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Effect of Dietary Energy Restriction on the Expression of Genes Encoding the Enzymes Involved in Steroidogenesis in Normal Breast Epithelium and Abdominal Adipose Tissue of Women with Excessive Adiposity

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ABSTRACT

Background: Weight gain and excessive adiposity are associated with an increased risk of breast cancer, especially in postmenopausal women with a high circulating level of testosterone. In this *in silico* study, the effect of the dietary energy restriction (DER) on the expression of a panel of genes coding for the main enzymes involved in androgens and estrogens production was investigated in breast epithelium and abdominal adipose tissue of healthy women with excessive adiposity and randomly assigned to DER for one menstrual cycle or asked to continue their usual diet.

Methods: Wilcoxon-Signed-Rank test was used to assess the difference between paired samples before and after DER in the breast epithelium or adipose tissue, and Spearman's rank correlation was used to investigate the correlation between genes.

Results: In response to DER, the expression of *HSD17B12*, the gene encoding the enzyme that catalyzes the conversion of inactive estrone into bioactive estradiol, was significantly (P=0.0059) downregulated in breast epithelium and adipose tissue. Furthermore, the expression of *HSD17B12* negatively correlated with that of *the LRP1* gene (r=-0.91, P<0.0001), which codes for a multitasking protein recently proposed as a tumor suppressor in breast epithelium.

Conclusion: The results showed that, in addition to the recognized systemic effects (reduction of the fatty mass and decrease of circulating biomarkers of breast cancer risk), DER could act locally by down-regulating the expression of some genes pivotally involved in the production of biologically active estrogens, thus contributing to preventing the estrogen-dependent initiation of breast cancer.

INTRODUCTION

Growing evidence indicates that weight gain and excessive adiposity are associated with an increased risk of breast cancer, especially in postmenopausal women.[1,2] Besides, it suggests that the changes occurring in the hormonal milieu of postmenopausal women may play a crucial role in promoting and sustaining neoplastic transformation. Indeed, after ovarian activity diminishes, the predominant biological mechanism associated with the risk of developing breast cancer is the elevated production estrogens by androgens aromatization in the adipose tissue,[3] which increases with the increase of the fatty mass. The bioactive estradiol can stimulate the breast epithelial cells that express estrogen receptors to synthesize growth factors that will act in a paracrine manner on the adjacent estrogen-negative epithelial

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cells, promoting their proliferation. Conversely, in premenopausal women with excessive adiposity, the cumulative effect of the physiological ovarian production of steroid hormones with the high level of estrogens produced in the adipose tissue will result in negative impacts on the hypothalamic-pituitary release of gonadotropins. This will lead to the subsequent reduction in ovarian steroid production, thus explaining the paradoxical protective role of fat accumulation against breast cancer development observed in young women.[4]

Clinical evidence has demonstrated that the risk of breast cancer in postmenopause decreases with weight loss, especially with a weight loss before menopause.[5,6] Based on the evidence that dietary energy restriction (DER) significantly reduces spontaneous mammary tumors in animals,[7] some studies investigated the changes induced by DER on the recognized systemic factors associated with the risk of breast cancer in overweight or obese women, such as the circulating levels of estradiol, testosterone, insulin, leptin, lipoprotein particles, triglycerides, sex hormone-binding globulin, and insulin-like growth factor-1. Others investigated the effects of DER on the local expression of the genes involved in glycolysis and lipids synthesis.[8-11] However, no study has investigated the impact of DER on the genes coding for the enzymes involved in the production of androgens and estrogens. Using the publicly accessible dataset associated with the study on glycolysis and lipids synthesis,[11] I investigated the effects of DER on the expression of these genes in a group of women with excessive adiposity and randomly assigned to DER for one menstrual cycle or asked to continue their usual diet.

