Obesity, Height, and Serum Androgen Metabolism among Postmenopausal Women in the Women's Health Initiative Observational Study

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ABSTRACT

Background: Anthropometric measures, including obesity, are important risk factors for breast and endometrial cancers in postmenopausal women. It is unknown whether these risk factors are associated with androgen metabolism, another risk factor for these cancers.

Methods: Using baseline data from 1,765 postmenopausal women in the Women's Health Initiative Observational Study, we conducted a cross-sectional analysis examining associations between anthropometric measures [current body mass index (BMI), waist-to-hip ratio (WHR), height, and recalled BMI at age 18) and serum androgen metabolites. Twelve androgens/androgen metabolites were quantified using LC-MS/MS. Geometric means of androgen/androgen metabolite concentrations were estimated using linear regression, adjusting for potential confounders and stratified by hormone therapy (HT) use.

Results: Regardless of HT use, higher current BMI (≥30 vs. <25 kg/m^2) was associated with higher serum concentrations of dehydroepiandrosterone sulfate (DHEAS), 5α-reduced glucuronide metabolites [androsterone-glucuronide (ADT-G), 5α-androstane-3α,17β diol-3-glucuronide (3α-diol-3G), 3α-diol-17-glucuronide (3α-diol-17G)], and DHEAS:DHEA ratio (all P trend ≤ 0.02). BMI was also positively associated with unconjugated estrone:androstenedione and unconjugated estradiol:testosterone ratios among never/former HT users (all P trend < 0.001) but not among current users (P-int < 0.001). WHR was positively associated with adrenal androgens and 5α-reduced glucuronide metabolites in obese women only (BMI ≥ 30 kg/m^2; all P-trend ≤ 0.01). BMI at age 18 was inversely associated with adrenal androgens (DHEA, DHEAS, androstenedione, testosterone) and 5α-reduced glucuronide metabolites in never/former HT users (all P trend < 0.06). Height was not associated with androgen metabolites.

Conclusions: Current BMI is associated with androgen metabolism among postmenopausal women.

Impact: This study contributes to our understanding of the link between obesity and cancer risk in postmenopausal women.

Introduction

Obesity is an important risk factor for female cancers including breast (1), ovarian (2), and endometrial cancers (3) in postmenopausal women. One of potential mechanisms that may explain the obesity–cancer relationships in women is sex steroid hormone synthesis and metabolism. Adipose tissues can produce estrogens by converting androgens via aromatase activity (4). Consistently, studies have reported elevated circulating levels of estrogens in postmenopausal obese (vs. normal weight) women (5–10). In our previous analysis of estrogen metabolites in the Women's Health Initiative Observational Study (WHI-OS), we further observed associations between current body mass index (BMI) and metabolism of estrogens (methylation of catechol estrogen metabolites; ref. 10). Some studies also suggest that obesity-induced hyperinsulinemia may stimulate androgen production (11–13). However, little is known about the associations of obesity with androgen metabolism beyond aromatization to estrogens. It is also unclear whether other anthropometric measures including waist-to-hip ratio (WHR), BMI at age 18 years, and height are associated with androgen metabolism, independent of current BMI, among postmenopausal women. High WHR indicates abdominal obesity and is associated with elevated risk of endometrial and postmenopausal breast cancers (3 14, 15), BMI at age 18 and height indicate early nutritional status and adolescent exposure to proliferative hormones. Understanding associations of anthropometric measures with serum androgen metabolism will improve our understanding of the potential mechanisms through which these risk factors influence cancer risk in postmenopausal women.

Androgens, as well as estrogens, are proliferative hormones that play important roles in breast (16–18), ovarian (19 20), and endometrial (21–29) carcinogenesis. Because androgens can be converted to estrogens, circulating levels of androgens may also reflect a reservoir of precursor substrates for estrogens. Some studies have

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shown that circulating adrenal androgens [androstenedione, testosterone, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS)] were associated with increased breast (16 30, 31), ovarian (21–27), and endometrial cancer risks (19). Testosterone and androstenedione can also be metabolized to 5α-reduced metabolites and 5β-reduced metabolites. Although adrenal androgens were more commonly evaluated in previous studies, circulating levels of total 5α-reduced glucuronide metabolites [androsterone-glucuronide (ADT-G), 5α-androstane-3α, 17β diol-3-glucuronide (3α-diol-3G), 3α-diol-17-glucuronide (3α-diol-17G)] are believed to better reflect tissue-level androgenic activity (32 33), as these metabolites cannot be converted back to adrenal androgens or aromatized to estrogens. Further, when metabolites are sulfated [e.g., dihydrotestosterone sulfate (DHTS)], the metabolites become less bioactive and may act as a reservoir for more potent androgenic forms [e.g., dihydrotestosterone (DHT)]. In the WHI-OS, we previously measured 12 individual androgens/androgen metabolites in serum and found associations between circulating 5α-reduced glucuronide metabolites (ADT-G, 3α-diol-3G, 3α-diol-17G) and an increased nonserous ovarian cancer risk (28). Similar positive associations were also observed with endometrial cancer risk but were not statistically significant (19). To elucidate the effects of anthropometric risk factors on androgen metabolism patterns, we conducted a cross-sectional analysis examining the associations of several anthropometric measures (current BMI, current WHR, BMI at age 18, and height) with 12 serum androgens/androgen metabolites among postmenopausal women in the WHI-OS at baseline. Because the concentrations of androgens/androgen metabolites and the associations with anthropometric measures may vary by hormone therapy (HT) use, we examined associations separately by HT use.

Materials and Methods

Study population

This analysis included participants from a nested case–control study of ovarian and endometrial cancers in the WHI-OS (20, 29). The WHI-OS is an ongoing cohort study of 93,676 postmenopausal women who were recruited at ages of 50 to 79 years from 40 clinical centers in the United States from 1993 to 1998 (34, 35). At study enrollment, trained medical staff conducted anthropometric measurements (height, weight, waist and hip circumferences) and collected blood samples. Baseline self-administered questionnaires were used to collect information on sociodemographic characteristics, medical history, reproductive factors, and lifestyle factors.

Details of the nested case–control study are described elsewhere (20 , 29). In brief, cases were women with ovarian or endometrial cancer diagnosed between baseline and 2012. At the date of diagnosis (index date) for each case, controls were selected among women who were cancer-free matched to the case based on age at baseline (5-year categories), year of blood draw (1993–1996, 1997–1998), self-identified race/ethnicity (White, Black, Hispanic, other/unknown), hysterectomy at baseline or during follow-up prior to the index date (for ovarian controls only), and HT use (never, ≤1 year since last HT use, >1 year since last HT use, current). Both cases and controls had no history of cancer (except nonmelanoma skin cancer) at baseline, bilateral oophorectomy, or hysterectomy (for endometrial controls only), and had ≥ 1.1 mL serum sample available.

Of the 1,824 participating women, we excluded women who had missing information on any anthropometric measures ($n = 49$) and had missing values for at least one androgen/androgen metabolite ($n = 10$). After exclusion, 1,765 women (489 cases and 432 controls among never/former HT users, 442 cases and 402 controls among current HT users) were included in the analysis. Because all serum samples were collected at baseline prior to any cancer diagnosis, we included both cases and controls in this cross-sectional analysis. We also accounted for case–control selection criteria using inverse probability sampling weights.

Anthropometric assessment

Height, weight, waist circumference, and hip circumference were measured at baseline. Height was measured on a stadiometer to the nearest 0.1 cm, and weight was measured on a balance-beam scale to the nearest 0.1 kg. Waist circumference was measured at the narrowest part of the torso and hip circumference was measured at the site of maximum extension of the buttocks over nonbinding undergarments to the nearest 0.5 cm using a measuring tape. All anthropometric measurements were conducted by clinic staff following standardized protocols. We calculated BMI by dividing weight (kg) by height squared (m^2). BMI at age 18 was calculated using recalled weight and height. WHR was calculated as baseline waist circumference (cm) divided by hip circumference (cm). Based on the World Health Organization obesity classification, current BMI was categorized into 3 groups: <25.0 (normal), 25.0–29.9 (overweight), ≥30.0 kg/m^2 (obesity). Height was categorized into 5-cm intervals: <160, 160–164, ≥165 cm. WHR and BMI at age 18 were categorized into tertiles.

