Int. J. Cancer: **118,** 197–202 (2006)

An inverse association between ovarian cysts and breast cancer in the Breast Cancer Family Registry

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Ovarian cysts of several types are common in women of reproductive age. Their etiology is not well understood but is likely related to perturbations in the hypothalamic-pituitary-gonadal axis. The relationship of ovarian cysts to breast cancer risk is not known, although a negative association with polycystic ovarian syndrome has been reported. Incident, invasive female breast cancer cases, population-based controls and unaffected sisters of cases were studied from 3 countries participating in the Breast Cancer Family Registry: Melbourne and Sydney, Australia; the San Francisco Bay Area, USA; and Ontario, Canada. Using the same questionnaire, information was collected on self-reported history of ovarian cysts and other risk factors. Analyses were based on 3,049 cases, 2,344 population controls and 1,934 sister controls from all sites combined. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using both unconditional and conditional logistic regression using an offset term to account for sampling fractions at 2 of the sites. A significantly reduced risk of breast cancer was observed for women reporting a history of ovarian cysts (OR = 0.70, 95% CI 0.59–0.82, among all cases and all controls). This risk estimate was similar regardless of control group used, within all 3 sites and in both premenopausal and postmenopausal women (ORs ranging from 0.68–0.75, all 95% CI excluded 1.00). A self-reported history of ovarian cysts was strongly and consistently associated with a reduced risk of breast cancer. Further study of ovarian cysts may increase our understanding of hormonal and other mechanisms of breast cancer etiology.

Key words: breast cancer; etiology; ovarian cysts; case-control study

An ovarian cyst is an enlarged fluid-containing follicle or corpus luteum that occurs commonly in women of reproductive age. An individual cyst can be simple or functional (*i.e.,* hormone producing). Polycystic ovaries contain multiple small follicular cysts, and when the latter occur along with other symptoms such as hirsutism, infertility and obesity the combination defines polycystic ovary syndrome (PCOS). PCOS is a heterogeneous endocrine syndrome with varying diagnostic criteria,[1,2] but it is usually associated with hyperandrogenemia and hyperinsulinemia. However, polycystic ovaries can occur in the absence of other PCOS symptoms. Endometriotic ovarian cysts or endometriomas, also called chocolate cysts, occur in some cases of endometriosis. The pathogenesis of endometriomas is unclear but may be related to functional ovarian cysts in at least some cases.[3]

The etiologies of individual simple or functional cysts and of polycystic ovaries are not well understood, but all cysts are likely to be linked to altered gonadotropin secretion, which influences and is influenced by steroid hormones including estrogens, progestins and androgens. Early oral contraceptive formulations were associated with reduced ovarian cyst occurrence, but this relationship appears to have attenuated with more recent, lower-dose formulations.[4,5] Conditions associated with increased prevalence of ovarian cysts include tubal ligation or other surgery leading to tubal blockage,[4,6] aromatase deficiency[7,8] and tamoxifen use in premenopausal women.[9,10] Conditions associated with polycystic ovaries include gestational diabetes[11–14] and irregular cycles or oligomenorrhia in girls and young women or in women with gestational diabetes.[12,15,16]

The link to alterations in the hypothalamic-pituitary-gonadal axis suggests that ovarian cysts in general, not only in PCOS, may be a marker of hormonal milieu associated with the risk of breast cancer. The literature, however, is limited. To date, published studies on ovarian cysts and breast cancer have focused specifically on PCOS. This syndrome was initially reported to be associated with an increased risk of postmenopausal breast cancer,[17] but subsequent studies either failed to find an association with breast cancer[18,19] or found evidence of a protective effect.[20] To the best of our knowledge, there are no published studies on the relationship between individual simple or functional cysts, polycystic ovaries other than PCOS or any cyst diagnosis and risk of breast cancer.

We conducted a case-control analysis, using both population controls and sister controls, of the association between self-reported history of ovarian cysts of any type and breast cancer risk in a large sample of women from 3 countries.