METHODS

Gene expression dataset (identified by the Gene Expression Omnibus (GEO) accession number GSE66159) and the associated clinical information were retrieved from the NCBI GEO database (HTTPS://www.ncbi.nlm.nhi.gov/geo/). As reported in the original article,[11] the case series consisted of 19 premenopausal overweight or obese (BMI between 28 and 40kg/m^2) women, aged between 35 and 45 years, randomly assigned to DER [liquid diet, which provided about 60% of the daily energy intake, 3,656kJ/d (864kcal/d); n=10] or asked to continue the usual diet (n=9) for one menstrual cycle. Briefly, core biopsies were obtained from breast tissue or abdominal fat before and after DER: the first biopsies were taken from either the left or right breast/abdominal side chosen by computer randomization, whereas the repeat biopsies were taken on the opposite side to avoid the gene expression changes due to the healing process. RNA was extracted from abdominal adipose tissue and breast epithelium (isolated from whole breast tissue by laser capture microdissection) and hybridized to Affymetrix HGU133 Plus2 GeneChips (GEO accession GPL570). After microarray running, raw data were processed and log^2-transformed. The Bolton (Lancashire) Local Research Ethics Committee approved the original study, and all participants signed written informed consent before participation. Further details on patients' selection criteria, sampling procedure and expression data processing (raw data filtration and normalization) are available in the original article.[11]

Gene set selection

According to the aim of the study, a group of 18 genes known as pivotally involved in the classical and alternative steroidogenic pathways (*AKR1C3, CYP11A1, CYP17A1, CYP19A1, HSD3B2, HSD17B1, HSD17B2, HSD17B6, HSD17B7, HSD17B12, SRD5A1, SRD5A2, STS, and SULT1A1*, Figure 1) or *coding for lipoprotein receptors* (*LDLR, LPR1, SCARB1, and VLDLR)* was selected.

Statistical analysis

The Wilcoxon-Signed-Rank test was used to assess the differential gene expression in the subgroup of women undergoing DER compared to those who continued their usual diet and the difference between paired samples before and after DER in the breast or adipose tissue. Spearman's rank correlation rho was used to investigate the correlation between the genes. Because of the exploratory aim of the analysis, according to Bender and Lange,[12] no multiple-testing corrections were adopted, and only a P-value<0.01 was considered statistically significant.

RESULTS

At baseline, in both breast epithelium and abdominal adipose tissue, no gene was differentially expressed in the subgroup of women undergoing DER compared to women that continued their usual diet.

Effect of *DER on gene expression in breast epithelium and abdominal adipose tissue*

Of the 18 genes selected for the study, only *AKR1C3, HSD17B12,* and *VLDLR* were found downregulated in response to DER in a statistically significant manner (P<0.01). In particular, *HSD17B12* and *VLDLR* were downregulated in breast epithelium, whereas *HSD17B12* and *AKR1C3* were downregulated in abdominal adipose tissue (Figure 2).

