

CORRESPONDENCE



RISK OF OVARIAN CANCER AFTER TREATMENT FOR INFERTILITY

To the Editor: The article by Rossing et al. (Sept. 22 issue)¹ may have generated undue anxiety in many women undergoing treatment for infertility. Although this study does prompt some interesting hypotheses about the future risks of ovarian cancer in patients with ovulatory dysfunction, it does not convincingly link any risk to the use of clomiphene. There are several confounding variables and biases that weaken the validity of the authors' conclusions.

Patients undergoing treatment for infertility, especially those who take medication to induce ovulation, undergo far more surveillance with ultrasound studies than other patients, solely because of their treatment. Furthermore, because of a suspicion bias, any abnormality in a clomiphene-treated patient will probably be evaluated more closely than would an ovarian mass in a patient in the general population.² The extremely high ratio of borderline tumors to invasive neoplasms identified in this study (5 of 11 neoplasms were borderline) gives strong evidence of a selection bias. This proportion is significantly higher than that usually found in the general population (approximately 1 in 10).³ Since borderline tumors are often asymptomatic, those detected in this study are probably attributable to the intensive screening these patients underwent.

Even more important than the extremely high ratio of borderline tumors to invasive neoplasms is the inclusion of two patients with granulosa-cell tumors. Granulosa-cell tumors of-

ten present with abnormalities of fertility and ovulation, and, as has been reported, they may have been the cause of the clomiphene treatment rather than its result.⁴ Given the small numbers of patients, excluding these two patients would further diminish the importance of this study.

The use of oral contraceptives is a major confounding variable in analyses of the development of ovarian cancer and is not addressed in this study. Oral contraceptives substantially decrease the risk of ovarian cancer even after only one year of use.⁵ The women undergoing infertility treatment are likely to have used contraception for less time than the women in the control groups. Other confounders, such as a family history of breast or ovarian cancer, though less important, are also not addressed.

Many of these questions might have been answered had the authors reported the tumor stages at diagnosis and the clinical context. If these characteristics differed substantially from those usually found in patients with ovarian neoplasms, then the conclusions would probably be due to unrecognized confounding variables and potential biases. We hope that this article leads to additional studies in this area. However, we believe that no changes in current practices are indicated on the basis of this report.

GIUSEPPE DEL PRIORE, M.D., M.P.H.

KATHLEEN ROBISCHON, M.D.

WILLIAM R. PHIPPS, M.D.

University of Rochester

Medical Center

Rochester, NY 14642

1. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331:771-6.
2. Feinstein AR. *Clinical epidemiology: the architecture of clinical research*. Philadelphia: W.B. Saunders, 1985.
3. Hart WR. Pathology of malignant and borderline (low malignant potential) epithelial tumors of ovary. In: Coppleson M, ed. *Gynecologic oncology: fundamental principles and clinical practice*. 2nd ed. Vol. 2. Edinburgh, Scotland: Churchill Livingstone, 1992:863-87.
4. Jansen R. Ovarian stimulation and granulosa-cell tumour. *Lancet* 1993;341:1345.
5. Herbst AL, Berek JS. Impact of contraception on gynecologic cancers. *Am J Obstet Gynecol* 1993;168:1980-5.

Instructions for Letters to the Editor

Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following:

- Your letter must be typewritten and triple-spaced.
- Its text, not including references, must not exceed 400 words (please include a word count).
- It must have no more than five references and one figure or table.
- It should not be signed by more than three authors.
- Letters referring to a recent *Journal* article must be received within four weeks of its publication.
- Please include your full address, telephone number, and fax number (if you have one).

You may send us your letter by post, fax, or electronic mail.

Our address: Letters to the Editor
New England Journal of Medicine
10 Shattuck St.
Boston, MA 02115

Our fax numbers: 617-739-9864 and 617-734-4457

Our Internet address: letters@edit.nejm.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. We are unable to provide prepublication proofs. Please enclose a stamped, self-addressed envelope if you want unpublished material returned to you.