Material and methods

This population-based case-control analysis was conducted using data from 3 study sites of the Breast Cancer Family Registry funded by the U.S. National Cancer Institute and other sources. Participants were recruited from the San Francisco Bay Area, California, USA; Melbourne and Sydney, Australia; and Ontario, Canada. The Breast Cancer Family Registry is described in detail elsewhere.[21] Additional methodologic details from 2 of the study sites have also been published elsewhere.[22–25] The analysis was based on Caucasian women with a first primary invasive breast cancer who were compared to their sisters and Caucasian women from the general population without a personal history of breast cancer. Women who reported other racial/ethnic backgrounds were not included in this analysis as recruitment of non-Caucasians is continuing. All studies received approval from local ethics boards.

Abbreviations: BMI, body mass index; CASH Study, Cancer and Steroid Hormone Study; CI, confidence interval; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; IWHS, Iowa Women's Health Study; LH, luteinizing hormone; OR, odds ratio; PCOS, polycystic ovary syndrome.

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Received 14 February 2005; Accepted after revision 10 May 2005
DOI 10.1002/ijc.21298
Published online 19 July 2005 in Wiley InterScience (www.interscience.wiley.com).

Cases

At each of the 3 study sites, incident breast cancer cases were identified through population-based cancer registries. In Melbourne and Sydney, all women with invasive breast cancer aged 18–39 years, resident in the 2 metropolitan regions at the time of diagnosis and diagnosed from 1996–1999 were identified. In Melbourne, women aged 40–49 years and aged 50–59 years were randomly sampled at 41% and 25%, respectively, whereas in Sydney, both of these age groups were sampled at 28%. A total of 1,660 cases were identified. Physician permission to contact patients was received for 1,492 (90%), of whom 1,112 (75%) completed risk factor and family history questionnaires at an in-person interview. Of these cases, 1,026 were Caucasian.

In both San Francisco and Ontario, a 2-stage sampling procedure was used to oversample women likely to be at increased genetic risk of breast cancer. At both study sites, cases were identified from local population-based cancer registries and then screened for indicators of genetic risk. All cases with such indicators and a random sample of cases without these indicators were invited to participate. In San Francisco, cases aged 18–64 years were included if they met any of the following criteria: diagnosed before age 35 years; bilateral breast cancer with the first diagnosis before age 50 years; previous diagnosis of ovarian or childhood cancer; one or more first-degree relatives with breast, ovarian or childhood cancer. In addition, among cases who did not meet the criteria listed above, 5% of Caucasians and 20% of cases with other racial/ethnic backgrounds were randomly selected. In Ontario, cases aged 18–69 years were included if they met any of the following criteria: Ashkenazi Jewish; diagnosed before age 36 years; previous ovarian or breast diagnosis; one or more first- or 2 or more second-degree relatives with breast or ovarian cancer; one or more second- or third-degree relatives with either breast cancer diagnosed before age 36 years, ovarian cancer diagnosed before age 61 years, multiple breast or breast and ovarian primaries or male breast cancer; 3 or more first-degree relatives with any combination of breast, ovarian, colon, prostate or pancreatic cancer or sarcoma, with at least one diagnosis before age 51 years. In addition, among cases who did not meet the criteria listed above, 25% were randomly selected.

In San Francisco, 7,359 women diagnosed with invasive breast cancer from 1995–1998 were identified who were less than 65 years of age and residing in the 9 counties of the Greater San Francisco Bay Area at the time of diagnosis. Of these, 112 (1.5%) could not be contacted because of physician-reported contraindications. A screening telephone interview that inquired about family history of breast, ovarian and childhood cancer as well as self-reported race/ethnicity was completed for 85% of cases, and 848 Caucasian cases meeting the above eligibility and selection criteria were invited to participate. Of these, 670 (79%) cases or a proxy respondent completed a detailed family history questionnaire by telephone and a risk factor questionnaire by in-person interview. After exclusion of cases with previous breast cancer and deceased cases for whom the questionnaires were completed by proxy respondent, there were 601 cases included in this analysis.