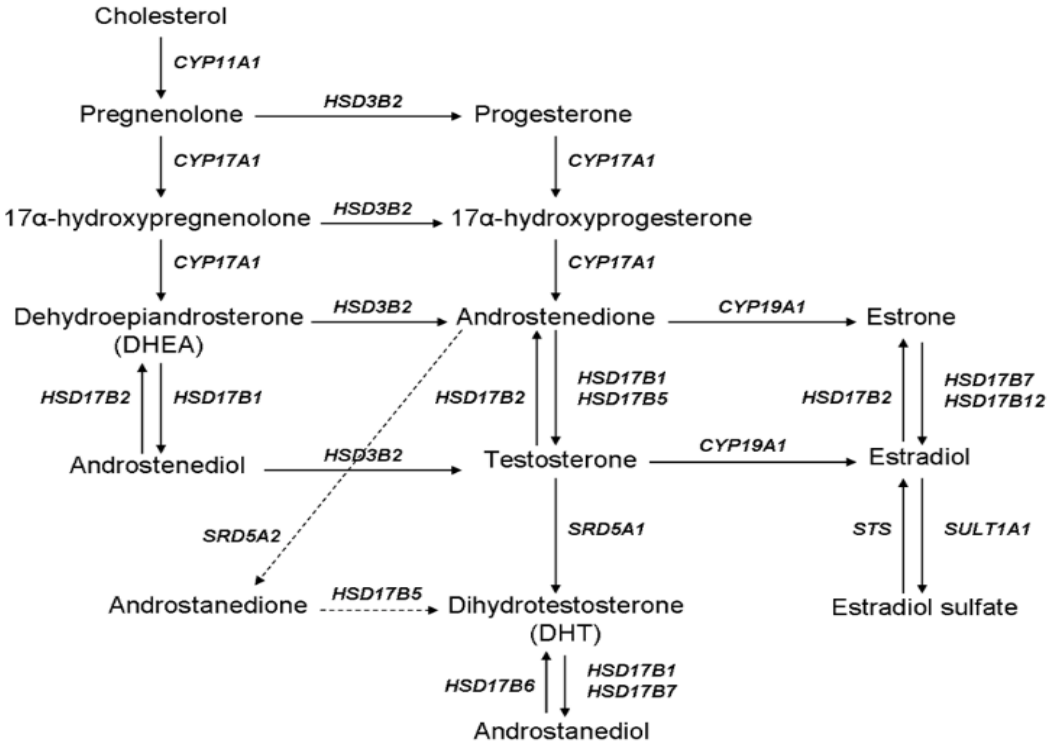


Figure 1. Schematic diagram depicting the genes coding for the enzymes involved in the classical steroidogenesis (solid line) and androgen alternative pathway (dashed line). *CYP11A1*, Cytochrome P450 family 11, subfamily A, polypeptide 1; *CYP17A1*, Cytochrome P450 Family 17 Subfamily A Member 1; *CYP19A1*, Cytochrome P450 family 19 subfamily A member 1, alias aromatase; *HSD3B2*, 3β-Hydroxysteroid dehydrogenase/Δ5-4 isomerase type 2; *HSD17B1*, Hydroxysteroid 17β-Dehydrogenase 1; *HSD17B2*, Hydroxysteroid 17β-Dehydrogenase 2; *HSD17B5*, Testosterone 17β-Dehydrogenase 5; *HSD17B6*: Hydroxysteroid 17β-Dehydrogenase 6; *HSD17B7*, Hydroxysteroid 17β-Dehydrogenase 7; *HSD17B12*, Hydroxysteroid 17β-Dehydrogenase 12; *SRD5A1*, Steroid 5α-Reductase 1; *SRE5A2*, Steroid 5α-Reductase 2; *STS*: Steroid Sulfatase; *SULT1A1*, Sulfotransferase Family 1A Member 1.

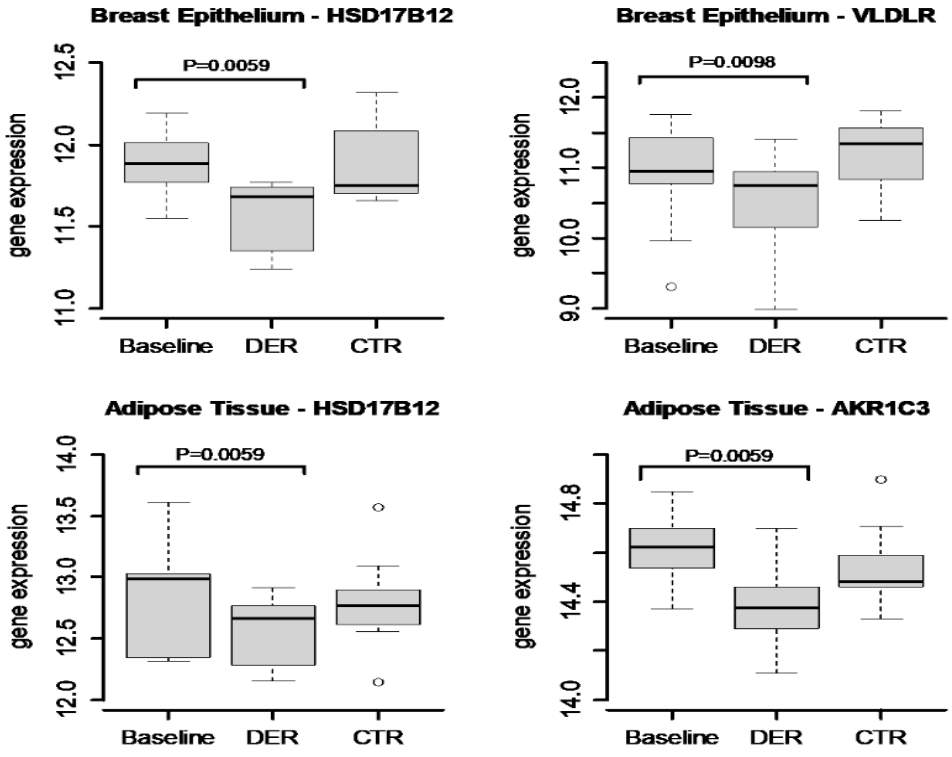


Figure 2. Expression of *HSD17B12* and *VLDLR* gene in breast epithelium and expression of *HSD17B12* and *AKR1C3* gene in abdominal adipose tissue before (Baseline), after DER (DER), or after usual diet (CTR). *P*-value refers to the difference evaluated by Wilcoxon paired test.

