J Korean Med Sci 1998; 13: 241-6
ISSN 1011-8934



# Female Sex Hormones and Body Mass in Adolescent and Postmenopausal Korean Women

A cross-sectional study was conducted to evaluate the relationship between body mass and serum level of female sex hormones among 153 adolescent girls, and 153 postmenopausal women in Korea. Information on lifestyles, and both menstrual and reproductive factors was collected by personal interview. Serum total estradiol ($E_2$), progesterone (Pg), and sex hormone binding globulin (SHBG) concentrations were measured by radioimmunoassay. Multiple linear regression analysis was used to determine whether the hormonal levels would be affected by the obesity indices. Body weight and body mass index (BMI) were inversely related to SHBG level in both premenopausal ($p<0.005$) and postmenopausal women ($p<0.005$) after adjusting for age. $E_2$ levels during any phase in premenopausal girls were not related to BMI, whereas heavier girls had significantly higher levels of late luteal-phase Pg ($p<0.05$). Taller postmenopausal women had lower $E_2$ levels ($p<0.05$). Results on the association between SHBG and BMI are consistent with previous results in Caucasian women, and might suggest the potential role of bioavailable estradiol in breast carcinogenesis in pre- and post-menopausal women. The finding that progesterone might be related to body mass in premenopausal women should be pursued in further studies.

Key Words : *Estradiol; Obesity; Progesterone; Reproduction; Sex hormone binding globulin*

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Received : January 5, 1998
Accepted : March 15, 1998

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## INTRODUCTION

The association between body size and the risk of breast cancer has been examined in numerous epidemiologic studies; in many (1-3), but not all (4), height is associated with breast cancer. The relatively consistent positive association between body mass and breast cancer risk has been seen in case-control studies as well as in prospective studies of postmenopausal women (5).

Although female sex hormones, particularly estrogens, are believed to play a key role in breast carcinogenesis, the mechanism of their action and relative significance is still not clear (6). It has been shown that estrogens, in the presence of progesterone, stimulate proliferation and cell division in breast epithelium (7, 8). Numerous epidemiologic investigations have demonstrated that increased levels of these two hormones increased the risk of breast cancer (9). Key hormonal risk factors for breast cancer could be explained by the hypothesis that estrogen is augmented by progesterone (10).

The contrasting effects of obesity in premenopausal and postmenopausal women can be explained by this hypothesis; the decreased risk associated with premenopausal obesity is gradually eliminated after menopause, when increased levels of bioavailable estrogen lead to a higher risk in postmenopausal obese women (10).

It was observed that in Korea (11) and in Japan (12) the association between obesity and breast cancer varies according to menopausal status. Although a number of reports have examined the relationship between anthropometric measures and levels of female sex hormones, the results have not been consistent (13-17). No studies have evaluated this association in Asian women, whose etiology of breast cancer might be different (18, 19). A cross-sectional survey was conducted to evaluate the relationships between height, weight and body mass index (BMI), serum estrogen ($E_2$), progesterone (Pg), and sex hormone binding globulin (SHBG) in adolescent and postmenopausal women in Korea.

## MATERIALS AND METHODS

### Subjects

Of 264 eligible adolescents, who were 13 to 17-year-old high school girls, 153 with a regular menstrual cycle were finally selected as the premenopausal group. Participants in a 'Health Screening Program of Multicenter Cancer Cohort Study in Korea' conducted in Haman County, Korea, were the source population of the postmenopausal group. Women whose last menstrual period had occurred at least six months prior to this survey and who were aged over 35 were eligible. Of the 679 thus selected, women with past or current disease which might be related to female sex hormones, those who had taken steroid medication during the previous 12 months, and those who during this same period had used oral contraceptives or other drugs containing estrogens were excluded. Due to limited hormone assay resources, a random selection of only 153 subjects was finally made.

To identify demographic characteristics, lifestyles, past medical and family history, menstrual cycle, years after menopause and other menstrual-reproductive factors, a personal interview was conducted by trained medical students and graduate students of public health. Height and weight were directly measured, and BMI was calculated by weight (kg) / height $(m)^2$.

### Laboratory methods

Individual blood was sampled, centrifuged, and stored at -80℃. $E_2$ and Pg levels were measured using solid-phase $^{125}I$ radioimmunoassay kits (Coat-A-Count®, Diagnostic Product Corporation). To antibody-coated tubes, 100 μl sera and 1.0 ml of $^{125}I$ labeled $E_2$ or Pg were added. For competition between the hormones in serum samples and the $^{125}I$-labeled hormones for coated antibodies, the tubes were incubated for 3 hours at room temperature, decanted thoroughly, and then counted in a gamma counter (Auto-Gamma® Model A5550, Packard Instrument Company). $E_2$ or Pg concentrations were calculated from a log (% bound) - log (hormone concentration) representation of the calibration curve with standards of known concentrations. Intra-assay CVs were 6.1 % ($E_2$) and 4.4% (Pg), and those of inter-assay were 6.1 % ($E_2$) and 12.5% (Pg).