In Ontario, 8,143 first breast primary cases (all women under age 55, a 35% random sample of women 55–69) were identified from 1996–1998 and physician permission to contact them was obtained for 7,384 (91%). These cases were sent a screening questionnaire on family history and race/ethnicity and 4,760 (64%) completed the mailed questionnaire. Of these, 2,390 were invited to participate after sampling as described above and 1,704 (71%) completed a detailed telephone interview on family history and a mailed risk factor questionnaire, and 1,579 of these were Caucasian.

Population-based controls

All 3 study sites recruited women without any reported invasive or *in situ* breast cancer from the general populations from which the cases were ascertained. Within each site, controls were frequency-matched by 5-year age group to the expected age distribution of cases at diagnosis. In San Francisco, controls were also frequency-matched by race/ethnicity. In Melbourne and Sydney, population controls were identified from electoral rolls (registration to vote is compulsory in Australia). Of the 898 controls identified, 613 (68%) completed the in-person interview and 519 were Caucasian. In San Francisco, of the Caucasian controls identified by random digit dialling, 67% completed the family history questionnaire by telephone and the risk factor questionnaire by in-person interview, and 313 were included in this analysis. In Ontario, 2,688 controls were identified by calling randomly selected residential telephone numbers. Of these, 1,713 (64%) returned the mailed risk factor and family history questionnaires and 1,576 of these were Caucasian.

Sister controls

All 3 study sites recruited sisters of cases if permission to contact them was given by the cases. The current analysis includes data from living full sisters with no reported history of invasive or *in situ* breast cancer. In Melbourne and Sydney, 1,331 sisters of cases were identified, and 902 (68%) completed the in-person interview. Of these, 832 were Caucasian. In San Francisco, 501 Caucasian sisters were identified, 416 contacted and 353 (85% of those contacted, 70% overall) completed the in-person interview. In Ontario, 2,077 sisters were identified, 1,484 were contacted, and 939 (63% of those contacted, 45% overall) returned the mailed risk factor questionnaire. Of these, 858 were Caucasian and included in this analysis.

Questionnaire

All study sites used the same risk factor questionnaire that asked about established and suspected risk factors. The questionnaire also asked specifically whether a doctor had ever told the participant that she had cysts in one or both ovaries and, if so, her age when this was first diagnosed.

Statistical analysis

χ^2 tests of association were used to test for differences in descriptive variables. Unconditional logistic regression was used to generate odds ratio (OR) and 95% confidence interval (CI) estimates. In addition, conditional logistic regression, conditioning on family, was used for the comparison of cases with sister controls. In all logistic regression models, we accounted for the oversampling based on genetic risk criteria used in 2 of the study sites by including an offset term to remove bias in the point estimates.[26] Offsets for cases in Ontario and San Francisco were set to the natural log of the sampling fraction. For all other groups where no sampling occurred (controls from all studies and cases in Melbourne and Sydney), the offset was set to the natural log of one, which is zero.

Each woman was assigned a reference age defined as the age 1 year prior to diagnosis for cases and as the age at questionnaire completion for controls. All variables were defined in relation to the reference age. The main variable of interest was ever having been diagnosed with ovarian cysts. Variables significantly associated with breast cancer risk, after age-adjustment, were included in the multivariate models as potential confounders. These included: number of full-term pregnancies, age at menarche, years of oral contraceptive use, born in the country of study (yes or no) and having a first-degree relative with breast cancer (yes or no). The latter was not included in analyses of cases *vs.* sister controls only. In addition, because of concern regarding residual confounding, all models also included reference age in 5-year categories, education in 3 categories and number of ovaries removed (0, 1, 2). Education was the best indicator of socioeconomic status available and could be related to detection of ovarian cysts. As oophorectomy reduces breast cancer risk and also may be the result of an ovarian cyst diagnosis, this variable was always included as a

potential confounder. In addition, a subgroup analysis of women without oophorectomy was also conducted. A variable representing study site (Melbourne and Sydney, San Francisco, Ontario) was always included when the data were pooled.

