Short Communication

Ovarian Volume: Determinants and Associations with Cancer among Postmenopausal Women

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Abstract

Clinical studies have reported associations between ovarian stromal hyperplasia and the diagnosis of hormonally related tumors such as endometrial cancer. To assess the hypothesis that characteristics of benign ovaries among postmenopausal women are related to risk for breast, endometrial, and colon cancer, we analyzed systematically collected transvaginal ultrasound data for participants enrolled in the screening arm of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Among women without cancer, median ovarian volume declined with age from 1.25 cm^3 for women between ages 55 and 59 years to 1.0 cm^3 for those between ages 65 and 69 years. African American and Caucasian women had larger median ovarian volumes than Asians. Larger ovarian volume was also associated with the highest quartiles of height and weight and ever having smoked. After adjusting for race, age, parity, body mass, smoking, and hormone use, women with median ovarian volumes $\geq$3.0 cm^3 were at increased risk for breast cancer [odds ratio (OR), 1.42; 95% confidence interval (95% CI), 1.11-1.70], endometrial cancer (OR, 1.97; 95% CI, 1.12-3.48), and colon cancer (OR, 2.00; 95% CI, 1.25-3.21). Significant trends of risk with increasing volume were found only for breast and endometrial cancers. We conclude that large ovaries among postmenopausal women may represent a marker of risk for hormonally related tumors. Confirmation of these findings in future studies, including analyses of serum hormone levels and tissues, may provide insights into hormonal carcinogenesis among older women. (Cancer Epidemiol Biomarkers Prev 2006; 15(8):1550–4)

Introduction

Postmenopausal women with high levels of circulating estrogens or androgens are at increased risk for developing breast and endometrial cancer (1-3) and may also have altered risk for colon cancer and other tumors (4-6). Recognition that aromatization of androgens to estrogens in peripheral adipose tissue represents the main source of circulating estrogens among postmenopausal women has fostered the development of a unified theory linking obesity to both elevated hormone levels and cancer risk (7). However, the importance of other factors that may directly influence cancer risk by increasing endogenous hormone production has received less attention in epidemiologic studies. In particular, clinical studies have reported that ovarian stromal hyperplasia and endometrial cancer are often identified concurrently, suggesting that ovarian morphology may represent a marker of cancer risk among older women (8). This association may reflect increased production of androgen, the main hormone product of the postmenopausal ovary. To assess the hypothesis that the morphology of postmenopausal ovaries is related to the development of endometrial, breast, and colon cancers, we analyzed transvaginal ultrasound data from the National Cancer Institute–sponsored Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

Materials and Methods

Subjects. Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial was a multicenter randomized clinical trial sponsored by the National Cancer Institute (Bethesda, MD), designed to assess the effects of specified screening tests on cancer mortality and other outcomes (9-12). The study was approved by ethical committees at the National Cancer Institute and participating sites. The trial enrolled consenting women ages 55 to 74 years at 10 centers between 1993 and 2001. Exclusion criteria included a history of colorectal, lung, or ovarian cancer, ongoing treatment for cancer (other than for skin cancer), and participation in other screening trials. Subjects were randomized to either screening (see below) or routine care and are currently being followed for 13 years to determine the incidence of cancers and deaths and to determine disease-specific mortality.

This analysis was designed as a case-control study, nested within the ovarian cancer screening arm, of women diagnosed with incident breast, endometrial, or colon cancer from study enrollment through November 2005. Subjects included 1,481 women diagnosed with breast cancer, 206 with endometrial cancer, and 314 with colon cancer who were diagnosed after enrollment, and 36,968 who were not diagnosed with cancer. Exclusion of women who refused to undergo transvaginal ultrasound or had nonvisualized ovaries reduced available subjects to 958 women with breast cancer, 128 with endometrial cancer, 191 with colon cancer, and 21,934 controls.

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Excluding women with a history of breast or endometrial cancer before enrollment resulted in an analytic data set including 926 breast cancers, 123 endometrial cancers, 181 colon cancers, and 20,881 controls.