SHBG level was measured using an immunoradiometric assay kit (IRMA-Count®, Diagnostic Product Corporation). Ten microliters of serum and 200 μl of ligand labeled SHBG monoclonal antibody were added serially to ligand coated tubes. After 30 minute incubation, 50 μl of anti-ligand was added. Tubes were shaken for 30 minutes, decanted, and washed with 2 ml of washing buffer. After adding 200 μl of $^{125}I$ SHBG monoclonal antibody, the tubes were shaken for 30 minutes, decanted and washed twice with washing buffer. Each tube was counted for 1 minute in the gamma counter. SHBG concentrations were calculated from a log (% bound) - log (SHBG concentration) representation of the calibration curve. Intra- and inter-assay CVs were 6.7% and 12.7%, respectively.

### Statistical analysis

Summary data are expressed as the geometric mean and standard deviation of total $E_2$, Pg, and SHBG levels. After adjusting for age, a multivariate linear regression model was used to determine whether the hormonal levels would be affected by the anthropometric indices. For the premenopausal group, the associations between hormonal levels and anthropometric indices were stratified by intervals between the first day of the last menstruation and the day of measurement, and divided into four subgroups as follows: follicular phase (11 days or less), ovulation phase (12-16 days), early luteal phase (17-24 days), late luteal phase (25 days or more). One extreme value of estradiol over 4,000 pg/ml was excluded from further analysis. For the postmenopausal group, associations between hormonal levels and anthropometric indices were stratified according to time since menopause, i.e. the interval between menopause and measurement as follows; 'less than 1 year', '1-5 years', '6-15 years' and '16 years or more'. For all statistical analysis, PC-SAS statistical package, V6.04, was used (20).

## RESULTS

### General characteristics of study subjects

The general characteristics of those participating in the study are shown in Table 1. Age ranged from 13 to 17 years in adolescent girls and from 46 to 88 years in postmenopausal women. In the premenopausal group, mean menstruation cycle was 27.4 days, and in the postmenopausal group, mean duration after menopause was 12.5 years. Mean values of height, weight, and BMI were 157.2 cm, 53.8 kg, and 21.8 $kg/m^2$, respectively, in premenopausal women and 151.0 cm, 53.4 kg, and 23.4 $kg/m^2$, respectively, in postmenopausal women (Table 1).

### Mean values of female sex hormone by menopausal status

In premenopausal girls, $E_2$ level was the highest in the ovulation phase (101.6 pg/mL) and lowest in the follicu-

**Table 1.** General characteristics of the study population by menopausal status: Haman County, Korea, 1993

| Premenopausal group | | | | | Postmenopausal group | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | % | Mean | (SD) | | No. | % | Mean | (SD) |
| Age in years | | | | | Age in years | | | | |
| 13 | 1 | 0.7 | | | ≤ 49 | 7 | 4.6 | | |
| 14 | 22 | 14.3 | | | 50 – 54 | 25 | 16.3 | | |
| 15 | 128 | 83.6 | | | 55 – 59 | 47 | 30.7 | | |
| 16 | 1 | 0.7 | | | 60 – 64 | 28 | 18.3 | | |
| 17 | 1 | 0.7 | | | 65 ≤ | 46 | 30.1 | | |
| Menstrual cycle in days[a] | | | 27.4 | (27.2) | Years after menopause[b] | | | 12.5 | ( 9.4) |
| Height (cm) | | | 157.2 | (11.2) | Height (cm) | | | 151.0 | (10.4) |
| Weight (kg) | | | 53.8 | (15.1) | Weight (kg) | | | 53.4 | (16.7) |
| BMI (kg/m$^2$) | | | 21.8 | ( 5.7) | BMI (kg/m$^2$) | | | 23.4 | ( 6.5) |

[a] Intervals between first day of last menstruation and day of measurement
[b] Intervals between menopause and measurement, in years

