HHS Public Access

Author manuscript

Pharmacogenet Genomics. Author manuscript; available in PMC 2016 August 01.

Published in final edited form as:

Pharmacogenet Genomics. 2015 August ; 25(8): 377–381. doi:10.1097/FPC.0000000000000146.

Genetic Polymorphism at Val^{80} (rs700518) of the CYP19A1 Gene is Associated with Body Composition Changes in Women on Aromatase Inhibitors for ER (+) Breast Cancer

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Abstract

Purpose—Polymorphisms in the CYP19A1 (aromatase) gene influence disease-free survival and bone loss in patients taking aromatase inhibitors (AIs) for estrogen receptor positive (ER+) breast cancers. Because AI use results in profound estrogen deficiency which may lead to changes in body composition, the objective of this study was to determine the effect of the rs700518 polymorphism in the CYP19A1 gene, on the changes in body composition among postmenopausal women who were treated with AIs for ER+ breast cancer.

Methods—This is a 1-year prospective study of changes in body composition in postmenopausal women who were initiated on third-generation AIs for ER+ breast cancer. Body composition was measured by dual energy absorptiometry at 6 and 12 months, serum estradiol by radioimmunoassay and genotyping by Taqman SNP allelic discrimination assay.

Results—Eighty-two women were able to provide at least one follow-up body composition measurement. Women with the GG genotype for the rs700518 (G/A at Val80) developed a significant increase in Truncal fat mass index (p=0.03) and a significant decrease in fat-free mass index (p=0.01) at 12 months relative to patients carrying the A allele (GA/AA). There was no significant difference in the changes in estradiol levels among the genotypes.

Conclusion—Patients with the GG genotype for the rs700518 polymorphism in the CYP19A1 gene are at risk for significant loss of fat-free mass and increase in truncal fat with AI therapy. Whether there are associated metabolic abnormalities and whether changes would persist with long-term AI therapy, need to be confirmed in a larger study with a longer duration of follow-up.

Keywords

aromatase inhibitors; CYP19A1; obesity; breast cancer

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Conflicts of Interest

None declared;

INTRODUCTION

Significant changes in body composition that follow after menopause have been hypothesized as the cause for most of the metabolic abnormalities that occurs in postmenopausal women [6;18;24;26]. This has been attributed to the loss of estrogen as estrogen replacement prevents or attenuates the increase in total body and truncal fat and improves the associated metabolic abnormalities [4;23]. We previously reported that estrogen metabolism into the hydroxylated metabolites is associated with differences in body composition in postmenopausal women [17]. Our findings showed that women with increased hydroxylation though the 2-hydroxyl pathway had lower body fat and higher lean mass suggesting that the changes in body composition may not be similar across postmenopausal women and may be influenced by remaining circulating estrogen metabolites.

In postmenopausal women, the conversion of adrenal androstenedione to estrone by the enzyme aromatase represents the main source if not the only source of estrogen [8]. Inhibition of this enzyme by aromatase inhibitors (AIs), therefore, may result in a more profound estrogen deficiency, and further increase in the risk for metabolic abnormalities. However, to our knowledge there are very few studies on the effect of AIs on body composition. Nevertheless, results from a study comparing the effect of tamoxifen and exemestane showed that contrary to what is expected for women with profound estrogen deficiency, women on exemestane had a significant reduction in fat mass and increase in the ratio of fat-free mass to fat mass compared to women on tamoxifen who demonstrated no significant changes in both parameters [9;15]. Furthermore, a recent study by van Londen et.al. showed that although women on AIs had a significant increase in total body mass from baseline, this was not significantly different from postmenopausal women not on AIs. More importantly, this increase in total body mass is accounted for by the increase in lean mass and not fat mass [25]. These authors attributed their findings on the significantly higher total and free testosterone among women on AIs compared to women not on AIs.