Effect of DER on the association of HSD17B12 or VLDLR with the other genes of the group in breast epithelium

Correlation analysis (Table 1) showed that the substantial reduction in the expression level of *HSD17B12* or *VLDLR* following DER was associated with some changes in the association with the other genes included in the group. The most remarkable of these changes were: the very high negative correlation between *HSD17B12* and *LRP1 (r=-0.91) or SRD5A2 (r=-0.74)*, the loss of the positive association of *HSD17B12* with *AKR1C3* or *STS*, the increase in the positive association of *VLDLR* with *AKR1C3* (r=0.86) and the negative association of *VLDLR* with *HSD17B7* (r=-0.67) (Figure 3).

Effect of DER on the association of AKR1C3 or HSD17B12 with the other genes of the group in abdominal adipose tissue

Correlation analysis (Table 1) showed that, following DER, the positive association between *HSD17B12* and *AKR1C3* or *HSD17B1* disappeared, and the negative association of *HSD17B12* with *CYP17A1* or *LRP1* decreased considerably (Figure 4).

DISCUSSION

Among the genes coding for the enzymes involved in the production of bioactive androgens and estrogens, only *HSD17B12* was differentially expressed in breast epithelium and abdominal adipose tissue of women undergoing DER compared to women that continued their usual diet. This finding is important because the *HSD17B12 gene en*codes a member of the 17β-hydroxysteroid dehydrogenase family (17β-HSD12) that converts the estrone formed by the aromatization of androstenedione into the biologically active estradiol and is specifically expressed in breast tissue.[13-16]