Cases were compared to population controls and sister controls separately as well as with a pooled control group. Subgroup analyses were performed for premenopausal and postmenopausal women, for women who had not had an oophorectomy and for each study site separately. Women were considered postmenopausal if they had not menstruated for at least 1 year or both ovaries had been removed. Also included in this group were women aged 55 years or older who had had a hysterectomy without bilateral oophorectomy or who were using hormone replacement therapy and still reported menstruating (those under 55 years were considered to have unknown menopausal status). All tests were 2-sided, and we used a 0.05 level of significance. All analyses were carried out using SAS versions 8 and 9.

Results

The analysis includes a total of 3,206 cases, 2,408 population controls and 2,043 sister controls. Table I compares various characteristics of the 3 groups. The proportion with a college or university degree did not differ statistically, nor did the proportion who had ever married. Differences in menopausal status did not remain significant after age adjustment. Distribution of body mass index (BMI) did not differ significantly between cases and controls in either premenopausal or postmenopausal women. Cases were more likely to be nulliparous and less likely than controls to have had 3 or more full-term pregnancies and were more likely to have had earlier menarche. Controls used oral contraceptives for a longer time and were more likely to have been born in the country where the study was carried out. There were 3,049 cases, 2,344 population controls, and 1,934 sister controls with complete information on all variables included in the models. A total of 70 (2%) cases and 81 (2%) controls had missing information on ovarian cysts.

Overall, 20% of all controls reported a history of ovarian cysts of any type compared to 15% among cases. A diagnosis of ovarian cysts was associated with a significantly reduced risk of breast cancer (OR = 0.70, 95% CI 0.59–0.82) as shown in Table II. The OR estimates were similar when controls were restricted to either population controls or to sister controls (0.70 and 0.75, respectively) and the confidence intervals clearly excluded unity in both instances. The OR estimate for the comparison of cases with sister controls using conditional logistic regression was similar to that from unconditional logistic regression (OR = 0.70, 95% CI 0.55–0.88 *vs*. OR = 0.75, 95% CI 0.63–0.90). As a diagnosis of ovarian cysts might be associated with having an oophorectomy, we restricted the analysis to those who had never had an ovary removed. The OR estimate, adjusted for the same variables except

