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Association of Estrogen Receptor 2 Gene Polymorphisms with Obesity in Women:

(Obesity and Estrogen Receptor 2 Gene)

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Abstract

Objective—Few studies have examined the association between genetic variants of the estrogen receptor β (ESR2) and obesity in postmenopausal women.

Methods—The relationship of three polymorphisms (rs1271572, rs1256049 and rs4986938) and their associated haplotypes in the ESR2 gene with obesity and overweight were evaluated in 561 apparently healthy women (median age 63 years) from the Women's Health Study. Most of the women were postmenopausal (99.1%). The associations between genotypes and haplotypes with obesity (BMI ≥ 30 kg/m²) and overweight (BMI ≥ 25 kg/m²) were evaluated by logistic regression, assuming an additive model.

Results—No association was observed for any of the three polymorphisms with BMI, overweight or obesity. In haplotype analyses, one haplotype (major allele for all polymorphisms) was associated with a borderline inverse association with overweight but not obesity (OR= 0.62, 95% CI = 0.39–.98).

Conclusions—An inverse and borderline significant association was found between the ESR2 G-G haplotype and overweight in postmenopausal women. Further investigation regarding to association between ESR2 and adiposity should be performed to confirm these findings.

Keywords

estrogen; gene expression; menopausal women

1. Introduction

Obesity is a complex disease, which is influenced by multiple genetic and environmental factors. Recently the Human Obesity Gene Map cited the estrogen receptor β gene (ESR2) as one of 127 candidate genes for obesity (1). Estrogen acts both in the periphery and in the central nervous system via at least two different estrogen receptors (α and β). Experimental studies have demonstrated an important role of ER- β in estrogen signaling. (2,3). Adipocytes are estrogen-responsive cells, and *in vitro* 17 β -estradiol up-regulates expression of both ER- α and ER- β mRNA in subcutaneous adipocytes from women (4). Higher ER- α and ER- β

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expression in adipose tissue was observed among obese postmenopausal women compared to nonobese postmenopausal women (5). Although ESR2 polymorphisms have been associated with cardiovascular disease, little is known about ESR2 polymorphisms and their impact on obesity (6-10). The ESR2 gene, which resides on chromosome 14 q22-24 and is comprised of 8 exons, belongs to the nuclear receptor (NR) super family, a family of ligand-regulated transcription factors (11). *To our knowledge, two prior studies have examined ESR2 polymorphisms and body mass index (6,10). Mansur et al have found a significant association with one ESR2 polymorphism (rs4986938) and increased body mass index among subjects homozygous for the variant allele (6). Nilsson et al have investigated the association of severe obesity (BMI $\geq 37\text{kg/m}^2$) with 11 polymorphisms in the ESR2 gene, including most of the common haplotype variation using HAPMAP data (including rs1271572 and rs4986938), among middle-aged women. (10). They found that no relationship between obesity and any of the polymorphisms tested. (10). No study has previously investigated the relationship between ESR2 and obesity in healthy postmenopausal women. Our purpose was to examine the associations of three polymorphisms in the ESR2 gene (rs1271572, rs1256049 and rs4986938) with obesity in women who were free of known cardiovascular disease or cancer.*

2. Material and Methods

Study participants were enrolled in the Women's Health Study, a recently completed, randomized, double-blinded, placebo-controlled trial of low-dose aspirin and vitamin E initiated in 1992 among 39876 female, predominantly white, U.S. health professionals, 45- 89 years of age at study entry (12,13). We evaluated data from a subset of women who were selected as controls for a nested case-control study of CVD within the WHS (12). Before randomization, 28,345 participants provided an EDTA-anticoagulant blood sample that was stored for genetic analysis. All participants were free of prior MI, stroke, cancer or any serious illness that might preclude participation at study entry (12). Women enrolled in the WHS completed a baseline questionnaire, which included questions on demographics (age, race, marital status and level of education), health characteristics/behaviors (height, weight, alcohol use, smoking status, physical activity, HT use), menopause (age at menopause, and type of menopause), and past medical history (history of hypertension, diabetes mellitus, elevated cholesterol and use of cholesterol drugs). Postmenopausal status was considered for anyone with 60 years or older as well as among those women who self-reported of permanent cessation of menstrual periods due to natural menopause, complete oophorectomy, radiation, or chemotherapy. At baseline, participants also completed a 131-item semi-quantitative food frequency questionnaire as previously described (14). Nutrient intake assessments based on this food frequency questionnaire have been previously shown to be valid and reliable (15). Yearly follow-up self-report questionnaires were used to provide reliable updated information on newly developed diseases and the presence or absence of other cardiovascular risk factors (12).