Clinical Procedures. Women completed a brief questionnaire related to obstetric and gynecologic history and major cancer risk factors and donated blood (9-12). At enrollment, women in the screening arm underwent bimanual pelvic examination (if enrolled from 1993 to 1998), cancer antigen-125 testing (abnormal >35 units/mL), and a standardized transvaginal ultrasound examination. Compliance with enrollment screening procedures was 83% (9). Pelvic examination was eliminated from the protocol because preliminary analyses showed that it failed to identify ovarian cancers and it was recognized that unscreened women were often undergoing the procedure outside of the context of the trial. Follow-up visits included annual cancer antigen-125 testing for 5 additional years and transvaginal ultrasound examination for 3 additional years. Transvaginal ultrasound examination included systematic measurement of the ovaries in three planes, and identification, measurement, and characterization of up to three cysts (largest) per ovary. Ovarian volume was calculated as the product of the longitudinal, transverse, and anteroposterior dimensions $\times$ 0.523. If the volume of an ovary or an adnexal cyst measured $\geq$10 cm^3, or a cyst showed solid, papillary, or mixed solid/cystic areas, the transvaginal ultrasound was considered suspicious for cancer. Both ovaries were visualized in 70% to 71% of cases and 71% of controls and the frequencies of repeated visualization were similar for the two groups.

Women with abnormal pelvic examinations, cancer antigen-125 levels, or transvaginal ultrasounds were referred to their personal physicians for management, which was considered outside the purview of the trial protocol. Following enrollment, women are contacted annually by mail to obtain follow-up information.

Analysis. Data for ovarian volume were based on the median and mean values of all available measurements (cm^3) per woman. Age-specific mean, median, and quartiles of ovarian volume were determined based on average and maximum values per subject and plotted in 3-year age increments: 55 to 57; 58 to 60; ...76/77 years. We reanalyzed these data stratifying by race/ethnicity (white non-Hispanic, black, Hispanic, Asian); quartiles of height, weight, and body mass index (BMI, 0-<25; 25-<30; 30-<35; 35+ kg/m^2); ever versus never smoked; oral contraceptive use (ever versus never); use of hormone replacement therapy (ever versus never); history of infertility (defined as 1 year of unprotected sex without conceiving); and history of tubal ligation. Based on International Classification of Disease for Oncology coding of pathology reports, we excluded non-endometrioid types of endometrial carcinomas, *in situ* breast carcinomas, and rectal carcinomas because the importance of hormones in the etiology of these tumors is unclear. We calculated odds ratios (OR) with 95% confidence intervals (95% CI) for associations between ovarian characteristics and cancer types using unconditional logistic regression. To explore possible effects of confounding, we did multivariate regression adjusting for race, age (5-year groups), parity (0, 1 or 2, 3+), BMI (obese versus nonobese), smoking (never, ever, current), and use of hormone replacement (never versus ever). In addition, to explore the relationship between BMI and ovarian size, we did analyses stratifying on both BMI and ovarian size, adjusted for confounders.

Results

Determinants of Noncystic Ovarian Volume. The median ovarian volume declined progressively from 1.25 cm for women ages 55 to 59 years to 1.0 cm^3 for those ages 65 to 69 years without declining further among older women (Fig. 1). The maximum volume declined across the entire age range of women studied. African American women had the largest median and maximum ovarian volumes, overall and among both obese and nonobese women (Table 1). Among both women of normal weight and those who were overweight (but not obese), Asians had the smallest ovaries. Among obese women, Asians had larger ovaries than Caucasians but this result was based on only 39 Asian women. Women in the highest quartiles for height and weight had slightly larger ovaries than shorter or lighter women. Compared with the ovarian volumes of nonobese women (BMI $\leq$30 kg/m^2), obese women showed progressively larger median and maximum volumes. Smokers had median volumes of 2.2 cm^3 and maximum volumes of 2.8 cm^3, which was twice that of never smokers. Use of hormone replacement therapy or oral contraceptives, prior tubal ligation, and infertility were not strongly associated with ovarian volume.