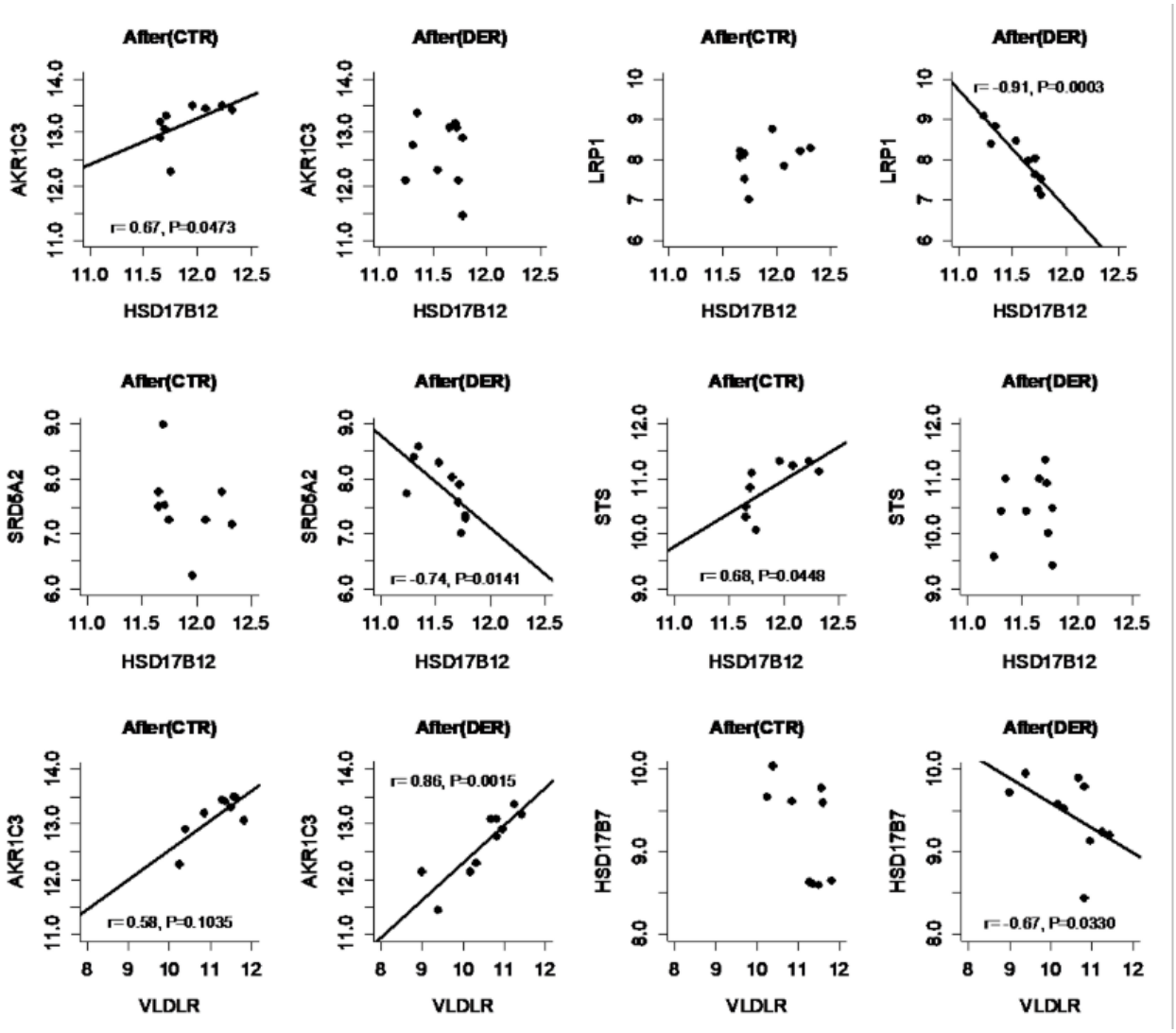


Figure 3. Correlation of *HSD17B12* or *VLDLR* with some other genes involved in steroidogenesis after DER regimen or usual diet (CTR) in breast epithelium. Spearman's correlation coefficient (r) and *p*-value are reported.

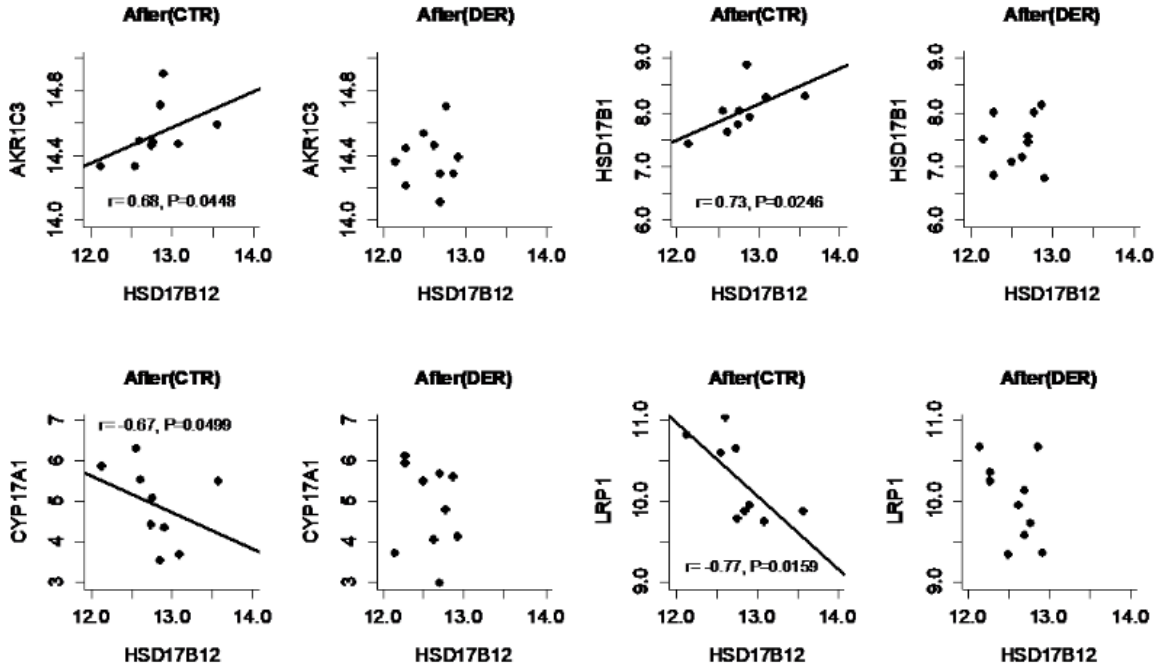
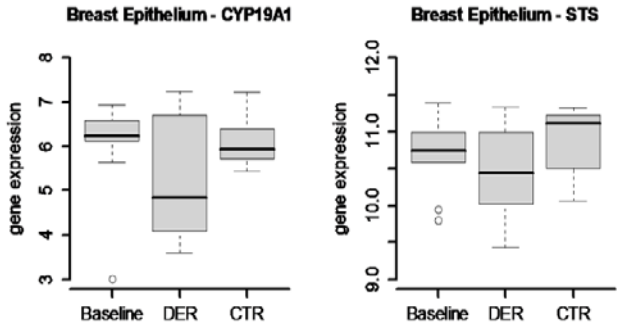


