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A BRIEF ORIGINAL CONTRIBUTION

Polycystic Ovaries and the Risk of Breast Cancer

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Data from a case-control study that was conducted between 1980 and 1982 were analyzed to investigate the possible association between polycystic ovaries and the risk of breast cancer. The multicenter, population-based study included in-home interviews with 4,730 women with breast cancer and 4,688 control women aged 20–54 years. The age-adjusted odds ratio for breast cancer among women with a self-reported history of physician-diagnosed polycystic ovaries was 0.52 (95% confidence interval 0.32–0.87). The inverse association was not an artifact of infertility, age at first birth, or surgical menopause. Because women with this syndrome have abnormal levels of certain endogenous hormones, the observation of a low risk of breast cancer in this group may provide new insights into hormonal influences on breast cancer. *Am J Epidemiol* 1991;134:818–24.

breast neoplasms; polycystic ovary syndrome

In a retrospective cohort study reported in 1983 (1), over a threefold significant increase in postmenopausal breast cancer was noted among women who had been previously diagnosed with polycystic ovaries. Since publication of the article, some clinicians have advocated aggressive hormone treatment for these women to induce ovulation and fertility, reduce hirsutism, and act as a prophylaxis against endometrial and breast cancer (2).

The classical definition of polycystic ovary syndrome, first described by Stein and Leventhal in 1935 (3), includes enlarged ovaries along with menstrual irregularities, hirsutism, and obesity. Current data show that of women with polycystic ovaries, 74 percent are infertile, 69 percent have hyper-

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androgenization, 51 percent are amenorrheic, and 41 percent are obese (4). Treatment often includes weight reduction, if appropriate, and oral contraceptives or other estrogen-progestogen regimens.

Polycystic ovaries are associated with abnormally high levels of luteinizing hormone, androstenedione, and testosterone along with normal or subnormal levels of follicle-stimulating hormone. Although estrone is often increased, estradiol may be normal. However, the normal fluctuation of estrogen and progesterone throughout the menstrual cycle is lacking (2, 4–6).

Because of the etiologic implications of the previously reported positive association between polycystic ovaries and postmenopausal breast cancer, we attempted to corroborate the relation. We used data from a population-based case-control study with a large sample size that would permit adjustment for potential confounders and exploration of effect modification.

MATERIALS AND METHODS

To investigate the relation between polycystic ovaries and breast cancer, we analyzed data from the Cancer and Steroid Hormone Study. The study was originally undertaken to investigate the association between oral contraceptives and cancers of the breast, endometrium, and ovary (7, 8). Cases included women aged 20–54 years with histologically confirmed primary breast cancer diagnosed between December 1, 1980, and December 31, 1982. All cases resided in one of eight geographic locations with a population-based tumor registry (Atlanta, Georgia; Detroit, Michigan; San Francisco, California; Seattle, Washington; Connecticut; Iowa; New Mexico; and the four urban counties of Utah). Of the 5,884 women identified, 4,730 (80.4 percent) were interviewed. Reasons for nonparticipation included death (0.9 percent), physician refusal (2.9 percent), debilitating illness (3.6 percent), subject refusal (4.1 percent), and failure to locate or interview the case within 6 months of diagnosis (8.1 percent).

Controls were women who resided in the same eight geographic locations and were frequency-matched within 5-year age groups to the cases. Eligible women were ascertained by random digit dialing (9). Of the 5,698 women selected, 4,688 (82.3 percent) were interviewed and fit the study criteria. Reasons for nonparticipation or exclusion included refusal (11.9 percent), failure to locate or interview the control within 6 months of selection (4.7 percent), and a history of breast cancer or a previous breast biopsy of unknown outcome (1.2 percent).

The in-home interviews were administered by trained personnel. A history of physician-diagnosed polycystic ovaries was ascertained through direct questioning of all participants during the 50-minute structured interview. The questionnaire focused primarily on reproductive and contraceptive histories, breast diseases and surgeries, family history of cancer, use of medical care, and personal characteristics and habits. The distributions of respondent attributes by case-control status have been published (8) and generally reflect what has been previously reported for breast cancer (10).

To estimate the association between polycystic ovaries and the risk of breast cancer, we calculated odds ratios and 95 percent confidence intervals using Woolf's method (11). Adjusted odds ratios and confidence intervals were also computed using logistic regression to control for potential confounding and to assess interactions among variables (12). Parameters indicating a difference between the logarithms of two odds ratios were exponentiated to yield an estimate of the ratio of the odds ratios (13).