Data on ESR2 genetic variation were available for 561 white WHS participants who had previously been selected as control subjects for a nested case-control study of genetic variation of ESR2 and CVD (16). Of these, 556 (99.1%) were post-menopausal, with an additional 5 women who had biologically uncertain menopause (age 58-59 at enrollment).

The study protocol was approved by the Brigham and Women's Hospital Institutional Review Board for Human Subjects Research.

Exposure Variables

The primary outcome was baseline body mass index (BMI), self-reported weight in kilograms divided by the square of self-reported height in meters (Kg/m^2). BMI was analyzed as a continuous and as a categorical variable, according to World Health Organization (WHO)

criteria as follows: $< 25 \text{ kg/m}^2$ (normal), $25 \text{ to } < 30.0 \text{ kg/m}^2$ (overweight) and $> 30 \text{ kg/m}^2$ (obesity) (17). BMI is highly correlated with absolute fat mass in women ($r=0.84-0.91$) (18). Self-reported and directly measured weight were highly correlated ($r=0.96$) in a validation study in a similar population female health professionals (19).

Genotype Determination

Three single –nucleotide polymorphisms in the ESR2 gene (rs1256049, rs4986938 and rs1271572) were evaluated. Two of these were previously described by Rosencranz et al (7): rs1256049 which represents a relatively rare G→A change at position 1082 in exon 5 (RsaI restriction site, also known as G1082A) and rs4986938 which is a G→A change at position 1730 in the 3'UTR of exon 8 (AluI restriction site, also known as G1730). Additionally, rs1271572, an A→C transportation in the promoter region, was selected.

Genotype determination was performed using ABI fluorescence–based allelic discrimination method (Applied Biosystems, Foster City, USA). Each 10 ml amplification reaction volume contained 1X Taqman Universal Master Mix (Applied Biosystems, Foster City, USA) and 10 ng of template DNA. Amplification reactions were carried out in duplicates on ABI 7900HT Sequence Detection System according to the manufacture's specifications.

To confirm genotype assignment, two independent observers carried out scoring. Discordant results (1% of all scoring) were resolved by a joint reading, and where necessary, a repeat genotyping.

Statistical Analysis

First, we examined the distribution of the baseline characteristics according to median BMI as well as BMI WHO categories (17). We calculated genotype and allele frequencies and performed a Hardy-Weinberg equilibrium test using χ^2 –analysis. Next, the association between ESR2 genotypes and BMI was examined using BMI as a continuous *variable* as well as according to WHO adiposity categories (17). Chi-square was used to test the association for categorical variables; while ANOVA was used for means of continuous variables, and Kruskal-Wallis test for medians of continuous variables. General linear regression models were used to determine whether BMI varied according to ESR2 genotypes. In addition, logistic regression was performed to *investigate* the relationship between genotypes and adiposity, using a dichotomous outcome, in which obesity was defined as $\text{BMI} \geq 30 \text{ kg/m}^2$ and overweight $\text{BMI} \geq 25 \text{ kg/m}^2$. Additional adjustment for age at randomization, age at menopause, smoking status (never, past and current), physical activity (rarely/never to $< 1/\text{week}$ and $1-3/\text{week}$ to $\geq 4/\text{week}$) and hormone replacement therapy use (yes/no), was also performed. Possible associations between several covariates [alcohol and red wine consumption; total intakes of carbohydrate, protein, saturated, monounsaturated and polyunsaturated fat (all of them adjusted by energy); educational level; marital status and income] were evaluated. The following covariates were included in the regression model using the forward stepwise method (20); alcohol consumption (≤ 3 drinks/month, 1-drinks/week to ≥ 1 drink/day), total fat adjusted for energy intake (continuous) and educational level (≤ 3 years of college, ≥ 4 years of college). All analyses were conducted assuming an additive mode of inheritance. Potential interactions between hormone therapy use (HT) and ESR2 genotypes were tested using a formal interaction model (genotype $\times$ HT) as well as in analyses stratified by HT. Potential effect modification was evaluated by subgroup analysis stratified by hormone replacement therapy. Further adjustment for history of diabetes (yes/no), hypertension (yes/no) and dyslipidemia (yes/no) was also performed.