Because aromatase activity may vary according to genetic polymorphisms in the CYP19A1 gene, it is possible that response to AIs may vary according to the sensitivity of aromatase enzyme to inhibition. In fact prior studies have shown inter-genotype differences in disease-free and overall survival, and time to progression among women variants in certain polymorphisms in the CYP19A1 gene [5;10;12;14]. The difference in response is assumed to result from variable hormonal levels resulting from varying degrees of aromatase enzyme inhibition. Since hormonal levels also influence body composition, we hypothesize that changes in body composition with AI therapy will vary according to sensitivity of the aromatase enzyme to inhibition, a function of polymorphisms in the CYP19A1 gene. We have previously described that a polymorphism in the CYP19A1 gene (rs700518) influences bone loss induced by AI, with subjects carrying the AA genotype experiencing a greater degree of bone loss than those with the G allele (GA+GG genotype) [16]. Thus, the objective of this study was to determine the effect of the rs700518 polymorphism in the CYP19A1 gene, on the changes in body composition among women who were treated with AIs for estrogen receptor positive (ER+) breast cancer.

PATIENTS AND METHODS

Study design and study population

This is a longitudinal prospective study on bone loss among community-dwelling postmenopausal women with ER+ breast cancer as previously described [16]. This study was conducted in accordance with the guidelines in the Declaration of Helsinki for the appropriate treatment of human subjects. The protocol was approved by the Washington University School of Medicine Institutional Review Board and written informed consent was obtained from each participant. Briefly, these women were living in the St. Louis, MO, USA, and metropolitan area and were referred from their oncologist's office to participate in the study. These women were at least 12 months from the last menstrual period or have history of bilateral oophorectomy, should have Stage 0-IIIA ER+ breast cancer and who were about to initiate a third generation aromatase inhibitor (anastrozole, letrozole or exemestane). Those who were taking medications (estrogen, bisphosphonates, selective estrogen receptor modulators, GnRH analogs, glucocorticoids [≥ 5 mg daily of prednisone or equivalent for ≥ 1 month] and phenytoin) or had conditions which affect bone metabolism (e.g. hyperthyroidism, osteomalacia, chronic liver disease, renal failure, hypercortisolism, malabsorption and alcoholism) were excluded from the study. Women on tamoxifen but switched to AIs at the time of enrollment were allowed into the study. Although current smoking was an exclusion criterion, those who resumed or started smoking (n=3) after they were enrolled in the study were allowed to continue participation.

Clinical, dietary, and anthropometric data

As previously described [16], all women were advised to take 1200 mg of calcium and 800 units of vitamin D daily. Age at menopause was obtained and years since menopause (YSM) was calculated by subtracting the menopausal age from the age at enrollment in the study. Body mass index (BMI) was calculated as weight in kilograms divided by square of height in meters (kg/m^2).

Biochemical data

Serum samples were collected in a nonfasting state. Serum estradiol was measured by an ultrasensitive radioimmunoassay technique (Diagnostic Systems Laboratory, Webster, TX, USA). The coefficient of variability for this assay in our laboratory is <10%.

Body composition

Total body mass, lean body mass, fat mass, truncal fat mass and whole body bone mineral content were measured using whole body dual-energy X-ray absorptiometry (Hologic Delphi, Hologic Inc., Bedford, MA; Enhanced Whole Body 11.2 software version; Hologic) as previously described [17]. The CV for these measurements in our laboratory is 1.5 % [17]. Fat-free mass was calculated by adding whole body bone mineral content to the lean mass. The following formula were used to calculate the: fat mass index= total fat mass (kg)/ square of the height in meters (m^2); truncal fat mass index=trunk fat mass(kg)/square of height in meters (m^2); and fat-free mass index= fat-free mass (kg)/square of the height in meters (m^2) [22].

Genotyping for CYP19A1 gene polymorphisms

Genomic DNA was extracted from peripheral leukocytes using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN, USA) and used as a template for genotyping procedures.