We examined whether the association between polycystic ovaries and breast cancer varied with menopausal status. Other variables evaluated as potential confounders and/or effect modifiers were: age; geographic location; race; marital status; religion; education; income; age at first birth; parity; gravidity; spontaneous abortions before a first birth; ectopic pregnancies; age at menarche; whether menstrual periods started by themselves; menstrual irregularity in the teenage years; Quetelet index (weight (kg)/height $(m)^2$) at age 18 or as an adult; use of oral contraceptives, replacement estrogens,

or other estrogens; smoking; alcohol; benign breast disease; family history of breast cancer; and history of infertility, galactorrhea, or conditions of the pituitary, adrenal, or thyroid glands.

RESULTS

In this data set, the risk of breast cancer was lower among women with a self-reported history of physician-diagnosed polycystic ovaries than among women without such a history; the age-adjusted odds ratio was 0.52 (table 1). Of the many covariates evaluated, age, age at first birth, history of infertility, number of spontaneous abortions before the first birth, and menopausal status confounded the relation, but only slightly. With adjustments for these covariables, the odds ratio was reduced to 0.47. Given that the number of women with polycystic ovaries was limited and the estimates of the odds ratios varied only slightly when the model was age-adjusted or multivariable-adjusted, only the results from the age-adjusted models will be shown.

With a few possible exceptions, stratified analyses and the inclusion of interaction terms in logistic regression models provided little evidence for a heterogeneous association within subgroups. The inverse association between polycystic ovaries and breast cancer was not observed to vary substantially by menopausal status (table 2). The age-adjusted odds ratios among premenopausal women and perimenopausal women were 0.56 and 0.52, respectively, and among those with natural menopause and those with surgical menopause, they were 0.38 and 0.62, respectively. Formal evaluation revealed no significant heterogeneity of the odds ratio.

The odds ratio for breast cancer in relation

TABLE 1. Adjusted odds ratios for breast cancer, by self-reported history of polycystic ovaries: Cancer and Steroid Hormone Study, 1980–1982

Polycystic ovaries*	No. of cases	No. of controls	Age-adjusted OR†	95% CI†	Model-adjusted OR‡	95% CI
No§	4,674	4,613	1.00		1.00	
Yes	23	44	0.52	0.32–0.87	0.47	0.26–0.85

* Thirty-three cases and 31 controls reported not knowing whether a doctor had ever told them they had polycystic ovaries or Stein-Leventhal syndrome.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age, age at first birth, history of infertility, number of spontaneous abortions before the first birth, and menopausal status.
§ Reference group.

TABLE 2. Adjusted odds ratios for breast cancer, by self-reported history of polycystic ovaries and by menopausal status: Cancer and Steroid Hormone Study, 1980–1982

Menopausal status*	Polycystic ovaries†	No. of cases	No. of controls	Age-adjusted OR‡	95% CI‡
Premenopausal	No§	2,118	1,781	1.00	
	Yes	10	15	0.56	0.26–1.32
Perimenopausal	No§	806	842	1.00	
	Yes	2	4	0.52	0.10–2.86
Postmenopausal, natural	No§	608	690	1.00	
	Yes	1	3	0.38	0.04–3.65
Postmenopausal, surgical	No§	998	1,171	1.00	
	Yes	10	19	0.62	0.29–1.33

* For 144 cases and 132 controls, menopausal status was other, unknown, or missing.
† Thirty-three cases and 31 controls reported not knowing whether a doctor had ever told them they had polycystic ovaries or Stein-Leventhal syndrome.
‡ OR, odds ratio; CI, confidence interval.
§ Reference group.

to polycystic ovaries did vary by infertility status (table 3). The age-adjusted odds ratio was 0.26 among women without a history of infertility and 0.96 among women with a history of infertility. Formal assessment showed that the ratio of the odds ratios was of borderline statistical significance ($p = 0.06$).

The association between polycystic ovaries and breast cancer also varied with the age at which a woman first began menstruating (table 4). The age-adjusted odds ratios for women who were less than 12, at least 12 but less than 13, at least 13 but less than 14, and at least 14 years old at menarche were 0.19, 0.57, 0.65, and 0.86, respectively. Formal evaluation, treating age at menarche as a continuous variable, showed that the heterogeneity of the odds ratio was significant ($p = 0.04$). Although the risk of breast cancer decreased with age at menarche among those women without polycystic ovaries, the risk actually increased, although not significantly, with age at menarche among those with polycystic ovaries.

