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Ovarian Volumes Among Women with Endometrial Carcinoma: Associations with Risk Factors and Serum Hormones

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Abstract

Objectives—Data suggest that post-menopausal women with larger ovaries are at increased risk for endometrial carcinoma; however, analyses comparing ovarian volume to serum hormone levels are limited. Accordingly, we assessed ovarian volumes in relation to serum sex hormone levels among post-menopausal women with endometrial carcinoma who participated in a multi-center case control study.

Methods—Data for established risk and protective factors for endometrial carcinoma were collected via in-person interviews. Ovarian volumes were estimated from pathology reports. Associations between exposures and age-adjusted ovarian volumes were analyzed for 175 cases with available data. For a subset of 135 cases, we analyzed relationships between ovarian volume, adjusted for age and body mass index (BMI), and serum hormone levels by analysis of variance.

Results—Ovarian volume declined progressively from 1.83 cm^3 among women ages 55–59 years to 1.23 cm^3 among women age 70 years or older (p-trend = 0.02). Larger ovarian volume was associated with early menarche (p-trend = 0.03), having given birth (p = 0.01), and weakly with elevated BMI (p- trend = 0.06). After adjustment, increased ovarian volume, was associated with higher estradiol (p - trend = 0.007); albumin-bound estradiol (p - trend = 0.01); and free estradiol (p - trend = 0.006) levels; androstenedione, estrone and estrone sulfate showed similar, though non-significant associations.

Conclusions—Among women with endometrial carcinoma, larger ovaries were associated with higher serum levels of estrogens. Further studies examining the role of the ovaries in post-menopausal hormonal carcinogenesis are warranted.

Keywords

Endometrial Carcinoma; Hormones; Ovary; Epidemiology

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Introduction

Exposure to excess estrogens relative to progestins is a central mechanism underlying most endometrial carcinoma risk factors [1]. After menopause, most estrogens are synthesized from androgens in adipose tissue, thereby linking obesity, elevated circulating estrogen levels, and heightened endometrial carcinoma risk [2–5]. Elevated serum androgen levels are also associated with increased endometrial carcinoma risk [4,5]; however, factors that affect androgen levels are poorly characterized.

After menopause, androgen synthesis occurs in the adrenals and the ovaries [6–8]. Historically, the importance of ovarian androgen production among older women was questioned; however, recent studies have consistently found that older women who have undergone oophorectomy have lower serum levels of testosterone and androstenedione, than those with intact ovaries, consistent with continued ovarian endocrine function after menopause [9–11]. Menopausal ovaries consist largely of stroma, which includes hormone synthesizing cells. In one post-mortem study, ovaries of women over age 60 years with prominent stroma were twice as large as ovaries with scant stroma. Larger ovaries were more likely to contain luteinized cells and hilar cells, overall suggesting a link between size and potential for hormone synthesis [12]. Therefore, post-menopausal ovarian volume may be related to androgen levels (previous or current) and carcinoma risk, but evidence for this proposal is fragmentary.

Ala-Fossi et al [13] found significantly higher median ovarian vein testosterone levels among women with ovarian stromal hyperplasia (n=13) compared to those without hyperplasia (n=39). In a study of 112 women with endometrioid endometrial carcinoma and 47 women with benign diseases, Jongen et al [14] found that increasing degrees of ovarian stromal hyperplasia were related to significantly higher levels of ovarian vein androstenedione and testosterone concentrations and endometrial carcinoma. Similarly, Sluijmer et al [15] in a smaller investigation reported significant associations between ovarian stromal hyperplasia and venous androgen levels. Lucisano et al [16] also found significant associations between ovarian stromal hyperplasia and ovarian vein androgen levels, but not with endometrial carcinoma based on an analysis of 35 cancer patients and 23 patients with benign diseases. In contrast, in a study that compared ovarian morphology of 100 endometrial carcinoma patents to 100 cancer-free women, Marcus [17] reported that ovarian stromal hyperplasia was significantly related to endometrial carcinoma. Finally, a nested case-control analysis of transvaginal ultrasound data from an ovarian cancer screening trial of post-menopausal subjects that included 123 endometrial carcinoma cases and 20,881 controls found that large ovaries were associated with a significantly elevated twofold risk, adjusted for potential confounders [18].

Stimulated by these findings, we tested the hypothesis that ovarian volume among post-menopausal women diagnosed with endometrial carcinoma is related to serum hormone levels. Accordingly, we evaluated case pathology data from an endometrial carcinoma study to determine associations of ovarian volume, epidemiologic factors and serum sex hormone levels.