Financial associations or other possible conflicts of interest must be disclosed. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various editions (print, data base, and optical disk) and in anthologies, revisions, and any other form or medium.

To the Editor: We were surprised to see a deviation from the accepted classification system in the article about the relation between an ovulation-inducing agent (clomiphene citrate) and ovarian tumors. In the Results section, the authors refer to two types of ovarian tumors that they identify as invasive or borderline malignant. They proceed to subclassify their five "borderline malignant" tumors into mucinous cystadenomas (two cases), papillary serous cystadenomas (two cases), and papillary mucinous cystadenomas of low malignant potential (one case).

The World Health Organization histologic classification of ovarian tumors considers the terms "borderline" and "low malignant potential" to be equivalent. These neoplasms are considered intermediate in their behavior between benign cystadenomas and frankly malignant invasive carcinomas. Accordingly, only one of the five cases reported by the authors as borderline is, in fact, borderline — the one reported as a "papillary mucinous cystadenoma of low malignant potential." The other four cases are benign neoplasms, and to include them in the "borderline" category is misleading. We question whether the conclusion that clomiphene citrate has an adverse effect in terms of the development of truly malignant or borderline ovarian tumors would still stand if these four benign ovarian cysts were excluded from the analyses.

ROBERT KURMAN, M.D.
EDWARD E. WALLACH, M.D.
HOWARD A. ZACUR, M.D., PH.D.
Baltimore, MD 21287-1201 Johns Hopkins University

To the Editor: In her editorial (Sept. 22 issue)¹ on the association between the use of fertility medications and ovarian cancer, Whittemore states that "concern about the risk of ovarian cancer associated with the use of fertility medications was heightened by . . . findings from a combined analysis" of three case-control studies.²⁻⁴ The authors of the three studies used in that analysis^{5,6} kindly provided me with the previously unpublished data shown in Table 1.

Various decision rules were applied to the pooled analysis (Hartge P: personal communication), and frankly invasive tumors² and tumors of low malignant potential³ were reported on separately. However, if the data are pooled for simplicity, then among 914 cases there was one exposure to clomiphene. As for the other drugs to which the patients were exposed, estrogens do not increase the risk of ovarian tumors, and when combined with progestogens they decrease it. Thyroid hormone and "speed" (dextroamphetamine and amobarbital) do not merit serious consideration; nor do unknown drugs, since the great majority of the women were treated in the early 1960s, when ovulation-inducing drugs were either unavailable (e.g., clomiphene) or hardly available (e.g., menotropins). Whatever the explanation is for the association described in the combined analysis,^{5,6} it was not due to clomiphene, and it is exceedingly unlikely that it could have been due to other fertility medications. The data give no grounds for heightened concern.

The validity of the findings of Rossing et al. is also in

Table 1. Use of Fertility Drugs in Three Case-Control Studies of Ovarian Cancer.*

DRUG	CASES				CONTROLS			
	HARTGE ET AL. (N = 296)	CRAMER ET AL. (N = 215)	NASCA ET AL. ¹ (N = 403)	ALL (N = 914)	HARTGE ET AL. (N = 343)	CRAMER ET AL. (N = 215)	NASCA ET AL. ¹ (N = 806)	ALL (N = 1364)
	no. with cancer		no. (%)		no. with cancer		no. (%)	
Clomiphene	1	0	—	1 (0.1)	0	1	—	1 (0.07)
Estrogens	3	1	—	4 (0.4)	1	0	—	1 (0.07)
Diethylstilbestrol	0	1	—	1 (0.1)	1	1	—	2 (0.1)
Estrogen and progestogen	0	1	—	1 (0.1)	1	0	—	1 (0.07)
Thyroid hormone	2	0	—	2 (0.2)	1	1	—	2 (0.1)
Dextroamphetamine and amobarbital	1	0	—	1 (0.1)	0	0	—	0
Unknown	4	0	6	10 (1.1)	3	0	1	4 (0.3)
All	11	3	6	20 (2.2)	7	3	1	11 (0.8)