Laboratory assays

All serum samples were collected at baseline. Details of the assay methods are described elsewhere (28). Briefly, serum concentrations of 12 individual androgens/androgen metabolites [four adrenal androgens: DHEA, DHEAS, androstenedione, testosterone; seven 5α-reduced metabolites: 5α-androstanedione, DHT, DHTS, ADT, ADT-G, 3α-diol-3G, 3α-diol-17G; one 5β-reduced metabolite: etiocholanolone-glucuronide (Etio-G)] were quantified by stable isotope dilution high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS; Thermo Fisher, Shimadzu Scientific Instruments; ref. 36). Only Etio-G was included from 5β-reduced metabolites because concentrations of other 5β-reduced metabolites were very low in serum, did not have internal standards, or bind very weakly to the androgen receptor. Because studies suggested that combined circulating levels of ADT-G and androstanediol-glucuronide metabolites (3α-diol-3G, 3α-diol-17G) may indicate androgenic activity in tissue (32, 33), we summed the concentrations of ADT-G, 3α-diol-3G, and 3α-diol-17G as a marker of tissue-level androgenic activity. Combined and unconjugated concentrations of estradiol and estrone were previously quantified using an independent LC-MS/MS assay (20, 37). We refer to estrone and estradiol as "parent estrogens" because they serve as precursors to downstream estrogen metabolites. Unconjugated estrone and estradiol are the most potent forms of parent estrogens. Using the measures on androgens/androgen metabolites and estrogens, we calculated five different ratios: DHEAS:DHEA, DHTS:DHT, DHT:testosterone, unconjugated estrone:androstenedione, and unconjugated estradiol:testosterone ratios. We included two estrogen-to-androgen ratios (unconjugated estrone:androstenedione, unconjugated estradiol:testosterone) to estimate the extent of aromatase activity (conversion of androstenedione and testosterone into estrone and estradiol, respectively). Laboratory coefficients of variation (CV) of the assay were less than 11% and intraclass correlation coefficients (ICC) ranged from 0.77 to 0.997 (28).

Statistical analyses

Because the concentrations of androgens and estrogens differ between never/former and current HT users (Supplementary

Table S1), we stratified all analyses by HT use ($n = 921$ never/former vs. $n = 844$ current users) and examined the variation in associations by HT use. For all analyses, study participants were weighted by inverse probability sampling weights to represent the entire cohort as described by Li and Gail (38). Sampling weights accounted for the case–control sampling fractions. Sampling weight were 1 for all cases, and for controls depended on their strata defined by matching factors. After log transformation of data to improve normality, we fit inverse-probability weighted multivariable linear regression to estimate geometric means (GM) and 95% confidence intervals (CI) of individual androgens/androgen metabolite concentrations (pmol/L) according to exposure categories (current BMI, WHR, BMI at age 18, height), adjusting for potential confounders. In multivariable models, we included age at blood draw, calendar year at blood draw, race/ethnicity, smoking status, alcohol drinking, parity, family history of breast and ovarian cancers, time since menopause, moderate- to vigorous-intensity physical activity, and HT use. Additional adjustment for history of oral contraceptive use did not change results and thus was not included in the final models. For WHR, BMI at age 18, and height, we additionally adjusted for current BMI to examine the associations independent of current BMI. For current BMI, we compared the models with and without additional adjustment for WHR. We tested for trend using Wald tests for continuous exposure variables. The percent change in GMs from the lowest to highest exposure categories was estimated by taking the ratio of GM difference between the two categories over the GM of the lowest category, multiplied by 100. We tested for the difference using Wald tests. To examine whether the associations of WHR vary by BMI, we also stratified the analyses by current BMI [≥30 kg/m^2 (obese) vs. <30 kg/m^2 (nonobese)]. We tested for an interaction between current BMI and WHR using Wald test for product terms. Because adrenal androgens (DHEA, DHEAS, androstenedione, testosterone) can serve as precursors for parent estrogens (estrone and estradiol) during aromatization, we compared the mean proportions of adrenal androgens out of summed concentrations of adrenal androgens and parent estrogens across BMI categories, with adjustment for the summed concentration of adrenal androgens and parent estrogens. This approach estimates the association with replacement of androgens for estrogens, while holding the summed concentration constant. We tested for any difference across BMI categories using a global F test. In sensitivity analysis, we conducted analyses separately in cases and controls to investigate the variation in associations by the case–control status.

All statistical tests were two-sided with a 5% type-I error rate. Q values reflecting the FDR were calculated to account for multiple comparisons (18 tests per exposure). Analyses were conducted using survey procedures in SAS version 9.4 software (SAS Institute).

Ethical approval and consent to participate

The Office of Human Subjects Research at the NIH approved this analysis. As required by the Women's Health Initiative (WHI) protocol, informed consent was obtained from all study subjects. Informed consent documents and procedures were approved by the Institutional Review Board (IRB) of the Fred Hutchinson Cancer Research Center, and by the IRBs of each of the participating clinical centers.

Results

Study population characteristics

The mean age at baseline was 64.5 years in never/former HT users and 61.3 years in current HT users. Ninety percent of never/former HT users and 94% of current HT users were White. Compared with never/former HT users, current HT users had lower concentrations of adrenal androgens (DHEA, DHEAS, androstenedione, testosterone) and 5α-reduced glucuronide metabolites (ADT-G, 3α-diol-3G, 3α-diol-17G), and higher levels of DHEAS:DHEA, DHT:testosterone, unconjugated estrone:androstenedione, and unconjugated estradiol:testosterone ratios (Supplementary Table S1). Current HT users (vs. never/former users) also had lower mean BMI (26.5 vs. 27.0 kg/m^2) and WHR (0.79 vs. 0.81) at baseline. Among never/former HT users, women with higher current BMI (≥30.0 vs. <25.0 kg/m^2) were less likely to be parous, current smokers, and physically active (**Table 1**). Among current HT users, women with higher current BMI were more likely to be parous, nondrinkers, and have family history of breast and ovarian cancer, and less likely to be physically active.

Current BMI

Among both never/former and current HT users, higher current BMI (≥30.0 vs. <25.0 kg/m^2) was associated with higher concentrations of DHEAS, 5α-reduced glucuronide metabolites (ADT-G, 3α-diol-3G, 3α-diol-17G), and DHEAS:DHEA ratio (all P trend ≤ 0.02; **Table 2**). Higher current BMI was also positively associated with the estrogen-to-androgen ratios among never/former HT users (GM = 50.0 vs. 36.9 unconjugated estrone:androstenedione; 38.5 vs. 17.0 unconjugated estradiol:testosterone; all P trend < 0.001) but not among current HT users (GM = 172 vs. 201, P-trend = 0.13; GM = 97.7 vs. 91.9, P trend = 0.57; respectively). For the estrogen-to-androgen ratios, the interactions by HT use were statistically significant (all P int < 0.001). The associations did not change after additional adjustment for current WHR (Supplementary Table S2).

Among never/former HT users, the proportion of adrenal androgens out of summed concentrations of adrenal androgens and parent estrogens was also lower in obese women (current BMI ≥ 30.0 vs. <25.0 kg/m^2: 66.7% vs. 72.2%, respectively; $P = 0.01$; **Figure 1**), while holding the summed concentrations constant. No association with proportion of adrenal androgens (vs. parent estrogens) was found among current HT users (current BMI ≥ 30.0 vs. <25.0 kg/m^2: 30.3% vs. 25.5%, $P = 0.08$; Supplementary Fig. S1).

Current waist-to-hip ratio

In models without adjustment for current BMI, current WHR (highest vs. lowest tertiles) was positively associated with serum 5α-reduced glucuronide metabolites (ADT-G, 3α-diol-3G, 3α-diol-17G) and, among never/former HT users, unconjugated estradiol:testosterone ratio (all P trend ≤ 0.01; Supplementary Table S3). After additional adjustment for current BMI, the associations were substantially attenuated (**Table 3**). The overall patterns of the associations were similar between never/former and current HT users.