Figure 4. Correlation of *HSD17B12* with some other genes involved in steroidogenesis after DER regimen or usual diet (CTR) in abdominal adipose tissue. Spearman's correlation coefficient (r) and *p*-value are reported.

The fact that, after only one month, DER downregulated the expression of *CYP19A1* and *STS*, although in a not statistically significant manner (Supplementary Figure 1), suggests that diet restriction may affect the local production of estradiol, thus reducing the proliferative stimulus on epithelial cells and consequently the risk of developing breast cancer. *CYP19A1* and *STS, in fact,* code, respectively, for *the aromatase that converts testosterone into estradiol and* steroid sulfatase that converts back sulfate estradiol into the bioactive estradiol.

Noteworthy, the downregulation of HSD17B12 was associated with substantial changes in the relationship with some other genes included in the group. The most evident of these changes is the appearance of a very high negative correlation with LRP1 (r= -0.91, P<0.001), an unexpected finding considering that DER per se did not affect LRP1 expression.

LRP1 codes for the low-density lipoprotein receptor-related protein-1 (LPR1). Also known as apolipoprotein E receptor, LRP1 is a member of the LDLR family broadly expressed in multiple cell types such as mesenchymal and epithelial cells.17 Initially identified as a transmembrane receptor for apoE-enriched lipoprotein particles (especially chylomicron remnants), LRP1 is now known as implicated in several cellular processes, including cell growth and migration18 and phagocytosis of apoptotic cells.19 Moreover, in addition to the documented capability of controlling the pericellular levels of various growth factors and proteases, LRP1 modulates gene transcription through its intracellular domain that, once cleaved, can enter the nucleus where it regulates gene transcription and then is recycled into the cytoplasm.20 Because of this modulatory activity on gene transcription, LPR1 has been proposed as a tumor suppressor.21 In agreement with this suppressive role, it is reasonable to hypothesize that LRP1 may block the production of bioactive estradiol, downregulating the expression of the HSD17B12 gene without a substantial increase of the expression level of the LPR1 gene but rather by increasing the recycling of the cleaved intracellular domain.



Supplementary Figure 1. Expression of CYP19A1 and STS gene in breast epithelium before (Baseline), after DER (DER), or after usual diet (CTR).

Table 1 Correlations of the genes significantly downregulated by DER in breast epithelium or abdominal adipose tissue with the other genes of the panel after usual diet (CTR) or following DER.