*Data were obtained from the authors of the studies by Hartge et al.,² Cramer et al.,³ and Nasca et al.⁴

[†]The subjects in this study were asked whether they had been treated for infertility but were not asked the name of the medication.

doubt, because of the acknowledged potential sources of error and bias and for three additional reasons. First, epithelial and granulosa-cell tumors cannot be considered as a single outcome because their embryologic, pathological, and epidemiologic features differ. It is also questionable whether borderline and invasive tumors can be combined. Insufficient numbers of tumors were studied for the three outcomes to be considered separately. Second, 6 of the 11 patients (54 percent) had infertility associated with ovarian abnormalities that may themselves have increased the risk of ovarian cancer; precancerous disease could have "caused" clomiphene therapy, rather than the reverse. Finally, several inferences are based on small numbers and are thus unjustified. For example, the contrast between the receipt of clomiphene for 1 to 11 cycles as compared with 12 or more cycles is based on three and five patients with exposure, respectively, yielding markedly unstable estimates of relative risk of 0.8 and 11.1. This difference was interpreted as substantive when it could easily have been due to chance ($P > 0.1$).

There are legitimate grounds for concern that fertility medications may increase the risk of ovarian cancer, and the matter is being studied. To date, however, the quantitative evidence to support that concern consists of equivocal data from a single study.

SAMUEL SHAPIRO, M.B., F.R.C.P.(E.)
Boston University
School of Medicine
Brookline, MA 02146

- Whittemore AS. The risk of ovarian cancer after treatment for infertility. *N Engl J Med* 1994;331:805-6.
- Hartge P, Schiffman MH, Hoover R, McGowan L, Leshner L, Norris HJ. A case-control study of epithelial ovarian cancer. *Am J Obstet Gynecol* 1989; 161:10-6.
- Cramer DW, Hutchison GB, Welch WR, Scully RE, Ryan KJ. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. *J Natl Cancer Inst* 1983;71:711-6.
- Nasca PC, Greenwald P, Chorost S, Richart R, Caputo T. An epidemiologic case-control study of ovarian cancer and reproductive factors. *Am J Epidemiol* 1984;119:705-13.
- Whittemore AS, Harris R, Itnyre J, Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:1184-203.
- Harris R, Whittemore AS, Itnyre J, Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential in white women. *Am J Epidemiol* 1992;136:1204-11.

The authors reply:

To the Editor: We agree with Dr. Shapiro that our findings are limited by the small number of tumors that developed in the study cohort, which points to the need for larger studies of this possible association. However, we observed an increased risk of an ovarian tumor associated with the use of clomiphene during 12 or more menstrual cycles, among women either with or without a known ovarian abnormality; this finding suggests that the association is not entirely attributable to the presence of ovarian disease that leads to clomiphene use.

Although Dr. Del Priore et al. note that the ratio of borderline tumors to invasive ovarian cancers is approximately 1:10 among the general population of women, borderline tumors constitute a much higher proportion of the tumors diagnosed in women in the age range of our study population. On the basis of data from the Cancer Surveillance System of western Washington State from 1989 through 1992, 43 percent of the ovarian tumors reportable to the Surveillance, Epidemiology and End Results program of the National Cancer Institute among women 20 to 50 years of age were borderline tumors. Also, although ultrasound screening during infertility treatment could potentially have resulted in the diagnosis of borderline tumors that might otherwise have remained occult, such screening does not appear to account for our study findings: 9 of the 11 women in whom ovarian tumors developed were no longer being treated for infertility at the time of the tumor diagnosis. If we eliminate women with granulosa-cell tumors from our analyses, the elevated risk associated with exposure to 12 or more cycles of clomiphene, though reduced, remains quite high (relative risk, 6.7; 95 percent confidence interval, 0.8 to 58.8). Although uncontrolled confounding by factors such as oral-contraceptive use may have influenced our results, we believe such confounding is not likely to be present to any important degree, because the comparisons were made within the study cohort of women evaluated for infertility.