After adjustment for age, the odds ratio relating polycystic ovaries to breast cancer ranged from 1.25 for women who were in the lowest quartile of Quetelet index at age 18 to 0.26 for women who were in the highest quartile (table 5). Formal assessment, with Quetelet index coded as a continuous variable, indicated significant heterogeneity of the odds ratio ($p = 0.01$). A similar pattern of interaction was apparent for Quetelet index as an adult and was of borderline significance ($p = 0.05$; data not shown).

TABLE 3. Age-adjusted odds ratios for breast cancer, by self-reported history of polycystic ovaries and by self-reported history of infertility: Cancer and Steroid Hormone Study, 1980–1982

Infertility*	Polycystic ovaries†	No. of cases	No. of controls	Age-adjusted OR‡	95% CI‡
No	No§	3,623	3,700	1.00	
	Yes	8	32	0.26	0.12–0.55
Yes	No§	818	725	1.00	
	Yes	13	12	0.96	0.44–2.12

* A total of 230 cases and 184 controls were nulligravid, had never married, and were never directly queried about their infertility status; for five cases and four controls, infertility status was unknown or missing.

† Thirty-three cases and 31 controls reported not knowing whether a doctor had ever told them they had polycystic ovaries or Stein-Leventhal syndrome.

‡ OR, odds ratios; CI, confidence interval.

§ Reference group.

DISCUSSION

Several limitations of our study should be considered. Although the prevalence of women diagnosed as having polycystic ovaries is unknown, the possibility of incomplete ascertainment of the syndrome is a concern. History of physician-diagnosed polycystic ovaries was self-reported, and there was no attempt to verify a positive history with the medical record. In addition, 64 women reported an unknown history of polycystic ovaries. Given that the condition

TABLE 4. Age-adjusted odds ratios for breast cancer, by self-reported history of polycystic ovaries and by age at menarche: Cancer and Steroid Hormone Study, 1980–1982

Age (years) at menarche*	Polycystic ovaries†	No. of cases	No. of controls	Age-adjusted OR‡	95% CI‡
<12	No§	1,108	985	1.00	
	Yes	3	14	0.19	0.06–0.67
12	No§	1,185	1,140	1.00	
	Yes	7	12	0.57	0.23–1.46
13	No§	1,308	1,290	1.00	
	Yes	6	9	0.65	0.23–1.84
≥14	No§	1,060	1,179	1.00	
	Yes	7	9	0.86	0.32–2.32

* Thirteen cases and 19 controls did not provide information on their age at menarche.

† Thirty-three cases and 31 controls reported not knowing whether a doctor had ever told them they had polycystic ovaries or Stein-Leventhal syndrome.

‡ OR, odds ratio; CI, confidence interval.

§ Reference group.

TABLE 5. Age-adjusted odds ratios for breast cancer, by self-reported history of polycystic ovaries and by Quetelet index at age 18: Cancer and Steroid Hormone Study, 1980–1982

Quetelet index* at age 18†	Polycystic ovaries‡	No. of cases	No. of controls	Age-adjusted OR§	95% CI§
<1.85	No‖	1,095	1,046	1.00	
	Yes	9	7	1.25	0.46–3.38
1.85–1.99	No‖	1,266	1,261	1.00	
	Yes	9	10	0.91	0.37–2.24
2.00–2.24	No‖	1,505	1,486	1.00	
	Yes	3	19	0.16	0.05–0.54
≥2.25	No‖	780	798	1.00	
	Yes	2	8	0.26	0.05–1.20

* Weight (kg)/height (m)^2.
† For 28 cases and 22 controls, information on Quetelet index at age 18 was unknown or missing.
‡ Thirty-three cases and 31 controls reported not knowing whether a doctor had ever told them they had polycystic ovaries or Stein-Leventhal syndrome.
§ OR, odds ratio; CI, confidence interval.
‖ Reference group.

is rare and the common feature of infertility has a large impact on a woman's life, most women with such a history would be aware of their diagnosis and answer affirmatively during the interview. Most of the women whose responses were coded as unknown probably were unfamiliar with the term and had never been diagnosed as having the syndrome. In addition, the primary symptoms of the condition for which treatment is sought, including teenage menstrual problems and infertility (2), did not confound the study results. Similarly, any differential reporting of polycystic ovaries that might vary according to levels of other risk factors for breast cancer (such as age at first birth) was also adjusted in the analysis. Such adjustments result in nondifferential misclassification within levels of a third variable (14). Therefore, any misclassification of polycystic ovaries due to the self-reported nature of the data probably does not differ for cases versus controls, and the results are most likely attenuated toward the null.

