POLYCYSTIC OVARY SYNDROME

Cancer risk among infertile women with androgen excess or menstrual disorders (including polycystic ovary syndrome)

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Objective: To define relationships of androgen excesses to cancer risk.
Design: Retrospective cohort study.
Setting: Five large infertility practices.
Patient(s): Among 12,193 women evaluated for infertility during 1965–1988 and traced for cancer incidence through 1999, 2,560 had androgen excess or menstrual disorders; among these, 412 met established criteria for polycystic ovary syndrome.
Intervention(s): None.
Main Outcome Measure(s): Cancer incidence. Derivation of standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for cancer risk comparisons with the general population and rate ratios (RRs) for comparisons with other infertility patients.
Result(s): Androgen excess/menstrual disorder patients showed significant SIRs for breast (1.31; 95% CI, 1.05–1.62) and uterine (2.02; 95% CI, 1.13–3.34) cancers and melanoma (1.96; 95% CI, 1.12–3.18). Significant associations for breast and uterine cancers were restricted to primary infertility patients (respective SIRs of 1.53 and 3.48). After adjustment for other cancer predictors, the only excess risk was for uterine cancer among primary infertility patients. Compared with women with secondary infertility and no androgen excess/menstrual disorder, those with primary infertility and a disorder had an RR of 1.88 (95% CI, 0.82–4.32). Cancer risks among the women with polycystic ovary syndrome or androgen excess disorders appeared to be similar to those in the more comprehensive group.
Conclusion(s): Previous findings linking androgen excess disorders to elevated uterine cancer risks might largely reflect underlying risk profiles. (Fertil Steril 2010;94:1787–92. ©2010 by American Society for Reproductive Medicine.)

Key Words: Androgen excess, PCOS, uterine cancer, breast cancer, ovarian cancer, risk

Although the effects of estrogens on female cancers are well recognized, the role of other hormones is less clear. Recent interest has focused on the role of androgens (1), which might affect uterine and breast cancers as well as other cancers.

A variety of conditions are associated with androgen excess, the best known of which is polycystic ovary syndrome (PCOS), a condition affecting 3–5% of reproductive-age women (2, 3). The clinical manifestations of PCOS are diverse and include menstrual dysfunction, hirsutism, acne, obesity, and the metabolic syndrome. The condition is a frequent cause of hyperandrogenism, oligoovulation, anovulation, and abnormal insulin activity. The definition of PCOS has been controversial (4), although recently developed criteria (5) have allowed progress in understanding its etiology and clinical associations.

A number of clinical reports (6, 7) have noted a link between PCOS and endometrial cancer, with additional support deriving from a limited number of epidemiologic investigations (8–12). However, most of these studies have limited numbers of patients or imprecise diagnostic criteria. Only a few studies have assessed relationships of androgen disorders to ovarian (13, 14) or breast (12, 13, 15–18) cancers. We took advantage of precise clinical workups among a large series of infertility patients to assess cancer risk associated with PCOS and androgen excess or menstrual disorders.

MATERIALS AND METHODS

Study Subject Eligibility

This study was reviewed by institutional review boards at the National Cancer Institute and the participating institutions. We identified 12,193 patients who had sought advice for primary or secondary infertility at five large practices in...
During 2000–2002, attempts were made to locate study subjects and ascer-
tain updated health status (Fig. 1). Various sources were used to trace patients
and identify occurrences of cancer, with 2,442 (20.0%) lost to follow-up. In-
formation on cancers was obtained through completed questionnaires as well
as linkages against the National Death Index and eight cancer registries in
states where many patients resided (California, Florida, Illinois, Massachu-
setts, Michigan, New Jersey, New York, and Texas).

A total of 1,151 (11.8%) of the located patients indicated that they did not
want to participate in the study or allow use of their medical record data. Of
the remaining patients, 168 patients did not live in cancer registry states and
we were unable to determine updated health information through other sour-
ces, 272 patients had died, 5,597 completed questionnaires, 216 continued
receiving care at the institutions where they were evaluated for infertility,
and 2,347 were linked against state cancer registries.

In addition to updated health status, the questionnaires collected informa-
tion on demographic factors and lifestyle factors that could affect health,
including menstrual and reproductive history, use of exogenous hormones,
anthropometric factors, cigarette smoking, alcohol consumption, and screen-
ing for breast and ovarian diseases.

### Analytics Dataset

Person-years, an individualized measurement of follow-up time, were
accrued beginning one year after the date of first evaluation for infertility
and continuing through the earliest date of cancer occurrence, death, the
date last known alive and free of cancer, or December 31, 1999. Patients
whose vital status depended on linkage against a cancer registry were
assigned variable study end dates, depending on when each registry had com-
plete information (range of 1997–1999). We eliminated 10 patients with
a cancer diagnosis during the first year of follow-up, leaving 8,422 analytic
study subjects and 155,624 person-years of follow-up.