TABLE I – CHARACTERISTICS OF THE STUDY POPULATION FROM THE 3 SITES BY CASE-CONTROL STATUS

	Cases (n = 3,206) n (%)	Population controls (n = 2,408) n (%)	Sister controls (n = 2,043) n (%)	All controls (n = 4,451) n (%)
Reference Age (years)				
< 30	96 (3)	92 (4)	77 (4)	169 (4)
30–34	352 (11)	168 (7)	180 (9)	348 (8)
35–39	390 (12)	276 (11)	268 (13)	544 (12)
40–44	452 (14)	336 (14)	333 (16)	669 (15)
45–49	694 (22)	457 (19)	327 (16)	784 (18)
50–54	547 (17)	466 (19)	343 (17)	809 (18)
55–59	361 (11)	300 (12)	240 (12)	540 (12)
≥ 60	314 (10)	313 (13)	275 (13)	588 (13)
Education				
No college/university degree	2,329 (73)	1,760 (73)	1,545 (76)	3,305 (75)
College/university degree	862 (27)	645 (27)	486 (24)	1,131 (25)
Full-term pregnancies				
0	708 (22)	432 (18)	383 (19)	815 (18)
1	423 (13)	366 (15)	249 (12)	615 (14)
2	1,181 (37)	879 (37)	698 (34)	1,577 (35)
≥ 3	894 (28)	731 (30)	713 (35)	1,444 (32)
Born in study country				
Yes	2,505 (78)	1,952 (81)	1,715 (84)	3,667 (83)
No	690 (22)	451 (19)	321 (16)	772 (17)
Age at menarche (years)				
< 12	622 (20)	497 (21)	332 (16)	829 (19)
12–13	1,774 (56)	1,306 (55)	1,050 (52)	2,356 (53)
≥ 14	781 (25)	591 (25)	642 (32)	1,231 (29)
Oral contraceptive use (years)				
< 1	915 (29)	639 (27)	491 (24)	1,130 (26)
1– < 5	773 (24)	570 (24)	458 (23)	1,028 (23)
5– < 10	778 (24)	622 (26)	525 (26)	1,147 (26)
≥ 10	712 (22)	564 (24)	553 (27)	1,117 (25)
Marital status				
Ever married	2,934 (92)	1,868 (91)	2,202 (92)	4,070 (92)
Never married	270 (8)	174 (9)	201 (8)	375 (8)
Menopausal status				
Premenopausal	1,904 (65)	1,136 (62)	1,281 (60)	2,417 (60)
Postmenopausal	1,029 (35)	709 (38)	870 (40)	1,579 (40)
Premenopausal BMI (kg/m^2)				
< 25	1,135 (60)	701 (62)	746 (58)	1,447 (60)
25– < 30	452 (24)	256 (23)	309 (24)	565 (23)
≥ 30	317 (17)	179 (16)	226 (18)	405 (17)
Postmenopausal BMI (kg/m^2)				
< 25	474 (46)	310 (44)	387 (44)	697 (44)
25– < 30	328 (32)	237 (33)	293 (34)	530 (34)
≥ 30	227 (22)	162 (23)	190 (22)	352 (22)

TABLE II – BREAST CANCER RISK ACCORDING TO HISTORY OF OVARIAN CYSTS

	Cases (n = 3,049) n (%)	Controls (n = 4,278) n (%)	OR[1]	95% CI
Cases *vs*. population controls				
No cysts	2,585 (85)	1,867 (80)	1.00	
Cysts	464 (15)	477 (20)	0.70	0.59–0.82
Cases *vs*. sister controls				
No cysts	2,585 (85)	1,561 (81)	1.00	
Cysts	464 (15)	373 (19)	0.75	0.63–0.90
Cases *vs*. all controls				
No cysts	2,585 (85)	3,428 (80)	1.00	
Cysts	464 (15)	850 (20)	0.71	0.61–0.81

[1]OR, odds ratio, adjusted for age, study site, education, number of full-term pregnancies, being born in country of study, age at menarche, family history of breast cancer in a first-degree relative, years of oral contraceptive use, number of ovaries removed. Family history was excluded from the model for cases *vs*. sister controls.–CI, 95% confidence interval.

for number of ovaries removed, remained virtually unchanged (OR = 0.71, 95% CI 0.60–0.83). Odds ratios were similar for both premenopausal and postmenopausal women (0.73 and 0.72, respectively), and a significantly reduced risk of breast cancer with ovarian cysts was observed in all 3 study sites (Table III). There was no relationship between reported age at first cyst diagnosis and breast cancer (OR = 1.01, 95% CI 0.99–1.02).

TABLE III – BREAST CANCER RISK AND A HISTORY OF OVARIAN CYSTS BY MENOPAUSAL STATUS AND SITE

	Cases n (%)	Controls n (%)	OR[1]	95% CI
Menopausal status				
Premenopausal				
No cysts	1,591 (87)	1,995 (85)	1.00	
Cysts	228 (13)	348 (15)	0.73	0.60–0.90
Postmenopausal				
No cysts	802 (82)	1,160 (77)	1.00	
Cysts	173 (18)	348 (23)	0.72	0.57–0.91
Study site				
Melbourne/Sydney				
No cysts	856 (86)	1,063 (82)	1.00	
Cysts	141 (14)	235 (18)	0.74	0.55–0.99
San Francisco				
No cysts	512 (87)	528 (81)	1.00	
Cysts	77 (13)	123 (19)	0.66	0.47–0.93
Ontario				
No cysts	1,217 (83)	1,837 (79)	1.00	
Cysts	246 (17)	492 (21)	0.71	0.59–0.86

[1]OR, odds ratio, adjusted for age, education, number of full-term pregnancies, being born in country of study, age at menarche, family history of breast cancer in a first-degree relative, years of oral contraceptive use, number of ovaries removed. OR by menopausal status also adjusted for study site.–CI, 95% confidence interval.

