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THE EPIDEMIOLOGY OF SERUM SEX HORMONES IN POSTMENOPAUSAL WOMEN

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Serum sex hormones may be related to the risk of several diseases in postmenopausal women. In the current report, the authors examined the epidemiology of serum sex hormones in 176 healthy, white postmenopausal women (mean age 58 years) recruited from the metropolitan Pittsburgh, Pennsylvania, area. The data were collected during 1982–1983; none of the women were on estrogen replacement therapy. Serum concentrations of estrone, estradiol, testosterone, and androstenedione were measured by a combination of extraction, column chromatography, and radioimmunoassay. Neither age nor time since menopause was a significant predictor of sex hormones. The degree of obesity was a major determinant of estrone and estradiol. The estrone levels of obese women were about 40% higher than the levels of nonobese women. There was a weak relation between obesity and the androgens. Cigarette smokers had significantly higher levels of androstenedione than nonsmokers, with little difference in serum estrogens between smokers and nonsmokers. Both estrone and estradiol levels tended to decline with increasing alcohol consumption. Physical activity was an independent predictor of serum estrone. More active women had lower levels of estrone. There was a positive relation of muscle strength with estrogen levels. The data suggest interesting relations between environmental and lifestyle factors and serum sex hormones. These environmental and lifestyle factors are potentially modifiable and, hence, if associations between sex hormones and disease exist, modification of these factors could affect disease risks.

androstenedione; estradiol; estrone; menopause; testosterone

Serum sex hormones may be related to the risk of several diseases in postmenopausal women, including osteoporosis (1), heart disease (2), and breast and endometrial cancer (3, 4). Estradiol, although a more biologically potent estrogen, is not the predominant estrogen, and concentrations are extremely low in postmenopausal women. Estradiol is formed by the aromatization of plasma testosterone and by the reduction of estrone. Testosterone is derived from the conversion of androstenedione and dehydroepiandrosterone. Estrone is the primary estrogen hormone in postmenopausal women and is not specifically bound in pre- or postmenopausal women (5). The principal source of estrone in postmenopausal women is the peripheral conversion of adrenal androstenedione (5),

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which is regulated, not by estrogens, but by the rate of production of androstenedione and by other factors that affect aromatization (6), such as the degree of obesity (7) and age (8). It is these other factors that may determine the degree to which sex hormones influence the risk of disease.

Determination of the biologic response to hormones is complex, since this response reflects not only the circulating levels of hormones but also the availability of free hormones for receptors and postreceptor actions (9). In the current report, the authors have addressed the determinants of circulating levels of hormones on the premise that the biologic response is somewhat dependent on the circulating levels. Although this is not always the case, e.g., with regard to insulin resistance, the circulating level of sex hormone may be considered a good indicator of its concentration at the target cell. For instance, the authors have demonstrated a direct relation between estrone level and bone density (1).

Most of the previous research on serum sex hormones in women has been based on relatively small samples, and, to our knowledge, there has been no previous study which has examined a combination of all possible determinants. The actions of one hormone may influence the effects of other hormones; thus, it is important to evaluate the degree to which the sex hormones interact with each other and with other independent factors. The current research, based on a fairly large sample, was designed to evaluate various factors, independently and combined, that may be determinants of serum sex hormone levels in postmenopausal women. Variables of interest included age, time since menopause, history of oophorectomy, the degree of obesity, physical activity, muscle strength, alcohol consumption, and cigarette smoking.

Materials and methods

Study population

This study was ancillary to a clinical trial designed to evaluate the effect of walking on postmenopausal bone loss. Results of the clinical trial have been published (10). The women were white and were recruited from the metropolitan Pittsburgh, Pennsylvania, area. The results reported in this paper are from year 1 (1982–1983) of the clinical trial. Women were selected for this sex steroid study solely on the basis of availability of serum and no hormone therapy for the entire duration of the study. One hundred seventy-six women were measured for levels of estrone and estradiol; of these, 143 were measured for levels of serum testosterone and androstenedione.