Pair wise linkage disequilibrium (LD) was examined as described by Devlin and Risch (21). Haplotype frequencies were estimated from genotype data using the PHASE v2.1 algorithm

and requiring $\geq 95\%$ certainty for inference. All haplotypes with frequency less than 10% were combined as one group (others). For each odds ratio, we calculated 95% confidence intervals (CIs). A two-tailed p -value of 0.05 was considered to represent a statistically significant result. All statistical analyses were conducted with the use of SAS software (version 9.1; SAS institute, Cary, NC).

3. Results

Baseline characteristics of these women, without known cardiovascular disease (myocardial infarction, coronary revascularization or ischemic stroke) are shown in Table 1. Most (991.%) were postmenopausal, and the median age was 63 years. For these women, the median BMI was 24.7 kg/m², and 13.7% were obese. Among obese women, only 25% were current hormone users compared with 48.7% of normal weight women ($P=0.001$). The highest levels of alcohol consumption and of physical activity were also inversely associated with obesity.

The allele frequencies for rs1271572 were 59% for G and 41% for T alleles; for rs1256049 the frequencies were 96% for G and 4% for A alleles, and for rs4986938 the G and A frequencies were 61% and 39%, respectively. All of the polymorphisms tested were in Hardy-Weinberg equilibrium ($p>0.05$), except rs1271572 ($p=0.02$). Median BMI did not differ by genotype for the three polymorphisms. No associations were observed between genotype frequencies and obese or overweight categories (Table 1).

In logistic regression analyses, no significant associations were found with obesity or overweight women for any of the polymorphisms (Table 2). Further adjustment for the potential confounders, including age, age at menopause, hormone therapy use, exercise, educational level, alcohol consumption, smoking status and energy adjusted fat intake did not alter the lack of association. No effect modification by hormone therapy was found in stratified analyses nor in a test of a formal interaction term between hormone therapy and ESR2 genotypes. Further adjustment for cardiovascular risk factors (medical history of hypertension, diabetes and dyslipidemia) did not materially modify the associations between BMI and ESR2 genotypes (Data not shown).

Overall, the polymorphisms had a weak to modest LD with one another; the strongest LD was observed between the rs1256049 and rs4986938 polymorphisms (normalized Lewontin's $D'=0.76$).

Of eight possible haplotypes, four had a frequency $<10\%$ and they were combined as one category (others) for logistic regression. The most common haplotype (T-G-G) had a frequency of 31%, while 30% were G-G-A and 26 % were G-G-G, where G represents the major allele at each site: rs1271572, rs1256049, rs4986938; A denotes minor allele at sites rs1256049 and rs4986938, and T denotes minor allele at rs1271572. In logistic regression analyses, adjusting for the same potential confounders used in the genotype models, a borderline association was observed with decreased risk of overweight, but not obesity, among women with the G-G-G haplotype (multivariate OR=0.62, 95% CI=0.39-0.98, $P=0.04$) compared to T-G-G (Table 3).

4. Discussion

We found no consistent association between 3 ESR2 polymorphisms and obesity in these women. However, one haplotype (major allele at all loci) was associated with a possible decreased risk of overweight. Although several observational studies have demonstrated significant relationships between ESR2 polymorphisms and cardiovascular disease (CAD)(6, 9,16), *few studies* have examined the association between ESR2 polymorphisms with BMI (6,10). In a *case-control* study by Mansur et al, the variant allele of rs4986938 was more prevalent in individuals with cardiovascular disease, and homozygous carriers for the variant

allele also had increased BMI (6). However, in Mansur's study, the results for women were not reported separately. *In a recent study, which investigated 11 ESR2 tag-SNPs, including rs1271572 and rs4986938, no association was found between these polymorphisms and severe obesity* (10). Whether, our observed associations are real, or due to chance, requires further evaluation.