Materials and Methods

Subjects

We analyzed data for post-menopausal cases included in a multi-center endometrial carcinoma case-control study conducted in the United States from 1987–1990, as described elsewhere [19]. Surgical pathology reports and microscopic slides for cases were centrally reviewed.

We analyzed data for a subset of 498 eligible consented cases who met all inclusion criteria: completed a risk factor questionnaire (n = 434); were naturally post-menopausal at diagnosis

(n = 304); had endometrioid histology (n = 267); did not report recent hormone use (n = 208); did not have significant ovarian pathology and had surgical pathology reports that included ovarian measurements of at least one benign non-cystic ovary (n = 175). Relatively few pre-menopausal women met inclusion criteria and we excluded these cases to avoid difficulties in evaluating hormonal levels among such women. Previous analyses of data from this study [20] showed that non-endometrioid carcinomas (e.g. serous carcinomas) are associated with different risk factors and serum hormone levels than "usual" endometrioid endometrial carcinomas and consequently, we excluded these women. We assessed relationships between ovarian volume and serum hormone levels for a subgroup of the 175 women (n = 135) who had donated blood that was previously assayed for hormones [5]. The age distribution for this subgroup was very similar to that of the group of 175 women.

Ovarian Volume, Epidemiologic Exposures and Serum Hormone Levels

Ovarian volumes were estimated as the product of the three ovarian dimensions X 0.523 [15, 21,22]. Ovaries that contained cysts ≥ 1.0 cm in maximum dimension (or multiple cysts measuring ≥ 1.0 cm in aggregate) or benign tumors were excluded. Although all women had two ovaries removed, volume estimates were based on one ovary for 33 women and for both ovaries for 142 women. For 10 women, we excluded one ovary that was cystic to avoid measurement error and for 23 women the surgical pathology report did not include the 3 dimensions required for volume computation. The mean ovarian volumes and hormone levels for subjects with one ovarian measurement were similar to those with two measurements (data not shown). For the latter, each woman's average ovarian volume was analyzed.

Data related to oral contraceptive use (0–1 month vs. >1 month); smoking (never, past, current); age at menarche (<12, 12, 13, 14 or ≥ 15 years); parity (0 vs. 1+); age at menopause; and past menopausal hormone therapy (HT) were obtained via in-person interviews. Body mass index (BMI) was determined using measured weight and height (Kg/m^2). Obesity was defined as a BMI ≥ 30 Kg/m^2.

Serum levels of estrone, estrone sulfate, estradiol, androstenedione and sex-hormone-binding globulin (SHBG) and estimates of free- and albumin-bound estradiol were determined as described previously [5].

Analysis

Ovarian volumes for each risk factor stratum are presented as age-adjusted geometric means. To compare ovarian volumes across exposure strata, we performed analysis of variance using the log-transformed ovarian volume for each study subject, and assessed differences across categories using an F test. We also used an F test to assess trends in ovarian volume with increasing category of exposure, modeled as a continuous variable. We also examined relationships of ovarian volume (tertiles) to log-transformed hormone and SHBG levels, adjusted for age (<55; 55–59; 60–64; 65–69; ≥70 years) and BMI (<25.0; 25.0–29.9; 30.0–34.9; ≥35.0), and assessed comparisons using similar methods. We repeated this analysis stratifying on obesity (BMI ≥ 30.0).

Results

Relationship of Epidemiologic Factors and Ovarian Volume

We assessed associations between epidemiologic factors and ovarian volume among 175 post-menopausal cases, of whom 156 (89.1%) were Caucasian; 13 (7.4%) were African-American and 6 (3.4%) were either Hispanic or of unknown race/ethnicity (Table 1). Ovarian volume declined progressively from 1.83 cm^3 among women ages 55–59 to 1.23 cm^3 among women age 70 years or older (p-trend = 0.02). Menarche before age 12 years was associated with larger

ovaries (mean = 1.76 cm^3) than menarche after age 14 years (mean = 1.02 cm^3, p-trend = 0.03). An association of larger ovaries among parous than nulliparous women was also noted (p = 0.01). BMI and weight were positively associated with ovarian volume, though not quite significantly. Age at menarche and BMI were correlated (r - Spearman = −0.22, p = 0.004), however, early menarche remained associated with larger ovarian volume after adjusting for BMI (p-trend = 0.06). Age at menopause, height, past oral contraceptive use, past HT use and smoking were not significantly associated with ovarian volume (Table 1 and data not shown). Mean ovarian volumes, adjusted for age and BMI were similar for women with stage 1 carcinomas (n = 140; 1.44 cm^3) and those with more advanced stages (n = 35; 1.57 cm^3, p = 0.58).

