with colorectal or lung cancer risks, but was related significantly to melanoma and non-significantly to thyroid cancer risks (respective HRs and 95% CIs of 1.95, 1.18-3.22 and 1.57, 0.89-2.75). The highest melanoma risks were seen among those with the lowest drug exposures, but thyroid cancer risk was most enhanced among the heavily exposed patients (HR=1.96, 0.92-4.17 for those receiving >2250 mg.). Clomiphene-associated risks for thyroid cancer were somewhat higher among nulligravid than 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 the assessed cancers.

Conclusions: Our results provide support for continued monitoring of risks of both melanoma and thyroid cancer risk among patients receiving fertility drugs.

Keywords: Cancer, risk, infertility, clomiphene citrate, gonadotropins

Capsule: Ovulation-stimulating drugs were unrelated to lung or colorectal cancer risks, but possibly related to slight increases for melanomas and thyroid cancers, supporting the need for further evaluation of these cancers.

Introduction

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

Although several case series have suggested potential links of fertility drugs with the development of melanomas (6;7)~~(6;7)~~, epidemiologic studies have produced conflicting results. Further, in most studies that have reported positive associations the risks have been limited to subgroups defined by reproductive history (8-12)~~(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)~~(8;13-15)~~, possibly again among only select subgroups defined by parity status (8;13)~~(8;13)~~. Fertility drug use has not been related to either colorectal (8;16;17)~~(8;16;17)~~ or lung (16;18)~~(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 totally 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 relations, capitalizing on extensive collected data on different treatments, indications for use (i.e., causes of

infertility), and other cancer risk factors. In initial analyses, which included approximately ~~xx~~20 years of follow-up, we previously addressed relations of fertility drugs to risk of some of these rarely studied cancers, although with limited power to detect drug effects (8)~~(8)~~. In extended follow-up, we had an enhanced ability to assess relations. We have recently evaluated associations with breast (19), endometrial (20) and ovarian (21) cancers, and herein address updated associations with some of the rarer cancers, including colorectal, lung, and thyroid cancers and melanomas--cancers of interest given suggestions that they also might be influenced by hormonal exposures.~~, capitalizing on extensive collected data on different treatments, indications for use (i.e., causes of infertility), and other cancer risk factors.~~

Materials and Methods

Study Subject Eligibility

Study subjects were women who had sought infertility advice between 1965-1988 at five 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 had 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 U.S. 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 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)~~(19)~~.

Follow-up of Patients

An initial attempt at follow-up was pursued during 1998-2001 (8)~~(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, SSA DMF; MaxCOA, a change of address service; LexisNexis, a legal database service; U.S. Postal Service National Change of Address); and the Center for Disease Control 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 against cancer registries in the 14 states in which the majority of patients resided (Arizona, California, Connecticut, Florida, Illinois, Indiana, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania and Texas). 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 SSA DMF search was completed at the end of the study in 2010 to identify new deaths.

The flow chart for inclusion and exclusion of study subjects is shown in Figure 1. After excluding the 1,319 patients who requested no additional follow-up, 8 who were enrolled twice, 6 found to be <18 years of age, 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 alive and free of cancer for 10,018 patients—or all but 840 subjects (7.7%) of the remaining 10,858 study subjects. 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 information available one or more years after first infertility evaluation in their original clinic records for 145 patients.

Analytic Approaches

Person years were accrued beginning one year after the date of first infertility evaluation at study clinics and continued through the earliest date of any ~~cancer~~ 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 (range of 2008-2010). We excluded from analysis 15 patients with missing information on a cancer diagnosis date and 111 with less than one year of follow-up, leaving 9,892 analytic study subjects and 285,332 person-years of follow-up.

Information on clomiphene 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 also defined through clinic records. Other potential confounding factors were obtained through questionnaire data, supplemented, as appropriate, by information in clinic records. The 1998-2001 questionnaire obtained extensive information on menstrual and reproductive history; use of exogenous hormones; anthropometric factors; cigarette smoking; and alcohol consumption. The

2010 questionnaire obtained updated information on reproductive history, body size, gynecologic operations, and use of menopausal hormones. Questionnaires were obtained from 6,756 patients (68.3% of the analysis subjects); 5,511 completed the 1998-2001 questionnaire and 4,824 the 2010 questionnaire (3,579 completed both).