Genotyping for rs700518 was performed by allelic discrimination using specific TaqMan SNP Genotyping Assays as previously described [16]. Briefly, ~15 μl PCR reactions were carried out containing 12.5 μl TaqMan Universal PCR Master Mix (Applied Biosystems, New Jersey, USA), 10–15.0 ng DNA template and 1.25 μL TaqMan® Assay primers and FAM/VIC labeled probes by Applied Biosystems as Assays-by-Design™ (Applied Biosystems, Foster City CA 94404). The assay ID was C__8794675_30 (rs700518),. The assay was performed in 96-well plates including negative template controls. After PCR, end point discrimination of alleles was performed on the ABI Prism 7500 using the Sequence Detection Software (Applied Biosystems, Foster City CA 94404). All genotype call rates for each assay were > 95% Quality Value.

Statistical analysis

Results were expressed as mean ± SD. Changes in body composition parameters were expressed as percent (%) change from baseline at 6 and 12 months. A p value of <0.05 was considered significant. Group comparisons were done by independent T-tests and analysis of covariance (ANCOVA) for continuous variables, while categorical variables were compared using chi-square analysis. Intention-to-treat analyses were performed for changes in body composition by including all available observations (3 visits) in the analysis. The data were managed using Excel 2010 (Microsoft, Redmond, WA) and were analyzed using Statgraphics Centurion version 16 (Statpoint Technologies Inc., Warrenton, VA, USA).

RESULTS

Out of the ninety-nine patients who participated in the study [16], 82 had at least one follow-up body composition measurement over 12 months. The mean age of the participants was 60.6±9.1 years, mean BMI was 31.0±7.5 kg/m^2 and mean years since menopause (YSM) of 14.4±14.7 years. There was a decrease of -1.42±9.9% in total fat mass index, -0.77±13.1% in truncal fat mass index, and -0.33±3.9% in fat-free mass index in the entire study population over the one year period of follow-up.

Because the phenotypes for the GA and AA genotypes were closely similar, both genotypes were grouped as one and compared to the GG genotype in the analysis. Table 1 shows the baseline characteristics of the study population according to genotypes for the rs700518. There was no difference in the chronological ages and years since menopause between the genotypes. The mean BMI and the number of past smokers were also not significantly different between the genotypes. Similarly, there were no significant differences in body composition parameters between the genotypes. As expected, average estradiol level is in the postmenopausal range and not different between the genotypes.

Table 2 shows the changes in BMI and body composition of the participants at 6 months and at 1 year of AI therapy. There were no significant differences in changes in BMI and body

composition among the different genotypes of the rs700518 polymorphism at 6 months. However at the end of one year, women homozygous for the G allele (GG) had a significant increase in truncal fat mass index compared to women with GA+AA genotypes who actually had a decrease in truncal fat mass index. In addition, women with the GG genotype also had a significant decrease in fat-free mass index compared to women with the GA+AA genotypes where no change in fat-free mass index was observed. There was also a significant decrease in lean mass among patients with the GG genotype compared to GA +AA genotype GG=-2.15±3.51vs. GA+AA=0.64±3.89, p=0.007. Analysis of change in estradiol levels at 6 months showed no significant difference between the genotypes (GG= +0.21±1.94 vs. GA+AA= -0.05±0.067 pg/ml, p=0.47) and estradiol levels were 10.09± for GG genotype and 12.33± for GA+AA genotype, p=0.41.

The genotype frequencies for the rs700518 polymorphism in this subgroup of women were: GG=26, GA=51 and AA=30, and were in agreement with the Hardy in Weinberg Equilibrium (http://krunch.med.yale.edu/hwsim/).

DISCUSSION

Our results showed differences in changes in body composition according to genotypes for the rs700518 polymorphism in the CYP19A1 gene at the end of 1 year among women on AIs for ER+ breast cancer. Women with the GG genotype were experiencing negative changes in body composition relative to women with the A allele (GA+AA), i.e. loss of fat-free mass accompanied by a significant increase in truncal fat mass.