The generalizability of the study's results to women under the age of 55 years only should also be considered. In this study, a history of polycystic ovaries was inversely associated with breast cancer in women between ages 20 and 54, and this apparent protective effect was not an artifact of infertility, age at first birth, or surgical menopause. The discrepancy between our results and those of the one previous study by Coulam et al. (1) may be due to the different age ranges of the two studies. In the latter study, over a threefold increase for postmenopausal breast cancer was noted among women with a previous definitive laboratory diagnosis of polycystic ovaries. Thus, there is the possibility that the association is modified by menopausal status and that our study was unable to document such an effect because of our restricted age range among postmenopausal women. However, in the Coulam study, only four women developed postmenopausal breast cancer during the follow-up period (1). Thus, the investigators had only limited ability to adjust for potential confounding or to explore potential effect modification. Because the evidence conflicts, clinical advice to treat polycystic ovaries to prevent breast cancer seems premature.

An advantage of the study reported here is the large sample of participants. By improving a study's power, one facilitates estimation of the effect of a rare condition such as polycystic ovaries. The precision of this estimation in our study is reflected in the narrow confidence intervals that surround the odds ratio (table 1). Even a large study, however, has a limited ability to detect effect modification. We were unable to determine whether the interactions found were independent, because of the few women with polycystic ovaries. Thus, caution should be exercised in interpreting our results, especially with regard to the interactions that were primarily of borderline significance.

Estrogen unopposed by progesterone, a characteristic of anovulation and polycystic ovaries, is an important biologic pathway in increasing the risk of endometrial cancer (15). However, as is apparent in these and other data, the relation between unopposed estrogen and breast cancer is not clear (16, 17). Alternative hypotheses include an etiologic role for excess estrogen alone or estrogen and progestogen together; either hypothesis predicts that anovulatory cycles protect against breast cancer (16, 18). Although the

results from our study appear to support these latter hypotheses, there is some inconsistency. Women who are most likely to be anovulatory in our study, for instance, are those with a history of polycystic ovaries along with infertility, yet a history of polycystic ovaries was not found to substantially reduce risk among infertile women. In addition, for women who reported a history of female infertility in our study, medical records were retrieved; among women whose physician indicated that the reason for the infertility was polycystic ovaries, the risk was not reduced (19). Similarly, teenage girls with a late age at menarche are more likely to be anovulatory (20), yet the negative association between age at menarche and breast cancer found among women without polycystic ovaries was not observed for women with polycystic ovaries.

The effect modification by body size is also unclear. Anovulatory cycles have been shown to be more common among females who are either very thin or very overweight (21). However, women who reported having polycystic ovaries and who were in the lowest quartile of Quetelet index at age 18 had a slightly elevated odds ratio, whereas those with the syndrome who were in the highest quartile had a decreased odds ratio for breast cancer.

It may be that women with polycystic ovaries have other hormonal abnormalities that may affect their risk for breast cancer. For example, the endocrine profiles for adolescent anovulatory cycles and polycystic ovary syndrome are similar; however, the elevated levels of testosterone and luteinizing hormone are more exaggerated among those with polycystic ovaries (22). Other subgroups with increased levels of these hormones include obese women (23) and late-maturing South African black girls as compared with early-maturing white girls (24). However, some evidence is not supportive of a possible protective role for these two hormones. One group of investigators (25) has repeatedly found increased testosterone among women considered at high risk for breast cancer. In contrast, others have been unable to document altered testosterone levels among women who later developed breast cancer in a follow-up study (26).

Future research designed to clarify the etiology of breast cancer may benefit from more precise hormonal characterization of study participants to identify those subgroups with especially high levels of testosterone and luteinizing hormone in relation to normal levels of estradiol or elevated levels of estrone, such as women with polycystic ovaries.

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