Statistical Analyses

Hazard rate ratios (HRs) and 95% confidence intervals (CIs) associated with fertility treatments, with adjustment for study site, calendar year of first infertility evaluation and gravidity at first clinic visit, for the various cancers were obtained using Cox proportional hazards regression with age as the time metric. We considered the impact on risk of a variety of additional potential confounding factors, including race, age at first birth, gravidity and parity at follow-up, age at menarche, use of exogenous hormones (including years of use), BMI at first clinic visit, cigarette smoking, and various causes of infertility. For causes of infertility, we adjusted for multiple non-mutually exclusive causes, including endometriosis, anovulation, tubal disease/pelvic adhesions, cervical disorders, uterine disorders and male factor problems. As we previously demonstrated (23), too few women were classified with polycystic ovarian disease to specifically adjust for this, although these would have been captured by the broader category of anovulation. The various adjustment factors that we considered~~; however, these~~ had minimal effects on drug relationships and we thus chose to present risks based on a parsimonious model. Missing information was assigned a separate level for each exposure and included in the models. Tests for linear trends across cycle and dose categories were calculated using an ordinal variable.

We also examined drug relations according to strata of several potential risk factors of interest, including age at follow-up, gravidity/parity at first clinic visit and at follow-up, and

causes of infertility. The latter parameters were of interest given that they could signal more resistant infertility or unique endogenous hormonal milieus with which exogenous hormonal exposures might interact. To test the significance of such interactions, we ~~We also~~ tested the assumption of proportional hazards for fertility treatments using the Wald test of interaction with the time-scale (continuous).

Results

Among the analytic cohort of 9,892 women, the mean age at first evaluation for infertility was 30.1 years. During a median of 30.0 years of follow-up, there were 91 colorectal cancers, 84 lung cancers, 55 thyroid cancers, and 70 melanomas that occurred among study subjects. The mean ages at diagnosis for these cancers were respectively 53.6, 55.9, 49.5, and 47.0 years.

An examination of risk factors for the cancer sites of interest showed few distinctive relationships with any of reproductive factors, including gravidity at first clinic visit or at follow-up, number of births at follow-up, age at first birth, or age at menarche, although nulliparous women were at a significantly reduced risk of lung cancer compared with women with first births that occurred prior to age 25 (Table 1). Somewhat, but non-significantly, higher risks of colorectal cancer were seen among obese women and smokers, whereas smoking was a significant risk factor for lung cancer (HR=3.61, 95% CI 1.76-7.36 for ever vs. never smoking). In terms of the various causes of infertility examined (endometriosis, anovulation, tubal diseases/pelvic adhesions, cervical and uterine disorders, male factor problems), the only one that was significantly related to risk of any of the cancers was that of tubal diseases/pelvic adhesions, which was related to a 58% increased risk of colorectal cancers (95% CI 1.00-2.50).

When we further interrogated relationships according to non-mutually exclusive causes of infertility among patients who did and did not have a history of a previous pregnancy at first clinic visit (primary vs. secondary infertility), we observed that the high risk of colorectal cancers associated with tubal disease/pelvic adhesions was restricted to gravid women (HR=2.11, 95% CI 1.15-3.88); this compared with a risk of 1.07 (95% CI 0.51-2.24 for tubal problems among nulligravid women (data not tabled). We also observed a higher risk of melanoma associated with anovulation among ever gravid as compared with nulligravid women (respective HRs and 95% CIs 1.84, 1.01-3.37 vs. 0.86, 0.34-2.17).

Clomiphene citrate, which was used by 38.1% of the study subjects, was unrelated to risk of colorectal or lung cancers, but was related to a significantly increased risk of melanomas (HR=1.95, 95% CI 1.18-3.22) and to a non-significantly increased risk of thyroid cancers (1.57, 0.89-2.75) (Table 2). The increased risk of melanoma was largely driven by high risks associated with use of <901 mg. (HR=2.35, 95% CI 1.28-4.33) and <6 cycles (2.11, 1.24-3.59) of clomiphene. Women who had been prescribed clomiphene prior to the age of 30 were also at a significantly increased risk (2.38, 1.34-4.23). For thyroid cancer, the largest increase in risk was observed for the most heavily exposed patients, with a risk of 1.96 (95% CI 0.92-4.17) for those receiving more than 2250 mg. (p_{trend}=0.06) and of 1.77 for those receiving 12 or more cycles (p_{trend}=0.14) of clomiphene. There was no consistent trend in thyroid cancer risk according to age at first use. For colorectal and lung cancers, the more detailed parameters of clomiphene use were not distinctively related to risk. These risks were unaltered by adjustment for additional risk factors, including for BMI and cigarette smoking for colorectal cancers and cigarette smoking for lung cancers.