When stratified by current BMI (≥30 vs. <30 kg/m^2) among never/former HT users, current WHR (highest vs. lowest tertiles) was positively associated with DHEA (GM = 4.87 vs. 3.65 pmol/L), DHEAS (1242 vs. 745 pmol/L), androstenedione (1.62 vs. 1.45 pmol/L), DHTS (1.32 vs. 0.86 pmol/L), ADT-G (28.8 vs. 15.6 pmol/L), 3α-diol-3G (2.57 vs. 1.09 pmol/L), 3α-diol-17G (1.51 vs. 1.21 pmol/L), and DHTS:DHT ratio (7.22 vs. 3.98) in women with higher BMI but not in women with lower BMI, in models additionally adjusted for current BMI as a continuous variable within each stratum (**Table 4**). However, the interaction by current BMI was not statistically significant for these metabolites. Among current HT users, no association for current WHR was

Table 1. Characteristics of study population according to current BMI, stratified by current use of HT: the WHI-OS.

Characteristics		Never/former HT users ($N = 921$, weighted $N = 29{,}839$) Current BMI (kg/m^2)			Current HT users ($N = 844$, weighted $N = 24{,}010$) Current BMI (kg/m^2)		
		<25.0	25.0–29.9	≥30.0	<25.0	25.0–29.9	≥30.0
		N (weighted %[a])			*N* (weighted %[a])		
HT use	Never	209 (56.6)	181 (56.1)	230 (59.6)	NA	NA	NA
	Former	125 (43.4)	101 (43.9)	75 (40.4)	NA	NA	NA
	Current	NA	NA	NA	426 (100.0)	251 (100.0)	167 (100.0)
Age at baseline blood draw	<55 years	38 (11.7)	18 (5.0)	22 (7.1)	44 (15.0)	28 (17.3)	26 (19.5)
	55–59 years	49 (13.0)	56 (18.6)	69 (24.8)	96 (28.2)	56 (21.6)	36 (27.7)
	60–64 years	76 (21.9)	58 (16.6)	84 (23.3)	100 (19.8)	60 (24.6)	48 (29.0)
	65–69 years	65 (19.3)	69 (27.2)	63 (26.2)	98 (20.2)	44 (18.6)	28 (14.8)
	70–74 years	68 (22.0)	50 (22.2)	46 (10.8)	67 (11.6)	41 (13.8)	21 (6.5)
	75–79 years	38 (12.1)	31 (10.5)	21 (7.8)	21 (5.2)	22 (4.0)	8 (2.4)
White		307 (93.7)	246 (86.5)	262 (88.5)	397 (90.4)	242 (96.3)	158 (96.3)
Calendar year at blood draw	1993–1996	201 (59.9)	173 (61.4)	191 (62.6)	282 (65.9)	144 (54.1)	96 (63.0)
	1997–1998	133 (40.1)	109 (38.6)	114 (37.4)	144 (34.1)	107 (45.9)	71 (37.0)
Smoking status	Never	175 (49.4)	150 (55.6)	150 (48.3)	213 (48.5)	116 (40.1)	79 (47.9)
	Former	126 (39.2)	117 (38.5)	141 (46.1)	195 (45.7)	127 (55.8)	80 (44.7)
	Current	33 (11.4)	15 (5.9)	14 (5.6)	18 (5.8)	8 (4.0)	8 (7.4)
Alcohol drinking	Nondrinker	81 (23.9)	78 (33.8)	103 (29.9)	79 (18.8)	55 (23.2)	46 (30.5)
	<1 drink/wk	93 (32.2)	95 (24.9)	105 (34.3)	122 (29.5)	84 (31.9)	72 (43.5)
	1–6 drinks/wk	98 (24.1)	67 (24.1)	60 (24.4)	138 (31.0)	75 (33.0)	37 (17.7)
	≥7 drinks/wk	62 (19.8)	42 (17.3)	37 (11.4)	87 (20.7)	37 (11.9)	12 (8.2)
Parous		280 (82.3)	249 (91.7)	244 (78.8)	368 (83.4)	225 (91.8)	143 (90.7)
Family history of breast or ovarian cancer		73 (19.2)	56 (21.8)	55 (20.7)	82 (17.6)	47 (16.6)	35 (24.2)
Time since menopause	<10 years	104 (31.5)	92 (29.6)	95 (29.1)	164 (44.7)	96 (42.5)	78 (46.1)
	10–20 years	124 (33.9)	102 (40.2)	120 (38.5)	168 (33.6)	91 (35.1)	57 (34.8)
	20+ years	92 (31.0)	80 (26.0)	68 (26.2)	94 (21.7)	64 (22.5)	32 (19.1)
	Missing	14 (3.6)	8 (4.2)	22 (6.2)	0 (0)	0 (0)	0 (0)
Moderate-to-vigorous intensity physical activity	0 MET-hr/wk	35 (11.8)	54 (16.7)	102 (36.1)	43 (14.9)	46 (16.4)	50 (29.3)
	0.1–9.9 MET-hr/wk	101 (29.2)	91 (28.9)	98 (33.5)	122 (26.3)	86 (41.1)	63 (42.5)
	≥10.0 MET-hr/wk	198 (59.1)	137 (54.4)	105 (30.4)	261 (58.8)	119 (42.5)	54 (28.3)

Abbreviations: hr, hours; HT, hormone therapy; MET, metabolic equivalent of task; NA, not applicable; wk, week.
[a]Percentages reflect weighted counts and refer to the study cohort.

observed in the analysis stratified by current BMI (Supplementary Table S4).

BMI at age 18 years

In models without adjustment for current BMI, BMI at age 18 was inversely associated with adrenal androgens (DHEA, DHEAS, androstenedione, testosterone) and positively associated with estrogen-to-androgen ratios (unconjugated estrone:androstenedione, unconjugated estradio:testosterone) among never/former HT users (all p trend ≤ 0.05; Supplementary Table S5). In current HT users, similar patterns of associations were observed but the associations were not statistically significant. After additional adjustment for current BMI, BMI at age 18 (highest vs. lowest tertiles) was inversely associated with adrenal androgens and 5α-reduced glucuronide metabolites among both never/former and current HT users (**Table 5**). Among current HT users, BMI at age 18 was also positively associated with DHT:testosterone ratio (GM = 0.45 vs. 0.38; P trend = 0.01). The positive associations between BMI at age 18 and estrogen-to-androgen ratios disappeared after adjustment for current BMI, except for unconjugated estrone:androstenedione in current HT users.

Adult height

Among both never/former and current HT users, height was not associated with any of the androgens/androgen metabolites (Supplementary Table S6).

When adjusting for multiple comparisons, most of the associations remained significant at a 5% FDR (**Tables 2–5**). Similar results were observed in cases and controls (Supplementary Tables S7 and S8).

Discussion

In this study, we conducted a comprehensive analysis of the relationships between anthropometric measures and 12 serum androgens/androgen metabolites in postmenopausal women. In this analysis, we found that higher current BMI was associated with higher circulating levels of sulfated adrenal androgens (DHEAS) and 5α-reduced glucuronide metabolites (ADT-G, 3α-diol-3G, 3α-diol-17G), suggesting increased androgen production (and/or increased retention) and tissue-level androgenic activity. Among never/former HT users, current BMI was also positively associated with the estrogen-to-androgen ratios and the relative proportions of parent estrogens (vs. adrenal androgens), suggesting an elevated conversion of androgens to estrogens in obese women. Current WHR was not independently associated with androgens/androgen metabolites among women with low current BMI (<30 kg/m^2) but was positively associated with circulating adrenal androgens and 5α-reduced glucuronide metabolites in women with high current BMI (≥30 kg/m^2). With adjustment for current BMI, BMI at age 18 was inversely associated with adrenal androgens and 5α-

Table 2. Geometric means (pmol/L) and 95% CIs of serum androgens/androgen metabolites by current BMI in postmenopausal women, stratified by HT use: the WHI-OS.