Selected Subject Characteristics and Associations with Cancer. White women composed >90% of subjects with each type of cancer and of controls. Univariate ORs and ORs adjusted for race, age, parity, BMI, smoking, and hormone use are shown for each cancer type in Table 2. Risk for breast cancer increased with age, BMI, and hormone use,

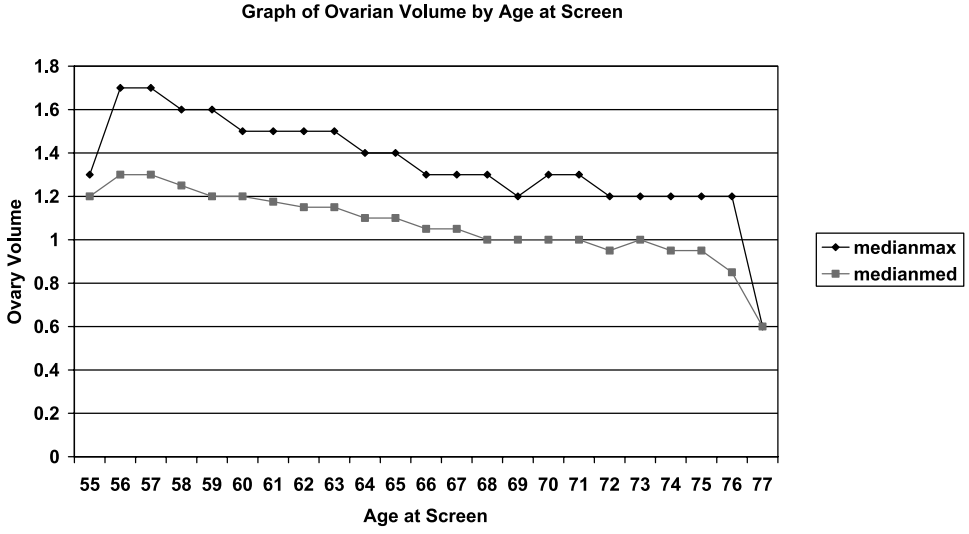

Figure 1. Ovarian volume (cm^3) calculated as the median of participants' maximum value and the median of participants' median value by age (years).

Table 1. Determinants of median ovarian volume

Factor	Median (25th-75th percentile)
Race	
Caucasian	1.10 (0.75-1.70)
Nonobese	1.10 (0.75-1.70)
Obese	1.20 (0.80-1.80)
African American	1.40 (0.90-2.40)
Nonobese	1.35 (0.90-2.35)
Obese	1.50 (0.95-2.40)
Hispanic	1.20 (0.70-1.90)
Nonobese	1.20 (0.70-1.90)
Obese	1.45 (0.80-2.00)
Asian	0.90 (0.65-1.35)
Nonobese	0.90 (0.65-1.30)
Obese	1.50 (1.05-2.10)
Height (quartiles)	
Q1	1.10 (0.70-1.60)
Q2	1.10 (0.75-1.70)
Q3	1.10 (0.80-1.70)
Q4	1.50 (1.00-2.40)
Weight (quartiles)	
Q1	1.10 (0.70-1.60)
Q2	1.10 (0.75-1.65)
Q3	1.10 (0.75-1.70)
Q4	1.60 (1.00-2.50)
BMI	
0-25	1.10 (0.75-1.60)
25-30	1.10 (0.70-1.70)
30-35	1.15 (0.80-1.80)
35+	1.30 (0.80-2.05)
Smoking (ever)	
No	1.10 (0.80-1.70)
Yes	2.20 (1.55-3.40)
Oral contraceptives (ever)	
No	1.10 (0.70-1.70)
Yes	1.15 (0.80-1.70)
Hormone replacement therapy (ever)	
No	1.10 (0.70-1.60)
Yes	1.15 (0.80-1.75)
History of infertility/parous	
No/no	1.10 (0.70-1.75)
No/yes	1.10 (0.80-1.70)
Yes/no	1.05 (0.70-1.70)
Yes/yes	1.15 (0.75-1.80)
Tubal ligation	
No	1.10 (0.75-1.70)
Yes	1.15 (0.80-1.70)

whereas parity was protective. Risk for endometrial cancer increased substantially with higher BMI and a borderline significant protective effect of parity was found. The strongest risk factor for colon cancer was increasing age with a suggestion of reduced risk among obese women and women with a history of hormone use.