Data collection

Annually, all women underwent a clinic visit, at which time a fasting blood sample was drawn, questionnaires were completed, and various anthropometric and strength measures were carried out. Data were gathered on health history, prior hysterectomy, prior oophorectomy, cigarette smoking, and medication use. Alcohol consumption and cigarette smoking were estimated by questionnaire. Physical activity was assessed using a survey developed by Paffenbarger et al. (11) and by an activity monitor which recorded body movements and thus serves as an objective measure of physical activity (12). Height and weight were recorded to form the body mass index (weight (kg)/ height$(m)^2$) to measure obesity. Both the triceps and suprailiac skinfolds were measured by trained observers. Grip strength was measured in the dominant arm as an index of upper body strength. The number of women varies in different tables because of missing data.

Hormone levels

Hormone concentrations were determined by highly specific methods involving extraction, column chromatography, and radioimmunoassay using a specific antibody in sheep (1, 13–16). The within- and between-assay variation, respectively, for each hormone was as follows: estradiol, 8 per cent and 10 per cent; estrone, 10 per cent and 15 per cent; testosterone, 9.4 per

cent and 9.0 per cent; androstenedione, 11.6 per cent and 12.4 per cent.

The sensitivity level was 2.5 pg/ml for the estrogen assay and 10 ng/dl for the androgen assay. For persons whose hormone levels were below the sensitivity of the assay, the sensitivity level was entered into the computer. Despite these low sensitivity levels, about 50 per cent of estradiol levels were found to be below the sensitivity of the assay. Comparison of the women in whom the authors could measure estradiol with those in whom the authors could not revealed a 6.8-kg difference in the mean body weight of the two groups, suggesting that women with measurable estradiol were basically obese. Hence, the estradiol results must be interpreted with caution.

Statistical analyses

Statistical analyses included computation of zero and first-order correlations. For comparisons involving two groups, *t* tests were done; for three or more groups, analyses of variance and covariance with tests for linear trends were used. Stepwise multiple regression analyses were done to examine the independent predictors of serum hormones. The software package used was the Statistical Package for the Social Sciences (SPSS) (17).

RESULTS

The descriptive characteristics of the women participating in this study are shown in table 1. At baseline, the mean age of the women was 58 years, with an average of nine years since the onset of menopause. The mean of 1,463 kcal/week was well below the activity level of 2,000 kcal/week observed by Paffenbarger et al. (11) as optimal protection against coronary heart disease. The activity level (expressed by the activity monitor in counts per hour) was one third of the activity level observed in college students (18), but it was similar to the activity level observed in another group of postmenopausal women (18). The mean of 10.8 ml of ethanol per day corresponded to approximately five glasses of wine per week. The anthropometric data were similar to that reported by the Lipid Research Clinics for women of similar age (19). Twenty-six women (15 per cent) reported current cigarette smoking, with a mean of 14 cigarettes per day.

The mean, standard deviation, and range of sex hormones are shown in table 2. The mean levels are similar to those found in the literature for postmenopausal women (20–22). There were no differences in serum sex hormones by randomized group, and therefore the two groups were combined.

Age

The relation between serum sex hormones and age is shown in table 3. Estrone tended to decrease with increasing age, but the data were not entirely consistent. For estradiol, testosterone, and androstenedione, there was little relation with age. Examination of estrone by years since menopause revealed a slight but not significant tendency to decline with increasing time since menopause (data not shown).

Bilateral oophorectomy

Twenty-two women (12.5 per cent) reported a history of bilateral oophorectomy. Comparison of women who reported a bilateral oophorectomy with those who did not (table 4) showed little difference in serum estrone, estradiol, or testosterone levels. For androstenedione, the mean levels were higher in women with an oophorectomy. This is contrary to what the authors would have expected given the possibility that ovarian stroma cells continue to secrete androgens after menopause, and thus women who have undergone an oophorectomy tend to have lower androgen values (23).