We used Rotterdam criteria (5) to define a subcohort of women with PCOS
based on the presence of two or more of the following: [1] oligoovulation or
anovulation, [2] clinical and/or biochemical signs of hyperandrogenism (not
caused by a specific disorder such as adrenal disease), or [3] polycystic
ovaries.

Although large numbers of our patients were oligoovulatory or anovula-
tory (19), few had hyperandrogenism (as defined on the basis of hirsutism
or total T levels > 75 ng/dL or free T levels > 7.3 pg/mL) or polycystic ova-
ries (defined by laparoscopy or laparotomy rather than by ultrasound). Only
412 women met the Rotterdam criteria for PCOS. We therefore expanded this
cohort to include women who had hyperandrogenism or polycystic ovaries
(androgen excess disorders). We also used a wider definition in which we
included all women whose records indicated that they had any one of the
criteria (androgen excess or menstrual disorders).

### Statistical Analyses

We calculated standardized incidence ratios (SIRs) and 95% confidence inter-
vals (CIs) comparing cancer incidence rates within each cohort with US rates.
SIRs were computed as the number of observed cancers among the patient
subgroups divided by the expected events based on age, race, and calendar
year–specific disease incidence rates from the Surveillance Epidemiology
and End Results Program of the National Cancer Institute (NCI).
The patients who had androgen excess disorders, although the SIRs were based on small numbers and not statistically significant. Non-significant elevations in risk were also seen for thyroid cancer (SIR, 2.68; 95% CI, 0.87–6.27; five cases) and lymphatic tumors (SIR, 1.99; 95% CI, 0.64–4.64; five cases). No increased risk of breast cancer was seen for these patients.

SIRs were also examined among the relatively small group of patients (n = 412) who met established criteria for PCOS. The risk for uterine cancer was consistent with that among the patients with androgen excess or menstrual disorders (SIR, 1.91; 95% CI, 0.2–6.0; based on two cancers) (data not shown). There was no evidence of elevated breast cancer risk among the patients with PCOS (SIR, 0.90; 95% CI, 0.4–1.7; based on nine breast cancers).

Significant increases in the risk of breast and uterine cancers were restricted to patients with primary infertility (no previous pregnancies; breast cancer: SIR, 1.53; 95% CI, 1.10–2.08; uterine cancer: SIR, 3.48; 95% CI, 1.66–6.40). Ovarian cancer was elevated among patients with secondary infertility (SIR, 2.18; 95% CI, 0.99–4.14), but not among those with primary infertility. Approximately twofold nonsignificant increases in melanoma risk were seen among both primary and secondary infertility patients.

We also examined cancer incidence among the patients with androgen excess disorders, although the number of events limited interpretation of most risks. Such patients with primary infertility demonstrated increased risks of both uterine cancer (SIR, 3.03; 95% CI, 0.61–8.85) and melanoma (SIR, 2.47; 95% CI, 0.50–7.22).

In internal analyses, the highest, albeit nonsignificant, RRs for the patients with androgen excess or menstrual disorders were seen for uterine cancer (RR, 1.33; 95% CI, 0.69–2.58) and melanoma (RR, 1.27; 95% CI, 0.67–2.40; Table 3). The increased risk of uterine cancer was somewhat attenuated after adjustment for BMI (RR, 1.17; 95% CI, 0.60–2.28). Similar RRs were seen for these two cancer sites (and for uterine cancer after adjustment for BMI) when only patients with androgen excess disorders were considered. These patients also demonstrated a statistically significantly elevated risk of thyroid cancer (RR, 3.64; 95% CI, 1.24–10.63), although this finding is based on only five observed cases.

We also calculated risks in reference to women who should have been at lowest risk—that is, those with secondary infertility and no evidence of a disorder (Table 4). For uterine cancer, the RR among women with primary infertility and androgen excess or menstrual disorders was somewhat elevated, but not significantly (RR, 1.88; 95% CI, 0.82–4.32). A similar increased risk was seen among

<table>
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</table>

a Patients who met defined criteria for PCOS according to Rotterdam criteria (n = 412). Patients with androgen excess disorder include those with PCOS plus those with androgen excesses (n = 855). Patients with androgen excess or menstrual disorder include all of the above-mentioned patients plus those with menstrual disorders (n = 2,560).
patients with androgen excess disorders, although the RR of 1.78 was based on only three cases. Breast cancer risk was fairly uniform across the four exposure levels, defined by type of infertility and endocrinologic abnormality, regardless of whether the focus was on patients with androgen excess or menstrual disorders or only those with androgen excess disorders.