After adjustment, women with median ovarian volumes ≥ 3.0 cm^3 were at increased risk for breast cancer (OR, 1.42; 95% CI, 1.14-1.77) and endometrial cancer (OR, 1.97; 95% CI, 1.12-3.48). Colon cancer risk was also highest among women with largest median ovarian volumes and adjusting for potential confounders strengthened the association (OR, 2.00; 95% CI, 1.25-3.21). However, whereas for breast and endometrial cancers, the risk increased progressively with larger median ovarian volumes (P for trend: breast cancer, 0.006; endometrial cancer, 0.02), colon cancer risk did not increase consistently with larger ovarian size. Risks for breast and endometrial cancers were also greatest for women with largest maximum ovarian volumes, but the magnitude of risk was smaller and only results for women with breast cancer were significant (OR, 1.31; 95% CI, 1.08-1.59). Ovarian cysts were identified in a minority of women and were not associated with cancer risk.

Results of analyses examining cancer associations stratified by both BMI and ovarian volume differed by tumor type. For breast cancer, associations between large ovarian volume (median volume ≥ 3.0 cm^3) were stronger among heavier women (BMI <25: OR, 1.04; 95% CI, 0.72-1.51; BMI 25-30: OR, 1.60; 95% CI, 1.12-2.28; and BMI 30+: OR, 1.70; 95% CI, 1.11-2.60). Risks of breast cancer among the heaviest women who had small ovaries were lower than those for the heaviest women with the largest ovaries, although the estimates were relatively imprecise (data not shown). In contrast, risk for endometrial cancer among women with the largest ovaries was highest among women of normal weight (OR, 3.85; 95% CI, 1.64-9.07), somewhat lower among overweight women (OR, 1.87; 95% CI, 0.57-6.13), and lowest among obese patients (OR, 1.08; 95% CI, 0.38-3.04). Endometrial cancer risk among the thinnest women with large ovaries was higher than that for any other strata defined by BMI and ovarian volume. Associations for colon cancer stratified by BMI and ovarian volume were less consistent, although the highest risk was found among obese women with large ovaries (OR, 2.78; 95% CI, 0.96-8.06).

Discussion

This study shows that the volume of noncystic benign ovaries among postmenopausal women declines with age, but the magnitude of change is small, and there is considerable interperson variation. Although our ovarian volume determinations were smaller than those previously reported, we confirmed reported associations between lower volumes and older age among menopausaul women and greater volumes with increased height (13, 14). We did not confirm the previously reported association of hormone replacement therapy and smaller volumes (13), whereas we did find that elevated BMI and smoking were related to larger ovaries. Given that most data (though not all) suggest that ovarian androgen production continues after menopause and that there may be substantial interperson variation, we hypothesize that ovarian volume represents a biologically plausible marker of current or past endogenous hormone exposure and cancer risk (15, 16).

Although some older, smaller studies have not concluded that the post-menopausal ovary is a source of androgens (15, 16), a recent study of 167 obese postmenopausal women using modern hormone assays provides affirmative evidence (17). This analysis showed that, compared with women with two intact ovaries, women who had undergone bilateral salpingoophorectomy had 35% lower levels of circulating testosterone (P = 0.01) and 23% lower levels of free testosterone (P = 0.03). Most menstrual characteristics of women were unrelated to androgen concentrations.

Our finding that Asian women have smaller ovaries than other women is consistent with data showing that Asians have lower testosterone levels (18). Similarly, we found that elevated BMI and larger ovaries were related. Elevated BMI has been associated with higher serum testosterone levels (19, 20). However, associations between epidemiologic characteristics and hormone levels have not been definitively defined.