Discussion

We observed a significantly reduced risk ($p < 0.0001$) of breast cancer associated with a reported history of ovarian cysts of any type. To our knowledge, there are no other studies that considered the relationship between an ovarian cyst diagnosis and breast cancer. Only a few studies have examined the relationship between PCOS and breast cancer.[17–20] No relationship was observed in the postmenopausal women of the Iowa Women's Health Study (IWHS) cohort, but the statistical power was limited.[18] In support of the present finding, the Cancer and Steroid Hormone (CASH) study, a large case-control study of women aged 20–54, found a significant protective effect of a history of PCOS on breast cancer risk in these mostly premenopausal women.[20] We did not observe any difference between premenopausal and postmenopausal women for a more general diagnosis of ovarian cysts. Age at first reported cyst diagnosis was not associated with breast cancer risk, but it is not known to what extent this reported age corresponds to initial cyst development.

Cysts vary in type and severity, which influences their likelihood of being diagnosed. Cysts may cause pain or discomfort and functional cysts may induce symptoms related to hormone production, both of which can lead to diagnosis. However, asymptomatic cysts are frequently identified from palpation during routine gynecologic examination. Cysts associated with PCOS are identified through the manifestations of the syndrome (*e.g.,* infertility, menstrual disturbance, hirsutism), whereas polycystic ovaries in the absence of PCOS are difficult to identify without ultrasound. Therefore, women who report a diagnosis of ovarian cysts (as in our study) are likely to have either symptomatic cysts, including PCOS, or frequent palpable cysts in order to be identified during a routine examination.

In our study, 20% of controls and 15% of cases reported a diagnosis of ovarian cysts of any type. A recent review of cross-sectional studies specifically focused on PCOS suggests a prevalence of about 7%,[27] although the prevalence varies with the definition used. The 2 large studies cited above (IWHS and CASH) reported a much lower prevalence of PCOS of 1% in cohort members or controls. Given the numbers above, in our present study, it is likely that the majority of the women who reported having cysts had individual enlarged cysts, with only a minority having PCOS. Some of the women reporting cysts may have had endometriomas. Estimates of the prevalence of pelvic endometriosis vary, ranging from 6–10% in a recent review.[28] However, not all women with pelvic endometriosis have endometriotic ovarian cysts, which in turn may have developed in some cases from follicular or luteal cysts.[3] Therefore, if real, the reduced risk is either associated with cysts in general or there is a much stronger protective effect associated with one or more specific subtypes.

There is a possibility that ovarian cyst diagnosis is related to the frequency of medical examination, which in turn may be related to education or access to medical care. However, the decreased breast cancer risk was observed after adjustment for education level. In addition, the prevalences of ovarian cysts among cases and controls and OR estimates were similar in all 3 study sites in 3 countries with different health care systems (USA, Australia and Canada). The consistency of the reduction in risk regardless of control group or study site reduces the likelihood that the observed result occurred because of differential selection or response bias as these likely vary across sites and control groups. The factors associated with participation, at least some of which we have adjusted for, likely differ between population and sister controls. For example, sisters are more likely to be more similar to cases in socioeconomic status than to population controls, in whom response is often greater with higher socioeconomic status. In spite of the expected differences between the 2 control groups, both yielded a similar and highly significant estimate for association between ovarian cysts and breast cancer. In addition, the sampling based on genetic risk used in San Francisco and Ontario is unlikely to have produced a spurious result, as findings in these study locations did not differ from those in Melbourne and Sydney, where there was no sampling according to genetic risk. Again, despite differences in sampling design among the study sites, all of them exhibited a similar and highly significant reduced risk of breast cancer associated with ovarian cysts. As ovarian cysts were more frequently reported by controls, misclassification due to recall bias arising from overreporting by cases is unlikely. Any nondifferential classification bias would only have attenuated the result, and therefore the true association could be stronger. As with any epidemiologic study, there is the possibility that the observed association could occur as the result of unmeasured confounding. That is, there could be an additional unknown factor related both to ovarian cysts and to breast cancer risk that explains the relationship. The most likely factor would be oophorectomy, but the OR estimate and significance were not altered by restricting the analysis to those who had never had an ovary removed. It is also possible that treatment for ovarian cysts could potentially