**DISCUSSION**

Patients with PCOS have been shown to have an increased risk of type 2 diabetes and cardiovascular diseases, but effects on other chronic diseases, including cancer, remain unresolved (24, 25). Our study demonstrates the difficulty of studying the relationship of PCOS to cancer, given that only 4.9% of our patients met Rotterdam criteria (5), a rate lower than might be expected among infertility patients. Although we expanded the PCOS group to include patients with hyperandrogenism or polycystic ovaries, this only slightly increased numbers. Therefore, we added patients with oligoovulation or anovulation, recognizing that this might have led to an inclusion of endocrinologic abnormalities that are not androgen-related. Nonetheless, this approach undoubtedly is superior to previous epidemiologic studies that have relied on patients’ reports of PCOS.

Many clinical studies have noted high rates of endometrial cancer among patients with PCOS (6, 7, 26–30), with particularly high risks...
often noted among younger women (26, 28, 29); however, few epidemiologic investigations have evaluated relationships. Coulam associated with chronic anovulation, whereas Wild et al. (12) found self-reports of PCOS (9, 11, 32). have also been noted in case-control studies that have involved ovulation type II ovulatory disorders (mainly PCOS). Elevated risks found twofold to threefold risks associated with World Health Organization type II ovulatory disorders (mainly PCOS). Elevated risks have also been noted in case-control studies that have involved self-reports of PCOS (9, 11, 32).

Comparisons based on the general population are difficult to interpret, given that patients with ovulatory disorders often have risk factors that place them at an inherently high risk of cancer (33). Our internal analyses, which allowed for adjustment for many of these factors, including obesity, found only a nonsignificant 17% elevated uterine cancer risk. Differences in the magnitude of risk between the external and internal analyses suggest that the apparent excess uterine cancer risk previously ascribed to PCOS or androgen excess disorders may be due to shared risk factors. In fact, given that we had only limited information on obesity (including no data on changes in weight over time), we cannot rule out that all of the increased risk was attributable to obesity. However, it was of interest that the highest, albeit nonsignificant, risk of uterine cancer was among patients with primary infertility, possibly indicating that only the more severe forms of these disorders predispose to uterine cancer.

Although a high risk of breast cancer mortality has been noted among patients with polycystic ovaries (18), we did not find breast cancer incidence to be elevated among any of our subcohorts. Results from previous epidemiologic studies have ranged from increased risk (34) to no association (15, 17) to possible reductions in risk (16), possibly reflecting divergent use of disease definitions. In one cohort study, the self-reported prevalence of Stein-Leventhal syndrome was 1.35% (15), whereas 4.9% of breast cancer cases reported having PCOS in a case-control study (16). In this latter study, PCOS was associated with a significantly reduced risk, possibly reflecting the widespread use of wedge resections for treatment of PCOS in the 1970s (35), a procedure that could have altered ovarian hormone secretion. Chance findings are also a possibility given small numbers involved.

A potential role for androgen disorders in ovarian carcinogenesis has been postulated (36), although few epidemiologic studies have been undertaken. Our initial findings of elevated ovarian cancer risk when comparisons involved the general population were not supported by more detailed internal analyses. One study noted a positive association between acne or hirsutism and risk, although the finding was based on small numbers (37). Two more recent studies have also reported positive relationships, although in one the increased risk was restricted to nonusers of oral contraceptives or thin women (14), and the other pertained only to the development of borderline serous cancers (38). The results must also be cautiously interpreted, given that self reports of polycystic ovarian disease were involved. The possibility of confounding by infertility treatment has also been acknowledged (14).

Our study had some limitations, including the fact that disorders were determined during a time when newer classification modalities (e.g., androgen assays) were generally unavailable, and we had no ability to update information beyond the time of the initial infertility evaluation. Whether our results are generalizable to women other than infertility patients must also be questioned. Further, our results might have been affected by residual confounding, either by factors that we were unable to completely measure (e.g., obesity) or by other factors for which we had no information, such as diabetes and metabolic syndrome.

In summary, we observed only an increased risk of uterine cancer associated with androgen excess and menstrual disorders, but much of the excess appeared to reflect shared characteristics between the two diseases. Although we were unable to extensively consider cancer risks in patients meeting strict criteria for PCOS, it appears from our findings that their cancer risks should not substantially exceed those of patients with broader definitions of androgen excess disorders.

Acknowledgments: We thank Jerome Mabie (IMS, Inc., Rockville, MD) for assistance with computer analyses.
REFERENCES