	Never/former HT users						Current HT users						
	Current BMI						Current BMI						
	<25.0 kg/m^2	25.0–29.9 kg/m^2	≥30.0 kg/m^2	P_{trend}[a]	%Δ[b]	P_{diff}[c]	<25.0 kg/m^2	25.0–29.9 kg/m^2	≥30.0 kg/m^2	P_{trend}[a]	%Δ[b]	P_{diff}[c]	P_{int}[d]
Median (kg/m^2)	22.5	27.1	33.7				22.4	26.9	33.0				
N	334	282	305				126	251	167				
Weighted *N*[e]	13,209	8,962	7,669				10,976	7,553	5,481				
	Geometric means (95% CI)						Geometric means (95% CI)						
Adrenal androgens													
DHEA	4.58 (3.98–5.26)	4.74 (4.16–5.40)	4.83 (4.20–5.55)	0.34	5.5	0.51	4.05 (3.56–4.59)	3.99 (3.39–4.71)	4.37 (3.73–5.11)	0.36	7.9	0.35	0.98
DHEAS	952 (811–1,118)	1,060 (905–1,241)	1,170 (982–1,394)	0.02[f]	22.9	0.03	911 (794–1,044)	941 (777–1,139)	1,171 (987–1,389)	0.01[f]	28.5	0.01[f]	0.82
Androstenedione	1.37 (1.24–1.52)	1.39 (1.26–1.54)	1.46 (1.30–1.64)	0.31	6.6	0.29	1.25 (1.14–1.36)	1.18 (1.05–1.32)	1.29 (1.16–1.44)	0.70	3.2	0.57	0.81
Testosterone	0.56 (0.50–0.64)	0.60 (0.53–0.68)	0.57 (0.49–0.65)	0.31	1.8	0.93	0.49 (0.44–0.55)	0.50 (0.44–0.57)	0.54 (0.48–0.61)	0.24	10.2	0.21	0.66
5α-Reduced metabolites													
5α-androstenedione	1.31 (1.19–1.45)	1.26 (1.13–1.40)	1.31 (1.16–1.48)	0.65	0.0	0.98	1.29 (1.18–1.42)	1.27 (1.14–1.42)	1.56 (1.37–1.77)	0.03	20.9	0.01[f]	0.29
DHT	0.19 (0.17–0.21)	0.18 (0.16–0.20)	0.19 (0.17–0.21)	0.49	0.0	0.83	0.21 (0.19–0.23)	0.21 (0.18–0.24)	0.21 (0.18–0.23)	0.67	0	0.81	0.18
DHTS	0.92 (0.82–1.04)	0.98 (0.86–1.11)	1.08 (0.93–1.26)	0.05	17.4	0.04	0.99 (0.85–1.15)	0.95 (0.82–1.11)	1.00 (0.85–1.18)	0.52	1.0	0.88	0.50
ADT	0.52 (0.49–0.56)	0.54 (0.49–0.58)	0.55 (0.50–0.60)	0.26	5.8	0.30	0.49 (0.46–0.53)	0.52 (0.48–0.56)	0.50 (0.46–0.54)	0.69	2.0	0.80	0.50
ADT-G	16.6 (14.3–19.2)	20.4 (17.5–23.8)	24.4 (20.3–29.3)	<0.001[g]	47.0	<0.001[g]	13.9 (11.8–16.5)	16.2 (13.1–20.0)	20.4 (16.9–24.7)	0.001[g]	46.8	<0.001[g]	0.94
3α-diol-3G	1.20 (1.02–1.41)	1.37 (1.16–1.61)	1.74 (1.42–2.14)	<0.001[g]	45.0	<0.001[g]	1.08 (0.94–1.24)	1.32 (1.11–1.56)	1.69 (1.42–2.00)	<0.001[g]	56.5	<0.001[g]	0.41
3α-diol-17G	0.95 (0.83–1.08)	1.23 (1.08–1.40)	1.46 (1.25–1.71)	<0.001[g]	53.7	<0.001[g]	0.72 (0.63–0.83)	0.85 (0.71–1.02)	1.02 (0.86–1.22)	<0.001[g]	41.7	<0.001[g]	0.70
Marker of tissue-level androgenic activity													
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	19.2 (16.7–22.1)	23.5 (20.3–27.2)	28.1 (23.5–33.5)	<0.001[g]	46.4	<0.001[g]	16.1 (13.8–18.9)	18.8 (15.3–22.9)	23.4 (19.5–28.1)	0.001[g]	45.3	<0.001[g]	0.97
5β-Reduced metabolites													
Etio-G	32.1 (27.1–38.1)	33.5 (28.4–39.6)	36.0 (29.5–44.0)	0.27	12.2	0.28	31.8 (27.7–36.7)	34.8 (29.4–41.2)	38.7 (32.5–46.1)	0.10	21.7	0.07	0.59
Ratios													
DHEAS: DHEA	208 (188–230)	224 (200–250)	242 (216–272)	0.02[f]	16.3	0.02	225 (203–249)	236 (207–268)	268 (241–299)	0.01[f]	19.1	0.004[f]	0.70
DHTS: DHT	4.86 (4.26–5.55)	5.45 (4.65–6.39)	5.78 (4.88–6.85)	0.03	18.9	0.06	4.71 (4.02–5.52)	4.59 (3.91–5.38)	4.85 (4.02–5.86)	0.71	3.0	0.77	0.15
DHT: Testosterone	0.34 (0.30–0.38)	0.30 (0.26–0.34)	0.33 (0.28–0.39)	0.15	−2.9	0.80	0.43 (0.38–0.48)	0.41 (0.36–0.48)	0.38 (0.33–0.45)	0.42	−11.6	0.20	0.51
Unconjugated estrone: Androstenedione	36.9 (32.3–42.1)	44.1 (38.6–50.5)	50.0 (42.4–58.9)	<0.001[g]	35.5	<0.001[g]	201 (171–237)	185 (147–233)	172 (137–216)	0.13	−14.4	0.24	<0.001[g]
Unconjugated estradiol: Testosterone	17.0 (13.7–20.9)	23.0 (19.0–27.7)	38.5 (31.3–47.2)	<0.001[g]	126.5	<0.001[g]	91.9 (74.6–113)	91.9 (73.1–116)	97.7 (77.1–124)	0.57	6.3	0.67	<0.001[g]

Note: Adjusted for age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), calendar year at blood draw (1993–1996, 1997–1998), race (White, non-White), smoking status (never, former, current), moderate- to vigorous-intensity physical activity (0, 0.1–9.9, ≥10 MET-hr/wk), alcohol drinking (nondrinker, <1 drink/wk, 1–6 drinks/wk, ≥7 drinks/wk), parous (yes, no), family history of breast and ovarian cancer (yes, no), and time since menopause (<10 years, 10–19 years, ≥20 years, missing). Additionally adjusted for HT use (never, former) among women never/former HT use.

[a]P_{trend} was estimated using the Wald test for continuous BMI (kg/m^2).

[b]%Δ indicates the percentage change in GMs of androgens/androgen metabolite levels, comparing women with current BMI ≥ 30 vs. < 25 kg/m^2.

[c]P_{diff} was estimated using the Wald test and indicates *P* value for comparing androgens/androgen metabolite levels of women with current BMI ≥ 30 vs. < 25 kg/m^2.

[d]P_{int} was estimated using the Wald test for an interaction term between current BMI and HT use.

[e]Weighted *n* reflects weighted counts and refers to the study cohort.

[f]FDR *q* value < 0.05 and ≥ 0.01.

[g]FDR *q* value < 0.01.

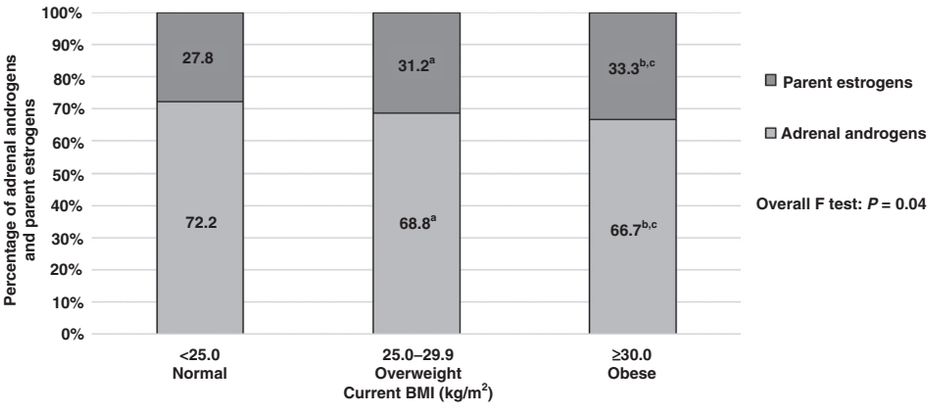

Figure 1.