account for the observed association rather than the cysts themselves.

If the observed inverse association between self-reported ovarian cyst diagnosis and breast cancer is not an artifact, biologic explanations can be considered, beginning with factors associated with cyst development including androgens, gonadotropins and tubal ligation. Androgens are elevated in those with PCOS and also in rare aromatase-deficient individuals who are also prone to ovarian cyst development.[7,8] However, the relationship between androgens and breast cancer is unclear since they may protect against breast cancer[29] but also may increase risk,[30] possibly depending on the levels of other hormones also present. Gonadotropins are responsible for both follicle stimulation and luteal persistence. Follicular cysts would result from increased follicle stimulating hormone (FSH) stimulation, whereas a persistent corpus luteum can occur in the presence of luteinizing hormone (LH) or from human chorionic gonadotropin (hCG) if conception has occurred. There is some evidence to support a protective effect of hCG on breast tissue,[31,32] but because this occurs only after a full-term pregnancy, it is unlikely to explain the protective effect of ovarian cysts. Tamoxifen increases cyst occurrence in premenopausal women,[9,10] but it is unclear whether this occurs through an effect on gonadotropins[9] or some other mechanism.[10] As the hypothalamic-pituitary-gonadal axis is responsible for follicular development, it is likely involved in the etiology of ovarian cysts, but the specific mechanism is currently unknown. Tubal ligation or blockage has also been associated with ovarian cyst development.[4,6] The reason for this association is not known but may involve inflammatory mediators.[6] A number of studies have also found a reduced risk of breast cancer associated with tubal ligation,[33–35] although other studies found no association.[36,37] The evidence for association between ovarian cysts and tubal ligation and between both of these and reduced breast cancer risk is intriguing.

The etiology of ovarian cysts is not well understood. The biologic mechanisms and contributing factors have not yet been fully elucidated and may differ for specific types of cysts. Although the present finding could be the result of confounding, it is unlikely that one or more confounding factors would operate in a similar manner in 3 different countries and in both population controls and sister controls. It is not known whether the observed reduced risk is due to ovarian cysts in general, implying one or more common factors related both to any type of cyst and to breast cancer, or whether it is due to a stronger effect within one or a few types of cysts. Further research, including studies with more detailed exposure assessments, are required to address this question. We present these results to stimulate a new avenue of investigation that could shed additional light on the complexities of breast cancer development.

Acknowledgements

This work was supported by the National Cancer Institute under RFA CA-95-003 and through cooperative agreements with The University of Melbourne, Northern California Cancer Center and Cancer Care Ontario, as part of the Breast Cancer Family Registry (Breast CFR). The Australian Breast Cancer Family Study was also supported by the National Health and Medical Research Council of Australia, the New South Wales Cancer Council and the Victorian Health Promotion Foundation. The recruitment of controls by the Northern California Cancer Center was supported in part by National Institutes of Health Grant U01CA 71966. The recruitment of controls in Ontario was supported by the Canadian Breast Cancer Research Initiative. The content of this article does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast CFR, nor does mention of trade names, commercial products or organizations imply endorsement by the US Government or the Breast CFR. We acknowledge the important contributions of Drs. D. West, N. Boyd and M. McCredie to the development of the 3 studies and the helpful advice on endocrinology from Drs. R. Casper and T. Brown.

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