Our analysis suggests that larger ovarian volume among postmenopausal women is associated with breast and endometrial cancer, and possibly colon cancer. The identification of similar relationships of ovarian volume with breast and endometrial cancer is affirming, given the etiologic similarities of these tumors. Adjusting for race, age, parity, BMI, smoking history and use of hormones did not alter these findings. In particular, the persistent association between large ovarian size and endometrial cancer after adjusting for BMI (a risk factor) and smoking (a protective factor) is notable and deserves further study. Although large ovarian volume was associated with increased risk for colon cancer, a clear link between progressively greater volume and risk was not found and the role of hormones (particularly androgens) in the etiology of this tumor is unclear. Interestingly, a previous report found

that colon cancer risk was increased among obese women with an apparently high estrogenic milieu (6). The presence of ovarian cysts was not associated with the three cancers studied; however, given the older age of the women in this analysis, surface inclusions cysts undoubtedly predominated (as opposed to follicular cysts or other types) and these are not known to dramatically affect hormone levels.

Although our data suggest that large postmenopausal ovaries are a marker of risk for breast and endometrial cancer, association among women cross classified by BMI and ovarian volume varied for these two cancers. Among women with breast cancer, the highest risk was found for obese women with large ovaries, whereas for endometrial cancer, risk was highest for the thinnest women with large ovaries. The mechanisms accounting for these associations are unknown. Large ovaries may represent a marker of higher androgen levels (current, past, or at both times), indicating greater availability of substrate for estrogen synthesis in peripheral adipose tissue, which is a factor that could increase risk for both tumor types. In contrast, mammary adipose tissue is a site of estrogen synthesis whereas benign endometrium shows relatively little aromatase activity (21). However, large ovaries among older women could represent a marker of higher premenopausal androgen levels, a characteristic which has been associated with anovulatory cycles characterized by estrogen exposure inadequately opposed by progesterone.

Ovarian assessment in this study was based on transvaginal ultrasounds rather than gross and microscopic pathology, precluding assessment of characteristics such as ovarian stromal hyperplasia, stromal luteinization, increased numbers of hilar cells, and other features. However, in noncystic postmenopausal ovaries, stroma accounts for the great majority of volume (22). Future studies evaluating ovarian size, serum hormone levels, and cancer risk in this cohort might provide additional data about the relevance of ovarian hormone production to carcinogenesis among older women. The observed associations between risk factors for breast and endometrial cancer and ovarian volume were modest, and although adjusting for these factors in multivariate models did not reduce ORs for these cancers, we cannot entirely exclude confounding as an explanation for our results.

Strengths of this analysis included its large size and standardization of procedures for transvaginal ultrasound assessment and data collection. Reliance on transvaginal ultrasounds provided us with an unbiased assessment of ovaries in a large control population, albeit with less detail about ovarian morphology than would be possible with pathologic study. However, the study was limited by exclusion of younger women and the relatively small number of endometrial and colon cases. In addition, we could not analyze women lacking transvaginal ultrasound data. In a prior analysis of Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial data, we found that nonvisualization was associated with older age, early menopause, a history of unilateral oophorectomy, and elevated BMI (12). Given that age was the strongest predictor of nonvisualization, we assume that nonvisualized ovaries were typically small and that their exclusion produced only slight effects on the analysis in the direction of weakening observed associations. This conclusion is supported by our exploratory attempts to predict ovarian volume using linear regression models (data not shown). All of our models accounted for <5% of the total variation in observed ovarian volume. Similarly, censoring of women with large ovaries, which were considered ''suspicious,'' may also have weakened associations between ovarian volume and cancer risk.

Table 2. Risks for breast, endometrial and colon cancers in the prostate, lung, colorectal and ovarian cancer screening trial