Proportions of adrenal androgens (DHEA, DHEAS, androstenedione, testosterone) and parent estrogens (estradiol and estrone) out of summed concentrations of adrenal androgens and parent estrogens according to current BMI categories among postmenopausal women not using HT. Adjusted for age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), calendar year at blood draw (1993–1996, 1997–1998), race (White, non-White), smoking status (never, former, current), moderate- to vigorous-intensity physical activity (0, 0.1–9.9, ≥10 MET-hr/wk), alcohol drinking (nondrinker, <1 drink/wk, 1–6 drinks/wk, ≥7 drinks/wk), parous (yes, no), family history of breast and ovarian cancer (yes, no), time since menopause (<10 years, 10–19 years, ≥20 years, missing), and HT use (never, former). [a]*P* value for comparing proportions of adrenal androgens between women with current BMI 25.0–29.9 vs. <25.0 kg/m^2 was 0.10. [b]*P* value for comparing proportions of adrenal androgens between women with current BMI ≥30.0 vs. <25.0 kg/m^2 was 0.01. [c]*P* value for comparing proportions of adrenal androgens between women with current BMI ≥30.0 vs. 25.0–29.9 kg/m^2 was 0.31.

reduced glucuronide metabolites. Height was not associated with any of the androgens/androgen metabolites.

Our findings of positive associations between current BMI and the relative proportion of parent estrogens (vs. adrenal androgens) are in line with biologic and epidemiologic evidence on the relationship between postmenopausal adiposity and estrogens (4, 10, 39, 40). In postmenopausal women, their ovaries stop producing estradiol and other potent estrogens, leading to reduced circulating levels. In postmenopausal obese women, adipose tissues produce estrogens via aromatization of androgens (4, 40), leading to elevated circulating levels of estradiol (from conversion of testosterone) and estrone (from conversion of androstenedione) as shown in a previous pooled analysis (39). Our previous analysis in the WHI-OS also identified strong positive associations between current BMI and serum parent estrogens among never/former HT users (10). To further investigate the association of postmenopausal adiposity on aromatase activity, in the present study we compared the serum concentrations of parent estrogens with adrenal androgens, while holding the summed concentration constant. Because androgens are converted to estrogens during aromatization, the proportion of estrogens should increase while the proportion of androgens decrease in the setting of elevated aromatase activity. In the present study, postmenopausal obese (vs. nonobese) women had a higher proportion of serum parent estrogens (vs. adrenal androgens), suggesting an increased replacement of androgens for estrogens. Our data further support the increased aromatization associated with postmenopausal adiposity. Higher concentrations of estrogens compared with those of androgens may stimulate cellular proliferation at a greater extent, leading to increased cancer risks (19, 28). Among current HT users, there was no difference in the proportions of parent estrogens according to current BMI, possibly due to the negative feedback that suppresses the aromatization of androgens in the presence of excess estrogens (from exogenous source). Among both never/former and current HT users, we also observed that circulating levels of adrenal androgens are elevated in obese women and most adrenal androgens were present in sulfated forms (DHEAS). In postmenopausal obese women, androgen production (or retention) may also be stimulated, and the excess androgens get stored as sulfated forms to be used later. Consistently, animal studies have demonstrated an increased aromatase activity (41) and hyperandrogenism (42) in obese mice. Studies also suggest that hyperinsulinemia may contribute to elevated androgen production in obese women (42–45). Together, our findings suggest that postmenopausal adiposity may be associated with estrogen production by stimulating androgen production/retention (i.e., increased total concentrations of precursor substrates for estrogens) and promoting aromatase activity (i.e., faster conversion of androgens to estrogens), particularly in women not using HT.

In this analysis, we examined current BMI in relation to androgen metabolism beyond aromatization to estrogens. Among both never/former and current HT users, we observed positive associations between current BMI and serum 5α-reduced glucuronide metabolites, the androgen metabolism profiles that have previously been associated with higher endometrial (19) and nonserous ovarian cancer risks (28). However, current BMI was not associated with serum Etio-G, one of major 5β-reduced metabolites. These findings suggest that postmenopausal obesity may alter 5α-reductase activity but not 5β-reductase activity. Studies have suggested that 5α-reduced glucuronide metabolites may better reflect the androgenic activity in tissue (32, 33). The 5α-reduced metabolites are also believed to have higher biologic activity than 5β-reduced metabolites and thus increased levels of 5α-reduced metabolites may indicate a more carcinogenic androgen metabolism profile. While the BMI-cancer relationships in postmenopausal women have been explained primarily by estrogenic, inflammatory, and metabolic pathways, the fourth mechanism, namely androgenic pathway, may also influence cancer risk. Postmenopausal obesity may have both estrogen-dependent (estrogen production) and estrogen-independent (androgen production and tissue-level androgenic activity) effects. Androgen signaling may contribute to cancer risk by stimulating cellular proliferation and inhibiting apoptosis (46–48). Circulating levels of androgens have been associated with increased breast (16, 30, 31), ovarian (21–28), and

Table 3. Geometric means (pmol/L) and 95% CI of serum androgens/androgen metabolites by current waist-to-hip ratio in postmenopausal women, stratified by HT use: the WHI-OS.

	Never/former HT users						Current HT users						
	Waist-to-hip ratio						Waist-to-hip ratio						
	T1	T2	T3	P_{trend}[a]	%Δ[b]	P_{diff}[c]	T1	T2	T3	P_{trend}[a]	%Δ[b]	P_{diff}[c]	P_{int}[d]
Median (range)	0.74 (0.49–0.77)	0.81 (0.78–0.83)	0.89 (0.84–1.37)				0.73 (0.38–0.74)	0.78 (0.75–0.80)	0.86 (0.81–1.22)				
N	306	308	307				281	282	281				
Weighted *N*[e]	10,270	9,779	9,790				7,813	7,361	8,836				
	Geometric means (95% CI)						Geometric means (95% CI)						
Adrenal androgens													
DHEA	4.97 (4.25–5.81)	4.40 (3.83–5.05)	4.79 (4.23–5.42)	0.83	−3.6	0.67	4.20 (3.56–4.94)	4.01 (3.46–4.64)	4.13 (3.59–4.76)	0.76	−1.7	0.86	0.66
DHEAS	1,070 (893–1,282)	1,044 (874–1,247)	1,058 (910–1,231)	0.66	−1.1	0.90	881 (723–1,075)	1,005 (864–1,169)	991 (854–1,151)	0.45	12.5	0.27	0.34
Androstenedione	1.48 (1.32–1.66)	1.25 (1.14–1.38)	1.48 (1.33–1.65)	0.75	0.0	0.99	1.26 (1.11–1.43)	1.24 (1.13–1.36)	1.22 (1.10–1.36)	0.79	−3.2	0.66	0.88
Testosterone	0.68 (0.58–0.78)	0.50 (0.44–0.57)	0.57 (0.50–0.66)	0.31	−16.2	0.05	0.52 (0.45–0.60)	0.51 (0.45–0.57)	0.49 (0.44–0.55)	0.69	−5.8	0.52	0.50
5α-Reduced metabolites													
5α-Androstenedione	1.44 (1.31–1.59)	1.34 (1.20–1.49)	1.19 (1.07–1.33)	0.11	−17.4	0.002[f]	1.37 (1.20–1.57)	1.35 (1.21–1.50)	1.32 (1.20–1.46)	0.77	−3.6	0.68	0.22
DHT	0.21 (0.19–0.23)	0.18 (0.16–0.19)	0.18 (0.17–0.19)	0.05	−14.3	0.01	0.21 (0.18–0.24)	0.21 (0.19–0.24)	0.20 (0.18–0.23)	0.35	−4.8	0.62	0.29
DHTS	0.98 (0.85–1.12)	1.00 (0.87–1.15)	1.00 (0.88–1.14)	0.84	2.0	0.77	0.95 (0.80–1.13)	0.98 (0.84–1.16)	0.99 (0.85–1.15)	0.95	4.2	0.72	0.82
ADT	0.55 (0.51–0.60)	0.52 (0.48–0.57)	0.53 (0.49–0.58)	0.97	−3.6	0.45	0.50 (0.46–0.54)	0.51 (0.47–0.55)	0.49 (0.46–0.53)	0.56	−2.0	0.86	0.78
ADT-G	19.6 (16.5–23.3)	19.0 (16.1–22.4)	21.6 (18.4–25.2)	0.16	10.2	0.35	14.0 (11.4–17.2)	15.4 (12.9–18.4)	17.1 (14.2–20.5)	0.18	22.1	0.11	0.48
3α-diol-3G	1.33 (1.10–1.60)	1.33 (1.13–1.57)	1.57 (1.29–1.89)	0.14	18.0	0.13	1.07 (0.90–1.27)	1.26 (1.08–1.48)	1.35 (1.18–1.56)	0.05	26.2	0.02	0.33
3α-diol-17G	1.12 (0.97–1.31)	1.15 (1.00–1.32)	1.27 (1.10–1.47)	0.11	13.4	0.17	0.70 (0.59–0.83)	0.82 (0.70–0.95)	0.88 (0.76–1.02)	0.003[f]	25.7	0.01	0.17
Marker of tissue-level androgenic activity													
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	22.5 (19.1–26.6)	21.8 (18.6–25.6)	24.9 (21.5–29.0)	0.15	10.7	0.30	16.2 (13.4–19.6)	17.9 (15.1–21.1)	19.7 (16.6–23.4)	0.12	21.6	0.08	0.43
5β-Reduced metabolites													
Etio-G	34.4 (28.4–41.7)	32.1 (26.7–38.5)	34.8 (29.3–41.4)	0.75	1.2	0.91	32.4 (27.2–38.7)	34.8 (29.6–40.9)	34.3 (29.9–39.4)	0.89	5.9	0.58	0.68
Ratios													
DHEAS: DHEA	215 (192–242)	237 (212–265)	221 (200–244)	0.34	2.8	0.70	210 (183–241)	251 (225–280)	240 (217–265)	0.16	14.3	0.07	0.36
DHTS: DHT	4.69 (4.03–5.46)	5.72 (4.90–6.68)	5.57 (4.81–6.46)	0.29	18.8	0.06	4.56 (3.76–5.54)	4.60 (3.89–5.44)	4.87 (4.15–5.72)	0.49	6.8	0.54	0.63
DHT: Testosterone	0.31 (0.27–0.35)	0.35 (0.30–0.40)	0.31 (0.27–0.36)	0.72	0.0	0.87	0.40 (0.35–0.47)	0.42 (0.37–0.48)	0.41 (0.36–0.47)	0.76	2.5	0.80	0.90
Unconjugated estrone: Androstenedione	45.0 (39.2–51.7)	43.6 (38.6–49.2)	42.4 (36.7–49.0)	0.39	−5.8	0.43	194 (156–241)	206 (171–248)	177 (146–215)	0.57	−8.8	0.48	0.07
Unconjugated estradiol: Testosterone	23.3 (19.0–28.7)	25.3 (21.1–30.4)	26.1 (21.4–31.8)	0.25	12.0	0.31	82.6 (65.1–105)	97.1 (77.4–122)	95.6 (78.2–117)	0.20	15.7	0.27	0.08