Gonadotropins were unrelated to risk of any of the cancers, although only a relatively limited proportion of study subjects (9.7%) had been prescribed these drugs. As a result, when we examined risks according to whether patients had been prescribed both clomiphene and gonadotropins and compared these to women who had never received either drug we observed risks that were similar to those noted for clomiphene use alone.

We also examined whether the risks associated with clomiphene use were modified by patient characteristics, including age at follow-up, gravidity at first visit or follow-up, or causes of infertility (Table 3). Although the highest melanoma risk was observed for women 60 years of age at follow-up, this was based on a small number of exposed subjects and the risk was not statistically significant. Slightly higher clomiphene-associated risks was seen for thyroid cancer among women who were either nulligravid at first clinic visit or follow-up as compared to women ever gravid at either of these times (e.g., HRs and 95% CIs for clomiphene use were 2.07, 0.89-4.82 for those nulligravid at first visit vs. 1.28, 0.60-2.73 for ever gravid women). None of the clomiphene-associated risks defined by causes of infertility were significantly elevated, although a non-significantly elevated risk (HR=9.31, 95% CI 0.78-111.6, based on 5 exposed cases) was seen for melanomas among women with cervical disorders.

Discussion

In this retrospective cohort study of women treated with pre-*in vitro* fertilization (IVF) fertility drugs (mainly clomiphene and gonadotropins), we found some evidence that these drugs may impact cancers other than breast and gynecologic malignancies, although the results were

far from conclusive. Although there was no evidence of an effect of fertility drugs on colorectal or lung cancers, we were unable to completely exonerate effects on thyroid cancers and melanomas. For thyroid cancers, risks were most enhanced among those with the highest clomiphene exposures, but the risk was of borderline statistical significance. For melanomas, we observed a significant association with ever use of clomiphene, although this excess was primarily among women who received lower drug dosages, leading to questions as to the biologic plausibility of the relationship.

Of the malignancies we studied, the one that has received the most prior epidemiologic attention with respect to fertility drugs is that of melanoma. There is some biologic foundation for a potential association given the frequent development of melanomas during pregnancy (24)~~(20)~~ and an influence of reproductive factors, such as parity and ages at first birth, on subsequent cancer development (5;25-29)~~(5;21-25)~~. In addition, estrogen receptors have been identified in melanoma cells, as well as in melanocytic nevi (30)~~(26)~~. Further, certain hormonal preparations, including oral contraceptives and menopausal hormones, can result in hyperpigmentation (31)~~(27)~~, and some (32;33)~~(28;29)~~, although not all (25;34)~~(21;30)~~, studies suggest increased risks of melanoma associated with such drug usage. These relations have all raised concern regarding a potential impact of use of fertility medications, particularly since melanoma incidence rates have been increasing during the time that use of fertility drugs has escalated (35)~~(31)~~.

Although a number of investigations have assessed relations of fertility drug use with melanoma risk, the findings have been contradictory, with some finding no association (16-18;36;37)~~(16-18;32;33)~~, others reporting positive relations (8-12;38)~~(8-12)~~, and one finding a

reduced risk (39)~~(34)~~. The inconsistency of the results may reflect that many of the studies had small numbers of exposed cases or merely compared the incidence of melanoma among fertility drug users to that of the general population, precluding the ability to control for important confounders. In one of the largest investigations (38), there was some evidence of risk increases associated with multiple IVF cycles, although the relationship was not linear. In ~~one of the studies~~another study that found a positive association, it appeared that the increased risk might have occurred as a result of the indications for usage rather than that of drug exposure (11)~~(11)~~. However, in several other investigations, some results possibly warrant concern, including an increased risk for any drugs among parous women (9)~~(9)~~, for gonadotropins or GnRH agonists among parous women (10)~~(10)~~, and for clomiphene among persistently nulliparous women or those followed for long periods of time (8)~~(8)~~.

In the current study, we did not observe any substantial variation in drug associations for melanoma according to gravidity or parity, but did observe a significantly elevated risk of melanoma associated with ever use of clomiphene. The lack of association with more detailed parameters of exposure leads to questions regarding the biologic importance of the association, although this could just reflect limited numbers and an inability to derive meaningful results for these more detailed parameters. Our findings, the positive findings from other epidemiologic studies, and the biologic plausibility of an association suggest a need for further inquiries regarding effects of fertility drugs on melanoma risk. However, it will be important for such studies to be appropriately powered and to include information on multiple potential confounders. This includes some melanoma risk factors that have not been appropriately accounted for in most studies to date, such as skin type and history of sunlight exposure (40)~~(35)~~.

although such factors would operate as confounders only if they also were correlated with fertility drug exposures.