Menopause is accompanied by changes in body composition which includes redistribution of fat mass from the gynoid habitus to a more central fat distribution with increase in abdominal or visceral fat [6;18;24;26]. This change in body composition has been attributed to the loss of estrogen and hypothesized to account for the increase in the risk of cardiovascular events in postmenopausal women [4;23]. Because AI use in postmenopausal women with breast cancer would lead to profound estrogen loss, theoretically one would expect a greater degree of fat redistribution and perhaps loss of lean mass in these women compared to normal postmenopausal women.

Although very little information is available on the effect of AIs on body composition, the few published studies on this subject seemed to indicate no clinically significant adverse effect of AIs on body composition [15;25]. In a study by van Londen et al., women with breast cancer on AIs did not experience a significant increase in total body fat over the 2-years observation period [25]. In fact women not on AIs had a significant increase in total body fat from baseline. Furthermore, women on AIs had a significant increase in lean body mass compared to those not on AIs who did not experience any change in lean body mass over 2 years. The authors also found a significant increase in free testosterone which they hypothesized was responsible for the increase in lean body mass among women on AIs. In our study, the subset of women carrying the GG genotype had significant decrease in fat-free mass and increase in truncal fat mass relative to women with carrying the A allele who appeared to be protected from these negative effects suggesting that a subset of women may be susceptible, while another subset could be protected from the negative effects of AIs on

body composition. Because aromatase enzyme activity varies according genetic polymorphisms in the CYP19A1 gene [11;19;20], it is likely that changes in body composition vary depending on the sensitivity of the enzyme to AI inhibition. Thus, it is possible that fat-free mass is preserved in women with the A allele perhaps because of increased sensitivity to AIs resulting in greater inhibition of the aromatase enzyme activity leading to increased levels of adrenal androgens. In this same cohort of women, we previously reported that women with the AA genotype for the rs700518 had significant AI-induced bone loss relative to women with the AG+GG genotype suggesting that women with the AA genotype are more sensitive to enzyme inhibition [16]. The current observation showing no significant loss of fat-free mass in women with the AA genotype (which is accounted for mostly by the preservation of lean mass in these patients) is in agreement with the above finding indicating perhaps that with enhanced sensitivity to AIs, enough androgen is available to exert positive effect on muscle mass. Therefore, despite the negative effect of reduced estrogen on bone, overall fat-free mass was preserved. The converse is true for women with the GG genotype. Taken together, the previous report [16] and current findings suggest that women with the AG genotype have the best musculoskeletal side effect profile. These women did not develop significant bone loss and adverse changes in body composition relative to AA and GG genotypes, respectively.

Polymorphisms in the CYP19A1 gene have been reported to be associated with differences in body mass index and the risk for obesity [1;7]. However no study has been done on body composition changes among the CYP19A1 gene variants in the context of aromatase inhibition. We have shown that women with the GG genotype were experiencing negative effects on body composition from AI use. Although fat redistribution influence cardiovascular risk profile [2;3], it remains unknown if the negative changes in body composition in a certain subgroup of women on AIs are associated with differences in cardiovascular outcomes. Women with the GG genotype had a significant increase in truncal fat suggesting central fat deposition. Following the well-recognized association between central adiposity and cardiometabolic risk factors such as lipid profile and insulin sensitivity [13] it is possible that these women will have increase in cardiovascular risks with longer exposure to AIs. Previous studies have shown that women on AIs had significant reduction in high-density lipoprotein cholesterol and increase in low density lipoprotein cholesterol among women on exemestane relative to women on tamoxifen [9;15], suggesting a potential for AIs to have a negative impact on cardiovascular risks despite the overall higher ratio of fat free mass to fat mass.