Note: Adjusted for age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), calendar year at blood draw (1993–1996, 1997–1998), race (White, non-White), smoking status (never, former, current), moderate- to vigorous-intensity physical activity (0, 0.1–9.9, ≥10 MET-hr/wk), alcohol drinking (nondrinker, <1 drink/wk, 1–6 drinks/wk, ≥7 drinks/wk), parous (yes, no), family history of breast and ovarian cancer (yes, no), time since menopause (<10 years, 10–19 years, ≥20 years, missing), and current BMI (kg/m^2, continuous). Additionally adjusted for HT use (never, former) among women never/former HT use. T1, T2, and T3 indicate tertiles, with T1 for the lowest tertile and T3 for the highest tertile.

[a]P_{trend} was estimated using the Wald test for continuous waist-to-hip ratio.

[b]%Δ indicates the percentage change in GMs of androgens/androgen metabolite levels, comparing women at the highest vs. lowest tertiles of waist-to-hip ratio.

[c]P_{diff} was estimated using the Wald test and indicates *P* value for comparing androgens/androgen metabolite levels of women at the highest vs. lowest tertiles of waist-to-hip ratio.

[d]P_{int} was estimated using the Wald test for an interaction term between waist-to-hip ratio and HT use.

[e]Weighted *n* reflects weighted counts and refers to the study cohort.

[f]FDR *q* value < 0.05 and ≥ 0.01.

Table 4. Geometric means (pmol/L) and 95% CIs of serum androgens/androgen metabolites by current waist-to-hip ratio in postmenopausal women, stratified by current BMI (<30 vs. ≥30 kg/m^2) among never/former HT users.

	Current BMI < 30 kg/m^2						Current BMI ≥ 30 kg/m^2						
	Waist-to-hip ratio						Waist-to-hip ratio						
	T1	T2	T3	P_{trend}[a]	%Δ[b]	P_{diff}[c]	T1	T2	T3	P_{trend}[a]	%Δ[b]	P_{diff}[c]	P_{int}[d]
Median (range)	0.74 (0.53–0.78)	0.81 (0.78–0.84)	0.88 (0.84–1.37)				0.75 (0.49–0.78)	0.81 (0.78–0.84)	0.90 (0.84–1.17)				
N	270	209	137				36	99	170				
Weighted *N*[e]	9,325	7,672	5,174				945	2,107	4,616				
	Geometric means (95% CI)						Geometric means (95% CI)						
Adrenal androgens													
DHEA	5.05 (4.28–5.97)	4.30 (3.64–5.08)	4.39 (3.75–5.15)	0.10	−13.1	0.17	3.65 (2.73–4.87)	3.97 (3.07–5.14)	4.87 (3.80–6.24)	0.003[f]	33.4	0.06	0.97
DHEAS	1,047 (866–1,267)	982 (802–1,202)	885 (730–1,073)	0.26	−15.5	0.16	745 (543–1,024)	1,093 (802–1,489)	1,242 (925–1,669)	0.003[f]	66.7	0.003[f]	0.53
Androstenedione	1.46 (1.30–1.63)	1.23 (1.10–1.37)	1.38 (1.22–1.57)	0.32	−5.5	0.51	1.45 (1.16–1.80)	1.20 (1.01–1.43)	1.62 (1.33–1.96)	0.01[f]	11.7	0.30	0.43
Testosterone	0.68 (0.58–0.79)	0.49 (0.42–0.56)	0.56 (0.48–0.66)	0.16	−17.6	0.07	0.68 (0.55–0.85)	0.53 (0.43–0.65)	0.63 (0.52–0.75)	0.36	−7.4	0.42	0.20
5α-Reduced metabolites													
5α-Androstenedione	1.44 (1.30–1.60)	1.35 (1.19–1.53)	1.16 (1.03–1.30)	0.05	−19.4	0.001[f]	1.48 (1.19–1.83)	1.30 (1.08–1.58)	1.32 (1.08–1.61)	0.79	−10.8	0.30	0.98
DHT	0.21 (0.19–0.24)	0.18 (0.16–0.20)	0.17 (0.16–0.19)	0.01	−19.0	0.01	0.22 (0.18–0.25)	0.16 (0.14–0.19)	0.18 (0.15–0.22)	0.90	−18.2	0.10	0.10
DHTS	0.93 (0.81–1.07)	0.99 (0.86–1.15)	0.90 (0.77–1.05)	0.27	−3.2	0.75	0.86 (0.57–1.29)	1.07 (0.76–1.51)	1.32 (0.94–1.84)	0.03	53.5	0.02	0.36
ADT	0.56 (0.51–0.61)	0.52 (0.47–0.57)	0.50 (0.45–0.55)	0.51	−10.7	0.04	0.47 (0.39–0.56)	0.55 (0.47–0.64)	0.58 (0.51–0.65)	0.16	23.4	0.03	0.91
ADT-G	18.0 (14.9–21.7)	16.2 (13.7–19.1)	17.0 (14.2–20.4)	0.91	−5.6	0.65	15.6 (10.5–23.1)	24.7 (16.6–36.5)	28.8 (19.6–42.4)	0.01[f]	84.6	0.003[f]	0.64
3α-diol-3G	1.12 (0.94–1.35)	1.10 (0.93–1.29)	1.20 (1.00–1.45)	0.63	7.1	0.56	1.09 (0.73–1.63)	2.05 (1.46–2.89)	2.57 (1.80–3.67)	0.01[f]	136	<0.001[g]	0.30
3α-diol-17G	1.02 (0.86–1.19)	0.99 (0.84–1.17)	1.11 (0.93–1.32)	0.39	8.8	0.42	1.21 (0.88–1.66)	1.48 (1.06–2.07)	1.51 (1.08–2.12)	0.28	24.8	0.22	0.89
Marker of androgenic activity													
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	20.5 (17.1–24.5)	18.5 (15.8–21.7)	19.8 (16.6–23.5)	0.94	−3.4	0.76	18.3 (12.5–26.8)	29.1 (20.1–42.1)	34.0 (23.8–48.6)	0.01[f]	85.8	0.002[f]	0.58
5β-Reduced metabolites													
Etio-G	32.8 (26.8–40.1)	29.8 (24.5–36.1)	29.0 (23.5–35.8)	0.56	−11.6	0.36	25.2 (16.7–38.2)	34.8 (24.3–49.9)	43.2 (30.6–61.0)	0.09	71.4	0.02	0.60
Ratios													
DHEAS: DHEA	207 (183–234)	228 (200–261)	201 (175–231)	0.63	−2.9	0.72	204 (162–258)	275 (230–330)	255 (220–296)	0.40	25.0	0.07	0.37
DHTS: DHT	4.32 (3.66–5.10)	5.45 (4.58–6.47)	5.14 (4.28–6.16)	0.52	19.0	0.13	3.98 (2.66–5.95)	6.69 (4.58–9.76)	7.22 (5.04–10.3)	0.04	81.4	<0.001[g]	0.90
DHT: Testosterone	0.32 (0.27–0.37)	0.37 (0.32–0.44)	0.31 (0.26–0.37)	0.68	−3.1	0.84	0.32 (0.25–0.40)	0.30 (0.24–0.39)	0.29 (0.22–0.38)	0.50	−9.4	0.49	0.02
Unconjugated estrone: Androstenedione	39.5 (34.3–45.5)	40.4 (35.4–46.2)	41.2 (35.2–48.1)	0.61	4.3	0.63	61.9 (43.4–88.2)	60.2 (46.0–78.7)	51.7 (36.1–74.1)	0.19	−16.5	0.31	0.51
Unconjugated estradiol: Testosterone	16.7 (13.3–21.1)	20.2 (16.1–25.4)	20.5 (15.8–26.5)	0.11	22.8	0.12	47.5 (33.4–67.5)	40.2 (30.2–53.5)	45.5 (32.6–63.7)	0.54	−4.2	0.82	0.44