**Table 2.** Geometric mean and standard deviation of estradiol, progesterone and sex hormone binding globulin, Haman County, Korea, 1993

| | No. | Estradiol (pg/mL) | Progesterone (ng/mL) | SHBG[a] (nmol/L) |
|---|---|---|---|---|
| Premenopausal | | | | |
| Intervals in days[b] | | | | |
| – 11 | 19 | 34.3 (26.5) | 0.33 (0.2) | 61.3 (31.7) |
| 12 – 16 | 16 | 101.6 (95.3) | 2.00 (4.7) | 84.7 (45.5) |
| 17 – 24 | 39 | 83.5 (73.5) | 2.63 (4.0) | 85.5 (42.3) |
| 25 – | 64 | 58.2 (46.5) | 2.08 (3.6) | 72.5 (34.1) |
| Postmenopausal | | | | |
| Intervals in years[c] | | | | |
| 0 | 13 | 44.5 (68.9) | 0.33 (0.5) | 122.6 (36.2) |
| 1 – 5 | 23 | 11.2 (19.9) | 0.57 (1.7) | 110.4 (33.4) |
| 6 – 15 | 52 | 10.5 (29.8) | 0.17 (0.1) | 124.4 (42.2) |
| 16 – | 49 | 5.0 ( 4.0) | 0.19 (0.1) | 129.0 (38.9) |

( ): standard deviation
[a] Sex hormone binding globulin
[b] Intervals between first day of last menstruation and day of measurement (premenopausal group)
[c] Intervals between menopause and measurement (postmenopausal group, in years)

lar phase (34.3 pg/mL). Mean Pg level gradually increased during ovulation and the early luteal phase; its lowest level was observed during the follicular phase. The highest mean SHBG level was observed in the early luteal phase (Table 2). In the postmenopausal group, $E_2$ and Pg levels markedly decreased as duration after menopause increased, but SHBG levels showed a substantial increase. SHBG levels were higher in postmenopausal than in premenopausal women (Table 2).

## Relationship between anthropometric indices and hormone levels

In premenopausal girls (Table 3), regression analysis between hormone levels and anthropometric indices according to menstruation cycle after adjusting for age found that $E_2$ levels during any phase in premenopausal girls were not related to any anthropometric indices whereas heavier girls had significantly higher levels of late luteal-phase Pg ($p<0.05$). SHBG levels were significantly inversely associated with BMI (regression coefficient: -4.817, $p<0.005$) and with weight (regression coefficient: -1.878, $p<0.005$) in the late luteal phase.

There were significant inverse associations between BMI and SHBG (regression coefficient: -3.833, $p<0.005$), and weight and SHBG (regression coefficient: -1.708, $p<0.005$) in postmenopausal women (Table 4). A significant inverse association between serum $E_2$ and height (regression coefficient: -1.087, $p<0.05$) was observed. Pg levels were not associated with any anthropometric indices.

**Table 3.** Regression coefficients of relationship between anthropometric indices for hormonal levels in adolescent girls by menopausal cycles, Haman County, Korea, 1993

| Intervals in days[a] | No. | Indices | Estradiol (pg/mL) | Progesterone (ng/mL) | SHBG[b] (nmol/L) |
|---|---|---|---|---|---|
| Total | 133 | Height | 1.713 (1.042) | −0.015 (0.058) | 0.129 (0.656) |
| | | Weight | 0.847 (0.794) | 0.065 (0.044) | −1.880 (0.469)** |
| | | BMI | −4.010 (2.055) | 0.184 (0.144) | −5.347 (1.212)** |
| − 11 | 16 | Height | 1.467 (1.309) | −0.014 (0.010) | 1.558 (1.439) |
| | | Weight | −0.049 (1.208) | 0.007 (0.010) | 0.898 (1.303) |
| | | BMI | −2.110 (2.962) | 0.037 (0.022) | 0.102 (3.314) |
| 12 − 16 | 14 | Height | 6.230 (4.193) | −0.064 (0.073) | 1.252 (2.164) |
| | | Weight | 0.900 (3.710) | 0.032 (0.060) | −1.205 (1.741) |
| | | BMI | −4.344 (9.346) | 0.009 (0.155) | −4.551 (4.299) |
| 17 − 24 | 36 | Height | 1.197 (2.114) | −0.133 (0.116) | −0.081 (1.246) |
| | | Weight | −2.626 (1.877) | −0.006 (0.107) | −1.880 (1.085) |
| | | BMI | −9.804 (4.988) | 0.154 (0.291) | −5.700 (2.928) |
| 25 − | 56 | Height | 0.249 (1.286) | 0.094 (0.098) | −0.887 (0.921) |
| | | Weight | 1.149 (0.841) | 0.143 (0.062)* | −1.878 (0.562)** |
| | | BMI | 3.121 (2.269) | 0.329 (0.171) | −4.817 (1.532)** |

( ): standard error of regression coefficient
* $p<0.05$; ** $p<0.01$
[a] Sex hormone binding globulin
[b] Intervals between first day of last menstruation and day of measurement (premenopausal group)