Alcohol

Both estrone and estradiol tended to decline with increasing alcohol consumption (table 5). This could not be totally explained by obesity and cigarette smoking. There was no significant relation between

TABLE 1

Descriptive characteristics of women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983

Variable	Mean	Standard deviation
Baseline		
Age (years)	57.80	4.20
Years since menopause	8.80	6.00
Age at menopause (years)	49.20	4.60
Year 1		
Weight (kg)	65.41	10.32
Height (cm)	161.54	5.84
Body mass index (weight (kg)/height $(m)^2$)	25.10	3.70
Triceps skinfold (mm)	27.40	6.30
Suprailiac skinfold (mm)	27.10	9.00
Grip strength (kg)	26.80	4.40
Kcal/week	1,463.60	1,014.70
Activity monitor (counts/hour)	36.80	23.50
Alcohol consumption (ml of ethanol/day)	10.80	16.80

TABLE 2

*Mean, standard deviation, and range of serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983**

Sex steroid hormone	Mean	Standard deviation	Range	Number (%) below sensitivity of assay
Estrone (pg/ml)	29.9	11.9	2.5–74.0	4 (2)
Estradiol (pg/ml)	4.1	2.5	2.5–16.5	92 (52)
Androstenedione (ng/dl)	68.6	43.9	10.0–189.6	27 (19)
Testosterone (ng/dl)	42.4	26.9	10.0–179.8	13 (9)

* For estrogens, $n = 176$; for androgens, $n = 143$.

testosterone and androstenedione levels and alcohol intake.

Obesity

Both estrone and estradiol were positively correlated with the degree of obesity. The correlation coefficients were similar for each obesity index. With estrone, the following correlation coefficients were observed: triceps skinfold, $r = 0.33$, $p < 0.001$; suprailiac skinfold, $r = 0.24$, $p < 0.001$; body weight, $r = 0.35$, $p < 0.001$; body mass index (BMI), $r = 0.38$, $p < 0.001$. The correlation coefficients with estradiol were triceps skinfold, $r = 0.31$, $p < 0.001$; suprailiac skinfold, $r = 0.31$, $p < 0.001$; body weight, $r = 0.36$, $p < 0.001$; body mass index, $r = 0.41$, $p < 0.001$. None of the correlations between obesity indices and the androgens were significant.

The authors then examined the data by classifying the women as either normal weight (BMI $\leq$ 27.0), overweight (BMI 27.1–30.0), or obese (BMI $\geq$ 30.1). Bray's cutoff for obesity categories was used (24). As shown in table 6, there was a linear increase in both estrone and estradiol for increasing degree of obesity. The estrone level of the obese women was 11.4 pg/ml greater than the estrone level of normal weight women; this represents a 41 per cent increase in estrone. The estradiol level in obese women was almost twice that of normal weight women. There was little difference in the testosterone level between normal weight and overweight women, but the testosterone level of obese women was significantly ($p = 0.06$) higher than that of the remaining women, suggesting some effect of obesity on testosterone levels. There

TABLE 3

Serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983, by age, unadjusted and adjusted for obesity

Age group (years)	*n*	Estrone (pg/ml)			Estradiol (pg/ml)		
		Unadjusted		Adjusted	Unadjusted		Adjusted
		Mean	SD*	Mean	Mean	SD	Mean
45–54	39	33.9	14.1	34.9	4.2	2.5	4.4
55–59	75	28.5	10.3	28.1	3.9	2.3	3.8
60–64	50	28.7	12.2	28.6	4.3	3.0	4.0
65+	12	31.3	11.0	31.6	4.3	2.1	4.3
Total	176						
F (linearity)		1.82		3.81	0.14		0.49
p		0.18		0.01	0.71		0.68

		Testosterone (ng/dl)			Androstenedione (ng/dl)		
		Unadjusted		Adjusted	Unadjusted		Adjusted
		Mean	SD	Mean	Mean	SD	Mean
45–54	31	45.6	26.1	46.6	74.1	40.5	75.5
55–59	58	38.7	22.0	38.3	62.9	43.7	62.3
60–64	42	42.1	27.5	41.8	74.8	46.2	74.4
65+	12	53.3	44.1	53.5	60.8	45.2	61.1
Total	143						
F (linearity)		0.27		1.40	0.04		1.01
p		0.61		0.25	0.84		0.39

* SD, standard deviation.