Note: Adjusted for age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), calendar year at blood draw (1993–1996, 1997–1998), race (White, non-White), smoking status (never, former, current), moderate- to vigorous-intensity physical activity (0, 0.1–9.9, ≥10 MET-hr/wk), alcohol drinking (nondrinker, <1 drink/wk, 1–6 drinks/wk, ≥7 drinks/wk), parous (yes, no), family history of breast and ovarian cancer (yes, no), time since menopause (<10 years, 10–19 years, ≥20 years, missing), HT use (never, former), and current BMI (kg/m^2, continuous). T1, T2, and T3 indicate tertiles, with T1 for the lowest tertile and T3 for the highest tertile.

[a]P_{trend} was estimated using the Wald test for continuous waist-to-hip ratio.

[b]%Δ indicates the percentage change in GMs of androgens/androgen metabolite levels, comparing women at the highest vs. lowest tertiles of waist-to-hip ratio.

[c]P_{diff} was estimated using the Wald test and indicates *P* value for comparing androgens/androgen metabolite levels of women at the highest vs. lowest tertiles of waist-to-hip ratio.

[d]P_{int} was estimated using the Wald test for an interaction term between waist-to-hip ratio and current BMI.

[e]Weighted *n* reflects weighted counts and refers to the study cohort.

[f]FDR *q* value <0.05 and ≥0.01.

[g]FDR *q* value <0.01.

Table 5. Geometric means (pmol/L) and 95% CIs of serum androgens/androgen metabolites by BMI at age 18, stratified by HT use: the WHI-OS.

	Never/former HT users						Current HT users						
	BMI at age 18						BMI at age 18						
	T1	T2	T3	P_{trend}[a]	%Δ[b]	P_{diff}[c]	T1	T2	T3	P_{trend}[a]	%Δ[b]	*P*diff[c]	*P*int[d]
Median (range)	18.4 (8.7–19.4)	20.2 (19.5–21.3)	22.8 (21.4–51.5)				18.3 (11.5–19.3)	20.3 (19.4–20.9)	22.1 (21.0–22.1)				
N	307	306	308				277	283	284				
Weighted *N*[e]	10,583	10,136	9,121				8,248	8,030	7,731				
	Geometric means (95% CI)						Geometric means (95% CI)						
Adrenal androgens													
DHEA	5.30 (4.57–6.14)	4.47 (3.91–5.12)	4.52 (3.93–5.19)	0.005[f]	−14.7	0.06	4.44 (3.85–5.13)	3.94 (3.37–4.61)	3.87 (3.33–4.51)	0.21	−12.8	0.12	0.68
DHEAS	1,197 (1,001–1,431)	1,030 (868–1,221)	979 (837–1,144)	0.001[f]	−18.2	0.03	1,130 (972–1,313)	908 (748–1,101)	863 (720–1,034)	0.02	−23.6	0.01[f]	0.83
Androstenedione	1.50 (1.36–1.67)	1.39 (1.24–1.56)	1.36 (1.22–1.50)	0.002[f]	−9.3	0.08	1.27 (1.15–1.42)	1.25 (1.12–1.40)	1.17 (1.04–1.33)	0.08	−7.9	0.30	0.90
Testosterone	0.60 (0.53–0.69)	0.57 (0.49–0.65)	0.57 (0.49–0.66)	0.02[f]	−5.0	0.46	0.55 (0.49–0.62)	0.49 (0.43–0.55)	0.47 (0.41–0.54)	0.04	−14.5	0.06	0.86
5α-Reduced metabolites													
5α-Androstenedione	1.27 (1.14–1.42)	1.28 (1.16–1.43)	1.35 (1.21–1.50)	0.39	6.3	0.39	1.42 (1.28–1.58)	1.31 (1.17–1.46)	1.29 (1.14–1.45)	0.76	−9.2	0.19	0.72
DHT	0.18 (0.16–0.20)	0.18 (0.17–0.20)	0.19 (0.18–0.21)	0.89	5.6	0.26	0.21 (0.19–0.23)	0.20 (0.18–0.23)	0.21 (0.19–0.24)	0.61	0.0	0.78	0.49
DHTS	1.03 (0.90–1.19)	0.93 (0.80–1.07)	1.03 (0.91–1.17)	0.55	0.0	0.96	1.03 (0.88–1.20)	0.96 (0.81–1.13)	0.94 (0.81–1.11)	0.34	−8.7	0.35	0.50
ADT	0.54 (0.50–0.58)	0.57 (0.52–0.61)	0.51 (0.47–0.55)	0.18	−5.6	0.25	0.51 (0.47–0.55)	0.50 (0.46–0.54)	0.50 (0.46–0.54)	0.29	−2.0	0.61	0.69
ADT-G	23.0 (19.4–27.2)	19.7 (16.6–23.4)	18.6 (16.0–21.6)	0.02[f]	−19.1	0.03	19.5 (16.3–23.3)	14.6 (12.0–17.9)	13.1 (10.7–16.1)	0.002[f]	−32.8	0.001[f]	0.12
3α-diol-3G	1.55 (1.31–1.84)	1.38 (1.12–1.69)	1.38 (1.17–1.62)	0.02[f]	−11.0	0.18	1.45 (1.25–1.68)	1.14 (0.96–1.35)	1.17 (0.99–1.37)	0.09	−19.3	0.02	0.99
3α-diol-17G	1.30 (1.12–1.51)	1.23 (1.06–1.43)	1.07 (0.94–1.22)	0.06	−17.7	0.02	0.95 (0.81–1.10)	0.77 (0.66–0.91)	0.72 (0.61–0.84)	0.001[f]	−24.2	0.003[f]	0.13
Marker of tissue-level androgenic activity													
Sum of ADT-G, 3α-diol-3G, 3α-diol-17G	26.3 (22.4–30.9)	22.9 (19.4–27.0)	21.4 (18.5–24.7)	0.01[f]	−18.6	0.02	22.2 (18.7–26.3)	16.9 (14.0–20.4)	15.5 (12.9–18.7)	0.002[f]	−30.2	0.002[f]	0.15
5β-Reduced metabolites													
Etio-G	35.7 (29.4–43.2)	32.8 (27.1–39.9)	33.5 (28.5–39.3)	0.01[f]	−6.2	0.49	37.9 (32.7–44.0)	31.7 (26.6–37.9)	32.2 (26.9–38.5)	0.24	−15.0	0.13	0.83
Ratios													
DHEAS: DHEA	226 (204–250)	230 (206–257)	217 (194–242)	0.12	−4.0	0.51	254 (228–283)	231 (204–261)	223 (197–252)	0.09	−12.2	0.07	0.41
DHTS: DHT	5.75 (4.92–6.72)	5.07 (4.31–5.97)	5.31 (4.56–6.19)	0.71	−7.7	0.41	4.93 (4.16–5.84)	4.69 (4.00–5.50)	4.46 (3.76–5.28)	0.24	−9.5	0.29	0.31
DHT: Testosterone	0.30 (0.26–0.34)	0.32 (0.28–0.38)	0.34 (0.29–0.39)	0.07	13.3	0.07	0.38 (0.33–0.43)	0.42 (0.37–0.48)	0.45 (0.39–0.52)	0.01[f]	18.4	0.04	0.49
Unconjugated estrone: Androstenedione	42.5 (36.4, 49.6)	41.9 (36.7, 47.7)	46.1 (40.0, 53.0)	0.29	8.5	0.33	172 (140, 211)	186 (153, 226)	221 (180, 272)	0.03	28.5	0.06	0.88
Unconjugated estradiol: Testosterone	25.1 (20.6, 30.7)	26.5 (21.7, 32.5)	23.6 (19.2, 29.0)	0.99	−6.0	0.58	81.2 (64.4, 102)	90.5 (72.5, 113)	114 (89.5, 145)	0.15	40.4	0.02	0.42