Serum hormone levels by ovarian volume

Increased ovarian volume, adjusted for age and BMI, was associated with significantly higher levels of estradiol (p - trend = 0.007); albumin-bound estradiol (p -trend = 0.01); and free estradiol (p - trend = 0.006; Table 2). Associations between ovarian volume and estradiol remained significant after adjusting for age at menarche. Highest tertiles of ovarian volume were also associated with higher levels of androstenedione, estrone, and estrone sulfate levels, but the associations were not statistical significant. Within each ovarian volume stratum, androstenedione levels did not differ consistently by obesity status. In contrast, within each ovarian volume stratum, obesity was associated with higher estrogen levels (data not shown).

Discussion

This analysis suggests that greater ovarian volume, as estimated directly from measurements made at the surgical pathology bench, is associated with higher serum sex-hormone levels among post-menopausal women with endometrial carcinoma, independent of age and BMI. Our analysis did not include a control group of women without carcinoma. However, ovaries of larger size have been linked to increased hormone production among healthy women (see Introduction for summary) and women with polycystic ovarian syndrome [23]. In addition, previous analyses have linked ovarian enlargement to increased endometrial carcinoma risk [14,17,18]. Based on these findings, we previously hypothesized that large post-menopausal ovaries may represent a marker of past and/or current hormonal imbalances, perhaps resembling a mild form of polycystic ovary syndrome [18]. We think that the current data provide additional support for future studies examining the contribution of post-menopausal ovarian enlargement in hormonal carcinogenesis.

In this analysis, increased ovarian volume was associated with younger age, early menarche, having had children and higher BMI/weight, although the last association was not statistically significant. Studies of healthy women that have assessed associations of epidemiologic factors with ovarian volumes determined by ultrasound have reported similar inverse associations between volume and age [21,22]. Associations between greater ovarian volume and higher BMI were found in at least one prior analysis based on ultrasound data [18], but not in other studies based on radiologic assessment [21,22]. Previous analyses have also found inverse associations between ovarian volume and use of oral contraceptives [21] or menopausal HT [22], consistent with non-significant results in our limited analysis. A positive association of ovarian volume and height has also been reported [22]. The isolated differences between the current results and those of previous investigations may reflect the fact that most prior analyses were conducted using ultrasound data collected from large groups of apparently healthy women undergoing ovarian carcinoma screening, rather than pathologic assessment of ovaries removed at the time of hysterectomy for endometrial carcinoma.

Our results show that greater ovarian size is associated with significantly increased circulating levels of total, free-, and albumin-bound estradiol and non-statistically significant elevations

in estrone, estrone sulfate and androstenedione levels. Increased ovarian volume could be related to increased androgen synthesis without producing markedly higher serum levels (i.e. androstenedione) if conversion to estrogen is rapid. This view is supported indirectly by several studies that have found that ovarian stromal hyperplasia is associated with elevated androgen concentrations in ovarian vein blood, but not with higher levels in peripheral venous blood [13,14,16]. Although some prior reports have found that higher BMI was associated with elevated testosterone levels [4,24], we found that the relationship between ovarian volume and androstenedione concentrations was unaffected by obesity status, as previously reported [25]. In contrast, ratios of estrogens to androgens were higher among obese women. If confirmed, these findings would suggest that ovarian volume is a marker of the availability of substrate for estrogen synthesis (i.e. androgen), whereas obesity affects the degree of conversion.

Ovarian enlargement and elevated androgen levels are key features of Polycystic Ovarian Syndrome (PCOS). Total or stromal ovarian volume may be linked to hyperandrogenism among women with PCOS [23]. Although pre-menopausal women with PCOS have been frequently studied, data for post-menopausal women are limited. One small analysis suggests that polycystic ovaries, hyperandrogenemia and hirsutism may be found after menopause [26]. Anecdotally, we noted that nine women with a surrogate finding of PCOS (having histories of both menstrual irregularity plus either acne or hirsutism) had a mean age- and BMI-adjusted ovarian volume of 1.99 cm^3 compared to 1.45 cm^3 for women without such a finding, although this comparison was not statistically significant. Accordingly, some post-menopausal women with ovarian enlargement and elevated serum androgen levels may have manifestations of PCOS or a similar, perhaps less severe syndrome. Ideally, longitudinal studies in which women with PCOS were followed through the menopausal transition could be performed to evaluate this hypothesis.