TABLE 4

Serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983, by history of bilateral oophorectomy

	Oophorectomy			No oophorectomy			*t*	*p*
	n	Mean	SD*	*n*	Mean	SD		
Estrone (pg/ml)	22	28.1	10.3	137	29.1	11.1	−0.40	0.69
Estradiol (pg/ml)	22	3.8	2.6	137	4.0	2.4	0.28	0.78
Testosterone (ng/dl)	17	36.6	20.5	113	43.2	28.8	−0.90	0.37
Androstenedione (ng/dl)	17	89.4	38.4	113	63.7	43.4	2.30	0.02

* SD, standard deviation.

TABLE 5

Serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983, by quartile of alcohol consumption

Quartile of alcohol consumption	Estrone (pg/ml)			Estradiol (pg/ml)			Testosterone (ng/dl)			Androstenedione (ng/dl)		
	n	Mean	SD*	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
I (low)	43	31.0	13.2	43	4.3	3.0	36	43.2	28.2	36	76.6	43.0
II	43	30.7	14.9	43	4.7	3.0	34	45.0	24.6	34	64.3	45.0
III	43	30.0	10.5	43	3.8	1.6	36	43.4	32.9	36	70.6	39.3
IV	47	28.1	8.3	47	3.6	2.3	37	38.3	21.3	37	62.9	48.2
F (linearity)		1.39			3.59			0.64			1.67	
p		0.24			0.06			0.42			0.28	

* SD, standard deviation.

TABLE 6

Serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983, by obesity and cigarette smoking

	Estrone (pg/ml)			Estradiol (pg/ml)			Testosterone (ng/dl)			Androstenedione (ng/dl)		
	n	Mean	SD*	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
						Obesity (body mass index)						
Normal	126	27.5	10.9	126	3.4	1.9	103	40.6	23.8	103	66.1	42.8
Overweight	27	33.6	11.1	27	5.2	3.1	21	40.3	11.8	21	84.3	41.0
Obese	23	38.9	13.3	23	6.3	3.3	19	54.9	45.6	19	65.4	50.9
F (linearity)		23.45			37.06			3.57			0.30	
p		<0.001			<0.001			0.06			0.58	
						Cigarette smoking						
Yes	26	28.5	10.7	26	3.5	1.3	22	43.2	27.1	22	82.1	52.3
No	150	30.1	12.0	150	4.2	2.7	121	42.4	27.2	121	65.9	42.1
F		0.38			1.55			0.01			2.57	
p		0.53			0.21			0.90			0.11	

* SD, standard deviation.

was no relation between androstenedione and the degree of obesity.

Smoking

There was little difference in serum estrogens between smokers and nonsmokers (table 6). Controlling for differences in the degree of obesity had little effect on the estrogen results. For the androgens, there was no relation between testosterone and cigarette smoking, but the data suggested that smokers had higher androstenedione levels than nonsmokers. After adjustment for the degree of obesity, this relation approached statistical significance ($F = 3.12$, $p = 0.08$), where the obesity-adjusted androstenedione level in smokers was 83.7 ng/dl compared with 65.6 ng/dl in nonsmokers.

Physical activity

A negative relation was present between physical activity and estrone and estradiol. This was true whether an objective or subjective measure of activity was used. Because more active women tend to be less obese, the authors controlled for obesity. The magnitude of the correlation decreased, but the coefficients remained statistically significant. The partial correlation (controlling for obesity) between estrone and the activity monitor (counts/hour) was $r = -0.22$, $p < 0.001$; the partial correlation between estrone and the Paffenbarger index (kcal/week) was $r = -0.22$, $p < 0.01$. The relation with estradiol was weaker but remained significant: The partial correlation between estradiol and the activity monitor was $r = -0.13$, $p < 0.05$; the partial correlation between estradiol and the Paffenbarger index was $r = -0.12$, $p < 0.05$. There was no relation between physical activity and the androgens.

Table 7 shows the mean hormones by quartile of activity. Both subjective and objective measures of activity are presented. Women who were the most active had the lowest estrogen levels. The relation was stronger for the activity monitor data. Although only the unadjusted data are presented, the relations remained significant after controlling for obesity.