Note: Adjusted for age at blood draw (<55, 55–59, 60–64, 65–69, 70–74, 75–79 years), calendar year at blood draw (1993–1996, 1997–1998), race (White, non-White), smoking status (never, former, current), alcohol drinking (non-drinker, <1 drink/wk, 1–6 drinks/wk, ≥7 drinks/wk), parous (yes, no), family history of breast and ovarian cancer (yes, no), time since menopause (<10 years, 10–19 years, ≥20 years, missing), moderate- to vigorous-intensity physical activity (0, 0.1–9.9, ≥10 MET-hr/wk), and current BMI (kg/m^2, continuous). Additionally adjusted for HT use (never, former) among women not using HT use. T1, T2, and T3 indicate tertiles, with T1 for the lowest tertile and T3 for the highest tertile.

[a]P_{trend} was estimated using the Wald test for continuous BMI at age 18 (kg/m^2).

[b]%Δ indicates the percentage change in GMs of androgens/androgen metabolite levels, comparing women at the highest vs. lowest tertiles of BMI at age 18.

[c]P_{diff} was estimated using the Wald test and indicates *P* value for comparing androgens/androgen metabolite levels of women at the highest vs. lowest tertiles of BMI at age 18.

[d]P_{int} was estimated using the Wald test for an interaction term between BMI at age 18 and HT use.

[e]Weighted *n* reflects weighted counts and refers to the study cohort.

[f]FDR *q* value <0.05 and ≥0.01.

endometrial cancer risks (19) in postmenopausal women. While it is yet unclear whether the associations vary by tumor subtypes, some studies suggested that the associations may be restricted to nonserous (vs. serous) ovarian cancer (28) and stronger for hormone receptor–positive (vs. negative) breast cancer risks (31, 49). Further studies are needed to formally investigate the mediating effects of androgen metabolism in the obesity–cancer relationship in postmenopausal women.

In addition to current BMI, we also observed associations between current WHR and androgen metabolism. In women with high current BMI, WHR may be a better proxy of abdominal and visceral adiposity, an independent risk factor for endometrial and postmenopausal breast cancers (3, 14, 15). Among these women with high current BMI, WHR was positively associated with circulating adrenal androgens and 5α-reduced metabolites. The associations are unlikely to be driven by residual effects of BMI because we additionally adjusted for current BMI as a continuous variable in the models. Based on our data, abdominal fat distribution may be independently associated with androgen metabolism by stimulating androgen production (or retention) and promoting tissue-level activity of androgens. However, given that we did not observe any association between WHR and estrogen-to-androgen ratios, it is likely that abdominal adiposity may not independently contribute to the increased aromatization in obese women. Consistently, previous studies have shown that women with abdominal body fat have higher androgen production rates and an increased amount of free testosterone, whereas women with lower body fat have an increased amount of estrone from peripheral aromatization (9).

Finally, we also found associations between BMI at age 18 and serum androgen metabolism, independent of current BMI. After adjustment for current BMI, BMI at age 18 was inversely associated with adrenal androgens and 5α-reduced glucuronide metabolites, whereas current BMI was positively associated with these metabolites. Our data suggest that obesity during early adulthood may be differentially associated with androgen metabolism. We also observed that the positive association with the estrogen-to-androgen ratios disappeared after additional adjustment for current BMI, suggesting that associations between obesity and aromatization are likely to be specific to postmenopausal obesity and not obesity in early adulthood. As obesity in early and later adulthood also show differential associations with breast cancer risk in multiple studies (50, 51), further studies are needed to investigate the effects of timing of obesity on hormone metabolism.

We acknowledge several limitations of this study. We used a single serum sample collected at baseline from each participant. If serum concentrations of androgens/androgen metabolites widely fluctuate within individuals, our data may not reflect participants' usual circulating levels of androgens/androgen metabolites. However, in a study of 12 postmenopausal women, we observed that most androgens/androgen metabolite concentrations were highly stable over a 2-year period. We also calculated BMI at age 18 based on recalled data but related measurement error is unlikely to be related to serum androgens/androgen metabolite levels. Given a cross-sectional design of the study, it is also difficult to clarify the temporal relationship of our results. Some studies suggest the opposite direction of causality (excess androgens increase body fat accumulation) is also possible (52). Therefore, further studies are needed to examine the changes in androgens/androgen metabolites with weight gain using a longitudinal study design. We also did not have information on polycystic ovary syndrome or other conditions (e.g., congenital adrenal hyperplasia) that may be related to abnormal concentrations of androgens/androgen metabolites and thus we were not able to adjust in the analysis. Further, because the WHI-OS participants were highly selected volunteers, our study findings may not be generalizable to overall postmenopausal women. Our study participants were highly motivated women who were mostly White. Because the relationship between BMI and body composition varies by race (e.g., greater body fat in Asian vs. White women for a given BMI; ref. 53), the associations between BMI and androgens/androgen metabolites may also vary by race. Given the increased obesity prevalence among the US women since the start of the WHI, it is also possible that the circulating levels of estrogens and androgens may differ in future studies that use more recently collected data. Lastly, due to the number of tests, some of the observed associations may be due to chance (e.g., false positives). However, when we accounted for multiple comparisons using FDR, most associations remained significant at a 5% FDR level.

This study has several strengths. By using measured data on BMI and WHR at baseline, we reduced measurement error in exposures. Use of a high-performance LC-MS/MS assay also allowed highly sensitive evaluation of serum androgens/androgen metabolites. We also examined both absolute (e.g., DHT) and relative (e.g., DHTS:DHT ratio) concentrations of androgens/androgen metabolites. While the associations with absolute concentrations may provide insights into the biologic mechanisms, the associations with relative concentrations may help us understand the pathway metabolism that can inform cancer risk. Finally, we increased the validity of our results by using a large sample and careful adjustment for potential confounders.

In summary, we observed positive associations between current BMI and circulating levels of adrenal androgens, 5α-reduced glucuronide metabolites, and proportions of parent estrogens (vs. adrenal androgens) among postmenopausal women. Our data suggest that postmenopausal obesity may be associated with increased androgen production (or retention), tissue-level androgenic activity, and aromatization of androgens. Similar androgen metabolism profiles have previously been associated with higher ovarian and endometrial cancer risks (19, 28), and thus prospective studies are needed to confirm the mediating role of androgen metabolism in the obesity–cancer relationship.

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Authors' Contributions

H. Oh: Formal analysis, methodology, writing–original draft. **R.A. Wild:** Writing–review and editing. **J.E. Manson:** Writing–review and editing. **J.W. Bea:** Writing–review and editing. **A.H. Shadyab:** Writing–review and editing. **R.M. Pfeiffer:** Writing–review and editing. **N. Saquib:** Writing–review and editing. **L. Underland:** Writing–review and editing. **G.L. Anderson:** Writing–review and editing. **X. Xu:** Data curation, writing–review and editing. **B. Trabert:** Conceptualization, data curation, supervision, writing–review and editing.

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