In summary, our study suggests that ovarian enlargement among endometrial carcinoma patients is associated with elevated serum concentrations of sex-hormones. However, our conclusions are limited by the lack of hormone data and ovarian measurements for controls and the small sample size. Nonetheless, our data provide impetus for further research on the relationship of ovarian endocrine function after menopause to risk for hormonally-related carcinomas, non-neoplastic diseases and protection against deleterious effects of aging. Clinical interest in this topic is heightened by recent studies supporting ovarian preservation for post-menopausal women at the time of hysterectomy for benign uterine diseases [27]..

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References

1. Cooke, LS.; Weiss, NS. Endometrial Cancer. In: Schottenfeld, D.; Fraumeni, JF., Jr, editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 2006.
2. Calle EE, Thun MJ. Obesity and cancer. Oncogene 2004;23:6365–78. [PubMed: 15322511]
3. Kaaks R, Lukanova A, Kurzer MS. Obesity, endogenous hormones, and endometrial cancer risk: a synthetic review. Cancer Epidemiol Biomarkers Prev 2002;11:153–43.
4. Lukanova A, Lundin E, Zeleniuch-Jacquotte A, et al. Body mass index, circulating levels of sex-steroid hormones, IGF-I and IGF-binding protein-3: a cross-sectional study in healthy women. Eur J Endocrinol 2004;150:161–71. [PubMed: 14763914]
5. Potischman N, Hoover RN, Brinton LA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. N Natl Cancer Inst 1996;88:1127–35.

6. Labrie F, Luu-The V, Labrie C, et al. Endocrine and intracrine sources of androgens in women: Inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. Endo Rev 2003;24:152–82.
7. Rinaudo P, Strauss JF III. Endocrine function of the postmenopausal ovary. Endocrinol Metab Clin N Am 2004;33:661–74.
8. Vermeulen A. Plasma androgens in women. J Reprod Med 1998;43:725–33. [PubMed: 9750201]
9. Chubak J, Tworoger SS, Yasui Y, et al. Associations between reproductive and menstrual factors and postmenopausal androgen concentrations. J Women's Health 2005;14:704–12.
10. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005;90:3847–53. [PubMed: 15827095]
11. Laughlin GA, Barett-Connor E, Kritz-Silverstein D, von Muhlen D. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab 2001;86:1842–4. [PubMed: 11297635]
12. Boss JH, Sculley RE, Wegner KH, Cohen RB. Structural variations in the adult ovary - clinical significance. Obstet Gynecol 1965;6:747–63. [PubMed: 14287465]
13. Ala-Fossi S-L, Maenpaa J, Aine R, Punnonen R. Ovarian testosterone secretion during menopause. Maturitas 1998;29:239–45. [PubMed: 9699195]
14. Jongen VHWM, Sluijmer AV, Heineman MJ. The postmenopausal ovary as an androgen-producing gland; hypothesis on the etiology of endometrial cancer. Maturitas 2002;43:77–85. [PubMed: 12385855]
15. Sluijmer AV, Heinman MJ, Koudstaal J, Theunissen PHMH, de Jong FH, Evers JLH. Relationship between ovarian production of estrone, estradiol, testosterone, and androstenedione and the ovarian degree of stromal hyperplasia in postmenopausal women. Menopause 1998;5:207–10. [PubMed: 9872485]
16. Lucisano A, Russo N, Acampora MG, et al. Ovarian and peripheral androgen and oestrogen levels in post-menopausal women: correlations with ovarian histology. Maturitas 1986;5:57–65. [PubMed: 3702762]
17. Marcus CC. Ovarian cortical stromal hyperplasia and carcinoma of the endometrium. Obstet Gynecol 1963;21:175–86. [PubMed: 13932912]
18. Sherman ME, Lacey JV, Buys SS, Reding DJ, Berg CD, Williams C, et al. Ovarian volume: determinants and associations with cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev 2005;15:1550–4. [PubMed: 16896048]
19. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, et al. Reproductive, menstrual and medical risk factors for endometrial cancer: Results from a case-controls study. Am J Obstet Gynecol 1992;167:1317–25. [PubMed: 1442985]
20. Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, et al. Analysis of risk factors and hormone levels in patients with uterine serous carcinoma. Mod Pathol 1997;10:963–8. [PubMed: 9346174]
21. Flaws JA, Rhodes JC, Langenberg P, Hirshfield AN, Kjerulff K, Sharara FI. Ovarian volume and menopausal status. J Am Menopause Soc 2000;7:53–61.
22. Pavlik EJ, DePriest PD, Gallion HH, et al. Ovarian volume related to age. Gynecol Oncol 2000;77:410–12. [PubMed: 10831351]
23. Kyei-Mensah AA, Tan SL, Zaidi J, Jacobs HS. Relationship of ovarian stromal volume to serum androgen concentrations in patients with polycystic ovary syndrome. Hum Reprod 1998;13:1437–41. [PubMed: 9688367]
24. Ukkola O, Gagnon J, Rankinen T, et al. Age, body mass index, race and other determinants of steroid hormone variability: the HERITAGE Family Study. Eur J Epidemiol 2001;145:1–9.
25. Madigan MP, Troisi R, Potischman N, Dorgan JF, Brinton LA, Hoover RN. Serum hormone levels in relation to reproductive and lifestyle factors in postmenopausal women (United States). Cancer Causes Control 1998;9:199–207. [PubMed: 9578297]
26. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Ann Intern Med 1997;126:32–5. [PubMed: 8992921]

27. Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. Obstet Gynecol 2005;106:21–26.

Table 1

Geometric Mean Ovarian Volume by Epidemiologic Factors Among Post-Menopausal Women with Endometrial Carcinoma

Epidemiologic Factor	Ovarian Volume Mean (cm^3)	P-Value
Age (Years)		
<55 (n=21)	1.67	0.02*
55–59 (n=27)	1.83	
60–64 (n=47)	1.62	
65–69 (n=44)	1.26	
≥70 (n=36)	1.23	
Age at Menarche (Years)		
15 (n=15)	1.02	0.03*
14 (n=23)	1.32	
13 (n=47)	1.54	
12 (n=59)	1.55	
<12 (n=31)	1.76	
Parity		
Nulliparous (n=30)	1.09	0.01†
Parous (n=145)	1.60	
Age at Menopause (Years)		
<45 (n=20)	1.91	0.72*
45–49 (n=55)	1.39	
50–54 (n=72)	1.46	
≥55 (n=22)	1.67	
Body Mass Index (Kg/m^2)		
<25.0 (n=40)	1.25	0.06*
25.0–29.9 (n=33)	1.49	
30.0–34.9 (n=40)	1.46	
≥35.0 (n=62)	1.72	
Oral Contraceptive Use		
No (n=161)	1.52	0.55†
Yes (n=14)	1.33	
Smoking		
Never (n=129)	1.50	0.83†
Past (n=31)	1.40	

Epidemiologic Factor	Ovarian Volume Mean (cm^3)	P-Value
Current (n=11)	1.63	

Adjusted for age group. Ovarian volume estimated as product of three dimensions X 0.523. Missing values: age at menopause (n = 6); smoking status (n = 4).

*P-trend

†P-value.

Table 2

Geometric Mean Serum Factors by Ovarian Volume Among Post-Menopausal Women with Endometrial Carcinoma

Serum Factor	Ovarian Volume <1.00 cm^3 (n=44) Mean (95% C.I.)	Ovarian Volume 1.00 - <2.03 cm^3 (n=46) Mean (95% C.I.)	Ovarian Volume ≥2.03 cm^3 (n=45) Mean (95% C.I.)	P-Trend
Androstenedione (ng/mL)	72 (61–85)	68 (58–80)	83 (70–98)	0.24
Estrone (pg/mL)	40 (36–46)	40 (35–46)	47 (41–53)	0.13
Estradiol (pg/mL)	8.1 (6.7–9.9)	10.5 (8.6–12.8)	12.0 (9.9–14.7)	0.007
Estrone Sulfate (pg/mL)	460 (359–590)	444 (349–565)	610 (477–779)	0.11
SHBG (nmol/L)	30 (25–36)	32 (26–38)	29 (24–35)	0.84
Albumin-Bound Estradiol (pg/mL)	2.2 (1.7–2.8)	2.8 (2.2–3.6)	3.5 (2.7–4.5)	0.01
Free-Estradiol (pg/mL)	0.13 (0.11–0.16)	0.17 (0.14–0.20)	0.20 (0.16–0.24)	0.006

Levels of serum factors adjusted for categories of age and body mass index. Ovarian volume estimated as product of three dimensions X 0.523, presented as tertiles.