Finally, we thank Dr. Kurman and colleagues for the opportunity to clarify our description of the histologic features of borderline tumors. The problematic phrase should have read: "Two mucinous cystadenomas, two papillary serous cystadenomas, and one papillary mucinous cystadenoma, each of low malignant potential."

MARY ANNE ROSSING, D.V.M., PH.D.

JANET R. DALING, PH.D.

NOEL S. WEISS, M.D., DR.P.H.

Fred Hutchinson Cancer
Research Center

Seattle, WA 98104

To the Editor: In attempting to piece together more precise information on fertility drugs from three studies included in the analysis by our Collaborative Ovarian Cancer Group,¹ Shapiro has incorrectly inferred the specific numbers of subjects using fertility-drug therapy, because he did not follow our rules for the exclusion of subjects. Four of the case patients included in his table (three studied by Hartge et al. and one studied by Cramer et al.) had borderline tumors and were excluded from our analysis of invasive ovarian cancers. Nor did we count as exposed the one case patient (and one control) in the study by Cramer et al. who used diethylstilbestrol only during a pregnancy, or the one case patient studied by Hartge et al. who did not see a physician for her infertility. Thus, these two studies contributed 8 exposed case patients with invasive ovarian cancer, whereas Nasca et al. contributed

12 case patients (not 6). In addition, many of the controls who had undergone hysterectomy in each of the three studies were excluded because of the uncertain status of their ovaries. (All the exclusion rules applicable to all subjects, regardless of disease or exposure status, were determined by the investigators before the start of any analyses.) As a result, the total number of controls used in our study was 1101, not 1364 as indicated by Shapiro, and the number of exposed controls was 5 in the studies by Hartge and Cramer and 6 in that by Nasca. Thus, the majority of the exposed case patients and controls were contributed by the study by Nasca et al., in which information on the specific fertility drugs used was not requested. In all, 16 of the 20 exposed case patients either were not asked or could not recall the medications they used, and 12 of these women were not asked when they used them.

Overall, fertility-drug treatment was reported by 20 of 622 case patients with invasive ovarian cancer (3.2 percent), as compared with 11 of 1101 controls (1.0 percent) — a significant difference that continues to be the basis of our concern about such exposure in relation to the risk of ovarian cancer. At this point, we do not think that ad hoc reanalyses of the data (especially those done without knowing the details of the study) are of particular use in addressing what, in Shapiro's own words, are "legitimate grounds for concern that fertility medications may increase the risk of ovarian cancer."

DANIEL W. CRAMER, M.D.

Boston, MA 02115

Brigham and Women's Hospital

PATRICIA HARTGE, SC.D.

Rockville, MD 28092

National Cancer Institute

PHILIP C. NASCA, PH.D.

Amherst, MA 01003

University of Massachusetts

ALICE S. WHITTEMORE, PH.D.

Stanford, CA 94305

Stanford University
School of Medicine

- Whittemore AS, Harris R, Itnyre J. Collaborative Ovarian Cancer Group. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am J Epidemiol* 1992;136:184-203.
- Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;331:771-6.

NIFEDIPINE IN SEVERE AORTIC REGURGITATION

To the Editor: It is unfortunate that Scognamiglio et al. (Sept. 15 issue)¹ chose to use digoxin instead of placebo to study the effects of nifedipine in asymptomatic patients with chronic, severe aortic regurgitation. Almost two decades since the short-term beneficial effects of vasodilator therapy in severe aortic regurgitation were first reported,² clinicians still await proof that vasodilator therapy reduces or delays the need for aortic-valve replacement in asymptomatic patients with severe, chronic aortic regurgitation. Although some authors^{3,4} have promoted the routine use of vasodilators to delay the need for valve replacement in these patients, an informal survey we made recently showed that most Canadian cardiologists (88 percent of those surveyed) do not use vasodilators for this purpose. None of those surveyed use digoxin in this setting.

The proper way to test whether nifedipine delays the need for surgery is to compare nifedipine therapy with conventional therapy. Conventional routine therapy in asymptomatic patients with chronic aortic regurgitation does not include digoxin. It is interesting that in an earlier study⁴ the same au-