Muscle strength

There was a weak positive relation between grip strength and estrone ($r = 0.14$, $p < 0.05$) and between grip strength and estradiol ($r = 0.14$, $p < 0.05$), with little relation with the androgens. The authors

then divided the grip strength into tertiles to examine the mean sex hormone by these tertiles. As shown in table 8, there was little difference in estrone or estradiol when the low and middle tertiles were compared. However, women who had the highest grip strength had significantly higher estrone and estradiol levels.

Combination of variables

The relations demonstrated above might be confounded by each other. In order to examine the combined effect of those variables that were related to the sex hormone levels, stepwise multiple linear regression analyses were done. Intercorrelating the predictor variables provides the opportunity to find independent relations for complex multivariate relations. These analyses are summarized in table 9.

For estradiol and estrone, the degree of obesity was the primary factor, explaining 14 per cent of the variance in estrone and 5 per cent of the variance in estradiol. These relations were independent of other hormone levels. For estrone, activity as measured by the objective activity monitors was also a significant determinant. If the

TABLE 7

Serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983, by physical activity as measured by the Paffenbarger index (kcal/week) and the large-scale integrated activity monitor (counts/hour)

Quartile	Estrone (pg/ml)			Estradiol (pg/ml)			Testosterone (ng/dl)			Androstenedione (ng/dl)		
	n	Mean	SD*	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
					Paffenbarger index							
I (low)	39	30.4	13 4	39	4 1	2 3	34	41.9	28.5	34	77.4	46.5
II	43	31.5	10.9	43	4.2	2 3	35	38 9	15.7	35	71.3	45.2
III	39	30.4	10.5	39	4.1	2.1	28	51 6	35.2	28	67.6	42.9
IV	40	26.2	11.6	40	3 6	3.3	34	39.2	29.7	34	60.8	42.8
F (linearity)		2 82			0 82			0.02			2 45	
p		0.09			0 36			0.88			0.12	
					Activity monitor							
I (low)	40	33.9	12.9	40	5.0	3.8	33	43.4	29 2	33	63 1	49.2
II	39	28.1	9.0	39	3 8	1 8	33	43 6	30 0	33	76 4	52 9
III	40	30.7	13.1	40	4.0	2 1	34	41 3	29.3	34	66.1	30.3
IV	39	25.5	10.0	39	3 4	1.9	33	40.3	19.2	33	63 0	38 0
F (linearity)		7.91			6.71			0.29			0.11	
p		0.006			0 01			0.59			0.75	

* SD, standard deviation.

TABLE 8

Serum sex hormones in postmenopausal women participating in the Pittsburgh, Pennsylvania, Sex Steroid Hormone Study, 1982–1983, by tertiles of grip strength

Grip strength tertile	Estrone (pg/ml)			Estradiol (pg/ml)			Testosterone (ng/dl)			Androstenedione (ng/dl)		
	n	Mean	SD*	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
I (low)	62	28.2	11.0	62	3.8	2.1	52	41.3	24.7	52	66.7	45.7
II	43	28.9	12.0	43	3.5	2.0	36	36.3	22.3	36	71.6	49.0
III	69	33.1	12.3	69	4.7	3.1	54	47.7	31.1	54	68.8	39.2
F (linearity)		4.11			5.48			2.21			0.06	
p		0.04			0.02			0.14			0.81	

* SD, standard deviation.

TABLE 9

Stepwise multiple regression analyses with sex hormones as the dependent variable, Sex Steroid Hormone Study, Pittsburgh, Pennsylvania, 1982–1983