**Table 4.** Regression coefficients of relationship between anthropometric indices for hormonal levels in postmenopausal women, Haman County, Korea, 1993

| Intervals in years[a] | No. | Indices | Estradiol (pg/mL) | Progesterone (ng/mL) | SHBG[b] (nmol/L) |
|---|---|---|---|---|---|
| Total | 134 | Height | −1.087 (0.496)* | −0.003 (0.003) | −0.996 (0.652) |
| | | Weight | −0.493 (0.314) | −0.004 (0.002) | −1.708 (0.385)** |
| | | BMI | −0.561 (0.788) | −0.007 (0.005) | −3.833 (0.972)** |

( ): standard error of regression coefficient
* $p<0.05$; ** $p<0.01$
[a] Sex hormone binding globulin
[b] Intervals between menopause and measurement (postmenopausal group, in years)

## DISCUSSION

This study evaluated female sex hormones in relation to the degree of premenopausal and postmenopausal obesity. The results suggest that in obese women, both adolescent and postmenopausal, higher bioavailable estrogen might result from lower SHBG levels. This change in hormonal environment according to body mass is a suggested possible explanation for the increased risk of breast cancer. The relationships in Asian women between obesity and breast cancer risk through serum level of unbound hormone should be further investigated.

Although higher levels of female sex hormones, particularly bioavailable hormones, are known to induce breast cancer, many reports have not been completely consistent in their descriptions of the mechanisms and the relative significance of different hormones in breast carcinogenesis. The majority of these reports have been case-control studies, in which hormone levels were measured after diagnosis (21); recent prospective cohort studies showed controversial results (22, 23).

Body size may modify breast cancer risk through a change of endocrine effects. There was positive correlation between obesity and estrone and estradiol concentrations, and peripheral conversion from androstenedione to estrogen increased in adipose tissue in which aromatase related to the peripheral production of estrone was sufficient. The relationship between weight and risk of breast cancer is critically dependent on age. In older postmenopausal women, breast cancer risk increases with weight. In contrast, in premenopausal women, increased weight has been found to be associated with a slightly

decreased risk of breast cancer.

Although several researchers have investigated the relationship between body size, particularly obesity, and hormone levels, there has been marked variation in the results. Our overall findings concerning the negative relationship of BMI and SHBG in both premenopausal and postmenopausal women are similar to those of previous studies involving both premenopausal (13, 14, 17) and postmenopausal women (13, 14, 16). This association seems to be related to the increase in free/albumin-bound estrogen caused by the decrease of SHBG-bound estrogen. In fact, an 85% decrease in SHBG concentrations was accompanied by a 60% increase in total, free and non-SHBG bound estradiol levels (10). Consequently, the greater the level of obesity the greater the proportion of bioavailable estradiol and the lower the levels of both estradiol-bound and total SHBG. This applies to both premenopausal and postmenopausal women.

We observed that in premenopausal women, estrogen levels were not related to obesity, whereas in the late luteal phase progesterone levels showed a significant increase. In addition, SHBG levels were the highest in the early luteal phase and a significant decrease in the late luteal phase. This reduction might induce a decrease of SHBG-bound estrogen and an increase of free and albumin-bound estrogen. Our study found a substantial rise in progesterone and probably in free-estrogens caused by decreased SHBG levels in the luteal phase as BMI levels increased. We speculated that in Korea, obesity is probably a significant risk factor for breast cancer, which is caused by the synchronous, synergistic effects of both estrogen and progesterone. These data provide some additional evidence that the relationship between obesity and subsequent breast cancer risk in premenopausal women may be mediated, at least in part, through hormonal levels. We also observed that in postmenopausal obese women, the greater the level of obesity the lower the SHBG levels and this might increase the proportion of bioavailable estrogen.

Although in both Caucasian and Asian premenopausal women a significant positive relationship between height and estradiol levels in the follicular phase has recently been reported (17), an inverse relationship between height and estradiol levels was observed in postmenopausal women in this study. It might be due to the assay variation in lower range of $E_2$, otherwise this finding is not yet understood.

In previous studies, there have been several limitations, including limited sample size, insufficient control of confounding factors associated with obesity and breast cancer, and biologic and laboratory variation of hormone levels (24). In this study we were unable to remove these limitations completely, but significant confounding variables such as age, education, drinking, smoking, and reproductive factors were relatively well controlled by including in the premenopausal group only adolescent girls who were first grade high school students since most girls of this age do not smoke or drink alcohol.

## Acknowledgements

This study was supported by the Basic Medical Research Fund from the Ministry of Education, 1994.

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