Our study has limitations. We have limited sample size with a short duration of follow-up and it is possible that the current finding may not apply to the larger population of women who are on AIs for a longer period of time. In addition, because we did not control for multiple comparisons in the statistical analysis, our results should be interpreted with caution. For instance, the p-value of 0.03 for trunk fat mass index may not denote true statistical significance most especially that the changes in trunk fat mass index in 6 months were almost identical between the two groups. Similarly for the changes in fat-free mass index; although there was greater statistical significance at 12 months, the changes at 6 months were again nearly identical and not close to significance as would have been

expected. In addition, we have no mechanistic studies to explain the findings observed in the current study.

In summary, our findings showed that women with the GG genotype for the rs700518 SNP in the CYP19A1 gene had significant increase in truncal fat mass and reduction in fat-free mass on AIs. On the other hand, women with the A allele (GA+AA) were experiencing favorable changes in body composition; i.e. reduction in truncal body fat and preservation in fat-free mass. Although we don't have any data on the cardiovascular profile of our patients, it is possible that these changes will impact the cardiovascular risks of these subjects when given AIs for a longer period of time. Since have no biologic explanation for this observation at this time, the current findings may serve as basis for a proposal to perform mechanistic studies to understand the observed changes in these parameters. In addition, our findings may also lay the foundation for a larger clinical trial on the effect of genetics on body composition, metabolic and cardiovascular risk factors in women on AIs over a longer period of time. Given the improved survival among women with breast cancer on these newer endocrine therapies [21], other health issues resulting from the use of these agents need to be addressed by the scientific community. Since this study is the first prospective study looking at the effect of polymorphisms in the aromatase enzyme gene on changes in body composition, our findings need to be confirmed in a larger study among women on chronic AIs.

Acknowledgments

Source of Funding:

this work has been supported by NIH grant 1 R21 AR053196-01A1 (RAV).

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Table 1

Baseline characteristics of the study population according to the genotypes for the rs700518 polymorphism

	GG (N=24)	GA+AA (N=81)	*P
Age (yrs)	62.7±6.4	60.1±9.1	0.27
BMI (kg/m^2)	29.4±6.6	31.1±7.8	0.41
YSM	12.7±9.1	13.0±11.0	0.89
Positive smoking history	38.9%	21.3%	0.19
Aromatase inhibitor used			0.65
a) Anastrozole	15	47	
b) Letrozole	3	8	
c) Exemestane	1	8	
Patients with chemotherapy	2/18 (11.1%)	28/64 (43.8%)	0.009
Fat mass index (kg/m^2)	12.52±3.98	12.30±4.45	0.83
Trunk fat mass index(kg/m^2)	6.02±2.16	5.71±2.48	0.58
Fat-free mass index (kg/m^2)	18.48±2.60	18.62±2.65	0.82
Estradiol (pg/ml)	14.16±8.16	12.65±4.60	0.31

Values are Means±SD; BMI: body mass index, YSM: years since menopause,

*P T-test for age, BMI, and YSM; analysis of covariance adjusted for age for other continuous variables; chi-square for categorical variables

Table 2

Changes in BMI body composition parameters at 6 months and 1 years of aromatase inhibitor therapy according to genotypes of the rs700518 polymorphism

	% Changes in BMI and Body Composition at 6 months			% Changes in BMI and Body Composition at one year		
	GG (=18)	GA+AA N=(64)	P	GG (N=18)	GA+AA (N=64)	*P
BMI	0.90±5.20	-0.41±7.78	0.44	1.62±8.92	0.25±8.12	0.53
Fat mass index	-2.48±6.39	-0.76±8.02	0.45	1.57±8.82	-1.13±8.30	0.23
Trunk fat mass index	-2.24±9.51	-2.20±10.43	0.99	4.63±11.73	-2.21±11.95	0.03
Fat-free mass index	0.19±2.92	0.29±4.81	0.94	-2.12±3.40	0.39±3.64	0.01

Values are Means±SD; BMI: body mass index;

* T-test for BMI otherwise analysis of covariance adjusted for age