Concern over potential effects of fertility drugs on thyroid cancer has been prompted by its female predominance, relationships of risk with a variety of hormonal risk factors, and reports of recent increases in incidence (4)~~(4)~~. Further, some studies have shown that ovulation-stimulating drugs ~~have been shown to~~ increase serum thyroid stimulating hormone (TSH) and free thyroxine ~~levels~~ concentrations above those normally associated with pregnancy~~, leading to concerns regarding increased mitotic activity in thyroid follicular cells (36)~~ (41). Several case-control studies (14;42)~~(14;37)~~ and one meta-analysis (15)~~(15)~~ have assessed associations of thyroid cancer with fertility drug use, with a significant positive relation noted in one of these investigations (14)~~(14)~~. Findings from cohort studies, usually involving small numbers of cases, have largely been equivocal, with most finding no association (8;9;13;16;18;37)~~(8;9;13;16;18;33)~~. However, two investigations have suggested possible increases in risk among subgroups defined by parity (8;13)~~(8;13)~~, a not surprising finding given that both pregnancy and estrogens cause elevations in TSH levels (13)~~(13)~~. However, the two studies that have found modifying effects of parity on fertility drugs have been at odds, with one showing an enhanced relation among women with persistent nulliparity (8)~~(8)~~ and the other showing the association restricted to parous women (13)~~(13)~~. This latter study, which involved 29 thyroid cancer cases, also found some support for a possible adverse relation with progesterone use among parous women.

With 55 cases of thyroid cancer, our investigation was larger than previous studies, but was still quite limited in terms of its ability to evaluate fertility drug effects. Thus, although we

did not observe a statistically significant association of thyroid cancer with clomiphene use, our highest observed risks were among the most heavily exposed women. The association with clomiphene use was slightly stronger among nulligravid women, defined either at first clinic visit or at follow-up, supporting previous findings from this same cohort study (8)~~(8)~~. This might suggest an effect of the indications for usage rather than a drug effect, but we did not observe significant variations in clomiphene associations according to different causes of infertility. Thus, while our findings are suggestive of a possible relationship of fertility drugs to thyroid cancer risk, it is apparent that further investigation is warranted. Since medications have changed substantially in recent times, it will be important for investigations to consider not only effects of clomiphene and gonadotropins--as given as first line therapies--but also of drugs administered in conjunction with IVF. Such investigations are beginning to assess relations with cancers other than breast and gynecologic cancers, but still face substantial limitations in terms of samples sizes, particularly for rare tumors.

While there were some possible increases of both melanoma and thyroid cancer risks associated with fertility drug use, it was of interest that we did not observe major alterations in risk for two other cancers that have been suggested to be influenced by hormonal factors—colorectal and lung cancers, malignancies for which we had the ~~greatest statistical power to detect associations~~largest number of cases. Hormonal factors have been postulated to protect against the development of colorectal cancers, with reports from some recent investigations of inverse associations with parity (43)~~(38)~~, oral contraceptives (3;44;45)~~(3;39;40)~~, and menopausal hormones (46-48)~~(41-43)~~, although the results are not entirely consistent across studies. We thus might have expected to see a reduced risk of this cancers associated with fertility drug use, but similar to the other studies (8;16;17)~~(8;16;17)~~ in which relations have been assessed we saw no

alteration in risk. Similar to a few other studies (16;18)~~(16;18)~~, we also did not observe that fertility drugs were related to the risk of lung cancer, another malignancy that has been suggested to have hormonal influences (2;49-51)~~(2;44-46)~~.

In sum, in this large cohort of infertile women, we found generally reassuring results regarding potential effects of fertility drugs on the risk of colorectal and lung cancers. Although limited by small numbers, we could not completely exonerate these drugs from having potential effects on the risks of thyroid cancers and melanomas, supporting the need for further detailed investigations. Given that fertility drug usage is increasing and treatment regimens changing, it will be important to monitor future effects of treatment details in well-designed investigations that have sufficient power to assess both overall relationships as well as those within defined subgroups of users.

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Figure 1. Flow Chart of Inclusion and Exclusion of Study Participants.

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