Variable	Standardized beta	Unstandardized beta	R^2	t	p value
		Estradiol			
Estrone	0.55	0.13	0.36	7.02	<0.01
Body mass index	0.26	1.84	0.05	3.32	<0.01
Androstenedione	−0.11	−0.00	0.01	−1.61	0.11
Physical activity	−0.03	0.04	0.00	0.46	0 65
Cigarettes/day	−0.02	0.09	0.00	0.28	0.78
Alcohol (oz)/day	0.02	−0.88	0.00	0.27	0.79
Age	0.01	0.07	0.00	−1.59	0 11
		Estrone			
Body mass index	0.29	9.22	0.14	3.47	<0.01
Androstenedione	0.29	0.08	0 07	3.60	<0.01
Physical activity	−0.18	−0.89	0.03	−2 25	0.02
Cigarettes/day	−0.13	−2 45	0.01	−1.54	0 13
Age	−0.07	−1.91	0.00	−0.87	0.39
Alcohol (oz)/day	0 07	12.50	0.00	0.78	0.44
		Testosterone			
Body mass index	0.16	12.53	0.03	1.75	0.08
Age	0.04	2.93	0.00	0 49	0.62
Cigarettes/day	−0 04	−1.72	0.00	−0 41	0 68
Alcohol (oz)/day	−0.01	−5.21	0.00	−0.12	0.91
Physical activity	0 01	0.07	0.00	0.07	0.88
		Androstenedione			
Cigarettes/day	0.25	17 65	0 03	2.67	<0 01
Body mass index	0.17	20.79	0.03	1.86	0.07
Alcohol (oz)/day	−0 10	−71.89	0.01	−1 05	0 30
Age	0.04	4.47	0 00	0.48	0 63
Physical activity	−0.00	0.03	0 00	−0.02	0.98

Paffenbarger index was used, activity was not significant. For testosterone, there was a borderline significant association with the degree of obesity. Cigarette smoking was significantly related to androstenedione levels even after controlling for obesity and alcohol consumption. Obesity was of borderline significance as a predictor of androstenedione.

DISCUSSION

Research on the epidemiology of serum sex hormones in postmenopausal women has been limited. Our research was designed to investigate the determinants of serum sex hormones in order to improve our understanding of how sex hormones may interact with disease processes and contribute to the etiology of diseases.

The authors confirmed previous findings of a lack of a relation between age, years since menopause, and serum estrogens. Although there are a few exceptions (25), the majority of previous studies have not reported a significant decline in estrogens with age or time since menopause in postmenopausal women (26–34). The major drop in estrogens appears to occur in the perimenopausal and immediate postmenopausal period (22, 27, 35), with little subsequent change with increasing age. For serum androgens, the authors did not find any relation with age or time since menopause. Mixed results have been reported on the relations between androgens and age and time since menopause, with some studies reporting a decline in testosterone late after menopause and no further decline in androstenedione after the early (<1 year) menopausal drop (27, 36), some reporting significant declines (37, 38), and other studies reporting no relation (26, 28, 29, 34).

The difference in the results of these studies may relate to whether or not the subjects had undergone an oophorectomy. It is generally accepted that after menopause, ovarian stroma cells continue to secrete androgens. Testosterone and androstenedione levels tend to be higher in postmenopausal women with intact ovaries than in oophorectomized women (23), with no difference in estrogens. Failure to see a difference in androgens in the current paper by oophorectomy status may relate to the relatively small numbers of oophorectomized women and the wide range of time since the oophorectomy. The significant higher concentrations of androstenedione observed in oophorectomized women are probably spurious. Most of the reports that found no relation between the androgens and age studied women who had undergone natural menopause (27–29, 34), while Crilly et al. (38) studied oophorectomized women and found a significant decline in androstenedione. With all of these conflicting results, it is doubtful that a major determinant of serum sex hormones in postmenopausal women is age, whether chronologic or menopausal.

There was a strong relation between the degree of obesity and serum estrogens in this group of postmenopausal women. This is consistent with the facts that the aromatization of estrone occurs primarily in fat tissue (7) and that obese women have higher conversion rates of androstenedione to estrone (6) and is consistent with previous reports (25, 26, 28–30, 32, 34). Obesity was the primary determinant of estrone and estradiol even after controlling for androstenedione. These data suggest a possible mechanism whereby obesity appears to be protective of osteoporosis and fractures (39) but may be a risk factor for breast and endometrial cancer (7).

Failure to see a strong relation between obesity and androstenedione is consistent with other reports (26, 28, 29, 31, 32, 40). In this study, there was some suggestion that obese women have higher testosterone levels than either normal or overweight women. O'Dea et al. (41) have suggested that although there is no clear relation with total testosterone, the levels of free testosterone may actually be elevated in obese women because of low androgen binding. In future studies, it may be of importance to measure not only the total testosterone but also the free testosterone.