Molecular mechanisms that govern the regulation of ER- β expression are relatively unclear. Estrogen β receptors, as well as ER-alpha receptors, are widely distributed throughout the body, including adipose tissue (5-7,9). Munoz et al demonstrated higher levels of both ER- β and ER- α in adipose tissue among obese, than nonobese postmenopausal women (5). Although one prior study suggested an association between ESR2 genotypes and obesity, we did not replicate this association for the rs4986938 genotype (6). The association between G-G-G haplotype and BMI $\geq 25\text{kg/m}^2$, but not obesity, may be a solely chance finding.

In our study, we had the ability to detect a risk ratio of greater than 1.7 with a minor allele frequency of 0.50, and of risk ratio greater than 2.5 with a minor allele frequency of 0.05 (assuming 80% power, and additive model, and alpha of 0.05) Thus, we cannot rule out a modest risk of obesity or overweight associated with the polymorphisms/haplotypes tested. We also cannot exclude the possibility that examination of different polymorphisms/loci (including ESR1) might obtain different results.

The candidate gene approach relies on prior knowledge of biological pathways and its associations with the phenotype of interest. In recent years, genome-wide association studies of common, complex diseases have become available, and have provided insights in the underlying pathophysiological mechanisms of several common disorders. Unfortunately, to date, no large genome-wide association investigations have been conducted in relation to BMI, thus, highlighting the need for large-scale, prospective studies in this important clinical condition. In this context, in addition to the candidate gene set described here, the Women's Genome Health Study project (22) will eventually include full genome-wide scan data (estimated completion end of 2008); thus, more detailed results regarding other potential genetic predispositions to obesity or overweight are expected in future analyses. Of note, the present investigation (the study population(12) and the ESR2 genotyping) was carried out prior to the initiation of the Women's Genome Health Study project.

In summary, an inverse and borderline significant association was found between the G-G-G haplotype and overweight in post-menopausal women. Further investigation of ESR2 genetic variants and obesity may be warranted.

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Table 1

Baseline characteristics according to body mass index categories in 543 apparently healthy Caucasian women in the Women's Health Study.

Body mass index (kg/m ²)				
Characteristics	Normal (<25)	Overweight (25-<30)	Obese (≥30)	P-value
Age * (IQR)	63 (57-68)	64 (59-68)	61 (58-65)	0.08
Age at menopause * (IQR)	49 (45-52)	49 (45-52)	49 (44-52)	0.61
Total fat † (IQR)	57.6 (50-65.3)	57.6 (49.4-64.8)	59.7 (53.3-69.7)	0.14
Saturated fat † (IQR)	19.4 (16.1-22.8)	19.5 (16.9-22.6)	20.6 (18.3-24.8)	0.06
Hormone use (%)				
Never	32.1	30.2	45.5	
Past	19.2	27.5	29.9	
Current	48.7	42.3	24.7	
Total	100	100	100	0.001
Smoking status (%)				
Never	40.7	44.5	48.0	
Past	35.4	37.9	36.4	
Current	23.9	17.6	15.6	
Total	100	100	100	0.36
Alcohol (%)				
Rarely/never	44.0	46.7	62.3	
1-3 drinks/month	13.2	17.0	11.7	
1-6 drinks/week	30.5	23.6	22.1	
≥ 1 drink/day	12.3	12.7	3.9	
Total	100	100	100	0.04
Exercise (%)				
Rarely/never	36.1	35.7	54.5	
< 1/week	18.9	18.1	22.1	
1-3/week	28.8	36.8	16.9	
≥ 4/week	16.2	9.4	6.5	
Total	100	100	100	0.002
Total cholesterol ≥240mg/dl	49.5	36.5	14.0	0.21
Hypertension % [‡]	40.4	38.8	20.8	< .0001
Diabetes %	17.6	47.1	35.3	0.003
Genotype distribution				
rs1271572 [‡]				
GG	55.7	29.9	14.4	
GT	52.7	33.9	13.4	
TT	52.7	31.1	16.2	0.89**
rs1256049 [‡]				
GG	53.6	32.6	13.8	
GA	61.6	25.6	12.8	

Body mass index (kg/m ²)				
Characteristics	Normal (<25)	Overweight (25-<30)	Obese (≥30)	P-value
AA	33.3	33.3	33.3	0.58 ^{**}
rs4986938 [‡]				
GG	56.0	31.6	12.4	0.68 ^{**}
GA	55.7	30.3	14.0	
AA	47.4	37.2	15.4	

* IQR is interquartile range (25 th to 75 th percentile).

[†] All macronutrients (mg/day) were adjusted for total energy intake.