Risk factor	Breast cancer (n = 926)		Endometrial cancer (n = 123)		Colon cancer (n = 181)		No. controls
	OR (95% CI)*	OR (95% CI)†	OR (95% CI)*	OR (95% CI)†	OR (95% CI)*	OR (95% CI)†	
Race							
Caucasian	1.0	1.0	1.0	1.0	1.0	1.0	17,580
Black	0.78 (0.53-1.15)	0.76 (0.51-1.13)	0.22 (0.03-1.55)	0.17 (0.02-1.25)	1.18 (0.58-2.41)	1.04 (0.48-2.26)	775
Hispanic	0.76 (0.41-1.44)	0.79 (0.42-1.49)	1.15 (0.28-4.67)	1.13 (0.28-4.60)	0	0	292
Asian	1.06 (0.78-1.44)	1.08 (0.79-1.49)	1.26 (0.59-2.72)	1.51 (0.69-3.29)	1.35 (0.73-2.51)	1.26 (0.66-2.43)	784
Age, y							
55-59	1.0	1.0	1.0	1.0	1.0	1.0	7,066
60-64	1.40 (1.16-1.68)	1.49 (1.23-1.80)	1.23 (0.76-2.01)	1.33 (0.81-2.19)	1.77 (1.11-2.82)	1.86 (1.15-3.02)	6,143
65-69	1.53 (1.26-1.83)	1.71 (1.40-2.09)	1.64 (1.01-2.68)	1.94 (1.17-3.22)	1.97 (1.22-3.19)	1.97 (1.19-3.28)	4,076
70+	1.22 (0.98-1.53)	1.41 (1.12-1.77)	0.61 (0.30-1.27)	0.76 (0.36-1.60)	3.06 (1.90-4.91)	3.11 (1.88-5.14)	2,295
Parity							
0	1.0	1.0	1.0	1.0	1.0	1.0	1,664
1, 2	0.86 (0.68-1.10)	0.86 (0.67-1.10)	0.84 (0.46-1.54)	0.86 (0.47-1.59)	0.95 (0.53-1.69)	0.93 (0.52-1.67)	6,071
3+	0.76 (0.60-0.95)	0.72 (0.57-0.91)	0.58 (0.32-1.05)	0.55 (0.30-0.99)	0.98 (0.57-1.68)	0.88 (0.51-1.52)	11,818
BMI							
20-25	1.0	1.0	1.0	1.0	1.0	1.0	8,339
25-30	1.09 (0.93-1.27)	1.11 (0.95-1.30)	1.23 (0.79-1.92)	1.24 (0.79-1.95)	1.18 (0.84-1.64)	1.16 (0.83-1.63)	6,791
30-35	1.13 (0.92-1.38)	1.19 (0.97-1.47)	0.91 (0.52-1.82)	1.04 (0.55-1.96)	0.81 (0.49-1.33)	0.84 (0.50-1.39)	2,864
35+	1.02 (0.77-1.34)	1.12 (0.84-1.48)	3.42 (2.04-5.75)	3.76 (2.20-6.43)	0.56 (0.26-1.23)	0.57 (0.26-1.26)	1,437
Smoking							
Never	1.0	1.0	1.0	1.0	1.0	1.0	11,037
Current	0.87 (0.66-1.13)	0.93 (0.71-1.21)	0.19 (0.05-0.78)	0.21 (0.05-0.87)	0.87 (0.48-1.55)	1.02 (0.56-1.84)	1,760
Former	1.20 (1.04-1.39)	1.19 (1.03-1.37)	1.16 (0.80-1.69)	1.12 (0.77-1.64)	1.14 (0.83-1.57)	1.20 (0.87-1.67)	6,778
Hormone							
Never	1.0	1.0	1.0	1.0	1.0	1.0	6,780
Ever	1.38 (1.19-1.61)	1.44 (1.23-1.68)	1.16 (0.78-1.72)	1.21 (0.81-1.83)	0.69 (0.51-0.94)	0.75 (0.54-1.03)	12,780
Median ovarian volume							
0-1	1.0	1.0	1.0	1.0	1.0	1.0	7,755
1-2	1.0	1.03 (0.88-1.20)	1.30 (0.85-2.00)	1.34 (0.87-2.09)	1.14 (0.81-1.59)	1.36 (0.96-1.94)	8,111
2-3	1.13 (0.87-1.45)	1.17 (0.90-1.51)	1.47 (0.74-2.89)	1.54 (0.77-3.05)	0.69 (0.34-1.38)	0.81 (0.38-1.70)	1,616
3+	1.37 (1.11-1.70)	1.42 (1.14-1.77)	1.95 (1.12-3.41)	1.97 (1.12-3.48)	1.53 (0.96-2.42)	2.00 (1.25-3.21)	2,098

*Univariate ORs.
†ORs adjusted for all variables in the table.

Future epidemiologic studies that include hormone measurements of blood or urine and analysis of tissues may contribute insights into hormonal carcinogenesis and the risks and benefits associated with oophorectomy after menopause (23).

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