Most of the previous research on the relation of alcohol consumption to serum sex hormones has been done on alcoholic women. In postmenopausal alcoholic women, generally lower levels of estrone sulfate, but higher levels of estrone and estradiol, were reported (42, 43). In premenopausal alcoholic women, a relative estrogen deficiency was noted (44). Hugues et al. (45) have suggested that chronic alcoholism may have more of an effect on sex steroid metabolism during the reproductive period. To our knowledge, there has been no previous examination of the association of *moderate* alcohol consumption to sex steroid hormone levels. Although alcohol consumption was not a significant predictor of serum estrogens, our data suggested a decline in serum estrogens with increasing alcohol consumption. These results need to be confirmed in future studies.

Of interest, the authors found a significant relation between cigarette smoking and androstenedione levels, suggesting that differences in adrenal hormones could contribute to the biologic effects of cigarette smoking. Cigarette smokers had significantly higher levels of androstenedione than nonsmokers. This relation was significant in the multivariate analysis and was therefore independent of obesity, alcohol consumption, and other possible confounders. This confirms previous observations in women (46, 47) and in men (48) and is consistent with animal research which showed nicotine as a potent stimulus for release of adrenocorticotropic hormone (49).

The relation of cigarette smoking to sex steroid hormone levels was confined to an-

drostenedione, despite the fact that androstenedione is a precursor of other hormones, such as estrone. Similar to other reports (47, 50) on postmenopausal women, this study found no difference in serum estrogens in smokers versus nonsmokers. Possible mechanisms for this lack of effect on estrogens have recently been suggested and include the following: 1) smoking may inhibit peripheral conversion in postmenopausal women; 2) decreased production of estrogens may occur because of fewer number of fat cells in smokers; and 3) there may be increased estrogen-protein binding in smokers (47). An antiestrogenic effect of cigarette smoking, as well as a possible mechanism, has been suggested in premenopausal women (51). It is not clear if this exists in postmenopausal women. Cigarette smokers appear to undergo an earlier menopause (52) and may be at an increased risk of osteoporosis (53) but a decreased risk of breast cancer (54). Future research should continue to explore the effects of cigarette smoking on estrogen metabolism in postmenopausal women.

Physical activity was inversely related to serum estrone levels. This association was true if activity was measured by the objective activity monitor and not by the subjective activity questionnaire. We have previously shown that each activity index may measure different components of activity (55).

It has been suggested that increased physical activity may be protective against the development of osteoporosis (56). Since increased activity was associated with decreased estrogen levels, these data suggest that the underlying mechanism whereby activity may protect one from osteoporosis is *not* through an effect on estrogen metabolism. For cancer of the breast and reproductive system, the relative risk was significantly higher in nonathletes compared with athletes (57). The current observation suggests a possible mechanism for this association. Previous research on amenorrheic athletes has shown decreased estrogen levels (58–61). To our knowledge, there has been only one paper on the relation between activity and sex steroid hormone levels in postmenopausal women (62). In this study, the hormone levels of postmenopausal women who ran an average of 23 miles per week were compared with the hormone levels of sedentary women. The estrone levels were significantly lower in the endurance-trained women. Our data suggest that the effect of activity on estrone levels is not confined to intense activity; that is, with only moderate activity, a lowering effect was also present. The positive relation between increasing muscle strength and serum estrone levels is consistent with the fact that aromatization occurs not only in fat tissue but also in muscle tissue (7).

In summary, our research suggests potentially modifiable environmental factors as determinants of sex hormones. Small changes in these environmental factors could influence serum hormone levels and in turn affect a person's risk of disease. In addition, when the relations of hormones to disease are evaluated, such as in prospective nested case-control studies, it is important to take into consideration specific lifestyle changes (e.g., smoking, exercise, weight loss/gain) that may have occurred during the follow-up period before the onset of disease, Finally, we could explain considerably more of the variance in estrogens than in androgens. The total amount of variance was small but was similar to the amount that we can explain for other risk factors, such as for lipoproteins. Yet, much of the variance remains unexplained, and future research should continue to identify both environmental and genetic factors that are critical to the determination of sex steroid hormone levels in postmenopausal women.

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