[‡] Hypertension defined as physician diagnosis of hypertension or reported BP of >140 mmHg systolic or >90 mmHg diastolic blood pressure.

P values were obtained from Kruskal-Wallis (nonparametric) for continuous variables and chi-square for categorical variables.

[‡] All the polymorphisms tested were in Hardy-Weinberg equilibrium (p > 0.05), except rs1271572 (p =0.02).

** Exact P-values for chi-square test.

Table 2

Odds ratios for obesity and overweight in 561 apparently healthy Caucasian women in the Women's Health Study, according to ESR2 genotypes (additive model).

Odds Ratio [†] (OR, 95%CI, P)			Odds Ratio adjusted [‡] (OR, 95%CI, P)	
Overweight [*]				
rs1271572				
Normal	Referent (1.0)	P-value	Referent (1.0)	P-value
Overweight	1.08 (0.83-1.40)	0.59	1.19 (0.89-1.57)	0.24
rs 1256049				
Normal	Referent (1.0)		Referent (1.0)	
Overweight	0.87 (0.49-1.55)	0.64	0.77 (0.42-1.43)	0.41
rs 4986938				
Normal	Referent (1.0)		Referent (1.0)	
Overweight	1.15 (0.89-1.47)	0.29	1.07 (0.82-1.41)	0.62
Obese [*]				
rs1271572				
Normal	Referent (1.0)	P-value	Referent (1.0)	P-value
Obese	1.04 (0.71-1.51)	0.84	1.12 (0.74-1.68)	0.60
rs 1256049				
Normal	Referent (1.0)		Referent (1.0)	
Obese	1.21 (0.55-2.66)	0.64	1.11 (0.47-2.61)	0.81
rs 4986938				
Normal	Referent (1.0)		Referent (1.0)	
Obese	1.14 (0.80-1.64)	0.47	0.95 (0.63-1.44)	0.81

* Overweight women (25.0-> 30.0kg/m²) were compared to women with normal BMI (< 25.0kg/m²). Obese women (≥ 30.0kg/m²) were compared to women with BMI < 30.0kg/m².

[†] Adjustment by age.

[‡] Multivariate adjustment by age at randomization, age at menopause, hormones use, exercise, educational level, alcohol consumption, smoking status, total fat adjusted for energy intake. OR, odds ratio; CI, confidence interval.

Table 3

Odds ratios for obesity and overweight in 561 apparently healthy Caucasian women in the Women's Health Study, according to ESR2 haplotype (additive model).

Odds Ratio [†] (OR, 95%CI, P)			Odds Ratio Adjusted [‡] (OR, 95%CI, P)	
Overweight [*]				
T-G-G	Referent (1.0)	P-value	Referent (1.0)	P-value
G-G-G	0.68 (0.45-1.04)	0.07	0.62 (0.39-0.98)	0.04
G-G-A	1.00 (0.71-1.40)	0.98	0.89 (0.61-1.29)	0.51
T-G-A	0.73 (0.40-1.32)	0.29	0.62 (0.33-1.20)	0.16
Others ^{‡‡}	0.69 (0.28-1.70)	0.42	0.55 (0.21-1.49)	0.24
Obese [*]				
T-G-G	Referent (1.0)	P-value	Referent (1.0)	P-value
G-G-G	0.99 (0.54-1.79)	0.97	1.08 (0.56-2.09)	0.82
G-G-A	1.01 (0.62-1.64)	0.97	0.84 (0.49-1.46)	0.54
T-G-A	1.34 (0.61-2.96)	0.47	1.26 (0.53-2.99)	0.60
Others ^{‡‡}	0.93 (0.24-3.53)	0.91	0.80 (0.20-3.20)	0.75

* Overweight women (25.0-> 30.0kg/m²) were compared to women with normal BMI (< 25.0kg/m²). Obese women (≥ 30.0kg/m²) were compared to women with BMI < 30.0kg/m².

[†] Adjustment by age.

[‡] Multivariate adjustment as in the table 3.

^{‡‡} Others: combined variable with all haplotypes with less than 10% of frequency. G denotes major allele at each site: rs1271572, rs1256049 and rs4986938, A denotes minor allele at rs1256049 and rs4986938; and T denotes minor allele at rs1271572. OR, odds ratio; CI, confidence interval.