	Breast Epithelium								Abdominal Adipose Tissue							
	HSD17B12				*VLDLR*				*AKR1C3*				*HSD17B12*			
	CTR		DER		CTR		DER		CTR		DER		CTR		DER	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P	r	P
Lipoprotein receptors																
LDLR	-0.47	0.203	-0.52	0.119	-0.63	0.067	-0.21	0.555	0.08	0.847	-0.26	0.466	-0.33	0.381	-0.09	0.802
LRP1	0.35	0.358	-0.91	0.0003	0.27	0.486	-0.12	0.751	-0.28	0.458	-0.47	0.172	-0.77	0.016	-0.42	0.226
SCARB1	-0.57	0.109	-0.61	0.064	-0.13	0.732	-0.18	0.625	-0.02	0.966	-0.32	0.364	-0.38	0.308	-0.43	0.211
VLDLR	0.29	0.444	0.02	0.960	NA	NA	NA	NA	0.23	0.544	-0.03	0.934	-0.33	0.381	0.05	0.894
Steroidogenesis																
AKR1C3	0.67	0.047	-0.18	0.625	0.58	0.104	0.86	0.002	NA	NA	NA	NA	0.68	0.045	0.02	0.953
CYP11A1	-0.29	0.442	-0.55	0.097	-0.17	0.667	0.27	0.446	0.09	0.814	0.17	0.638	-0.30	0.433	-0.48	0.159
CYP17A1	0.12	0.764	-0.16	0.651	0.42	0.265	0.39	0.260	-0.59	0.092	-0.20	0.578	-0.67	0.049	-0.15	0.674
CYP19A1	-0.51	0.160	-0.52	0.126	0.28	0.460	-0.12	0.751	0.39	0.295	-0.08	0.828	0.48	0.187	-0.60	0.065
HSD3B2	0.38	0.318	0.27	0.454	-0.08	0.831	-0.24	0.498	0.16	0.682	0.18	0.614	-0.16	0.417	-0.51	0.136
HSD17B1	-0.53	0.145	-0.46	0.184	-0.03	0.932	-0.38	0.283	0.45	0.222	-0.39	0.265	0.73	0.025	0.09	0.794
HSD17B2	-0.14	0.715	0.18	0.626	-0.75	0.019	-0.77	0.009	0.48	0.194	0.09	0.815	0.25	0.516	0.05	0.880
HSD17B6	-0.69	0.040	-0.64	0.047	0.08	0.847	-0.09	0.803	-0.35	0.354	-0.13	0.713	-0.42	0.265	-0.27	0.454
HSD17B7	-0.41	0.273	0.24	0.506	-0.37	0.332	-0.67	0.033	-0.08	0.847	-0.13	0.724	-0.13	0.732	-0.23	0.529
HSD17B12	NA	NA	NA	NA	0.29	0.444	0.02	0.960	0.68	0.045	0.02	0.953	NA	NA	NA	NA
SRD5A1	-0.33	0.383	-0.32	0.374	-0.13	0.748	0.09	0.803	0.45	0.222	0.56	0.093	0.03	0.932	0.01	0.973
SRD5A2	-0.47	0.196	-0.74	0.014	0.34	0.366	0.28	0.425	-0.25	0.515	0.24	0.498	-0.22	0.575	-0.07	0.841
STS	0.68	0.045	-0.10	0.789	0.67	0.049	0.88	0.0008	0.55	0.121	0.09	0.814	0.59	0.092	-0.56	0.089
SULT1A1	-0.38	0.318	-0.41	0.243	0.22	0.576	-0.12	0.751	-0.13	0.731	0.35	0.316	0.07	0.865	0.02	0.953

Following DER, LRP1 expression was associated positively with SRD5A2 (r=0.78, P=0.008), which, in turn, was associated negatively with HSD17B12. The finding is relevant because SRD5A2 encodes the 5α-reductase 2, the enzyme that catalyzes the conversion of androstenedione (the direct precursor of testosterone) into the less potent androgen androstenedione, following the so-called androgen alternative pathway.22 On the one hand, such a conversion reduces the amount of testosterone available to be converted directly into estradiol by aromatase and, on the other hand, the amount of androstenedione to be aromatized into estrone which will be, in turn, converted into estradiol by HSD17B12. These two effects will concur in reducing the estradiol production and the subsequent proliferative stimulus on epithelial cells.

Regarding the abdominal adipose tissue, the most remarkable finding is that, compared to breast epithelium, the substantial decrease in the expression level of *HSD17B12* was not associated with a change in the correlation with *LRP1* and *SRD5A2*. The negative association of *HSD17B12* with *LRP1* was weak and not statistically significant (r=-0.42, P=0.226), and the association with *SRD5A2* disappeared. Conversely, a negative association between *HSD17B12* and *CYP19A1* (r=-0.60, P=0.065) was observed following DER, suggesting the cellular attempt to restore the local estradiol by increasing testosterone aromatization.

Undoubtedly, the small number of subjects who participated in the study, mainly caused by the invasiveness of the sampling procedure that required repeated biopsies in both breasts and the abdominal adipose tissue of healthy women, may represent a potential concern about the reliability of the results. That was overcome, at least in part, by the homogeneity for weight, age, and parity of the subjects,[11] which resulted in an almost superimposable gene expression profile of baseline and repeat biopsies of the breast epithelium or abdominal adipose tissue in the control subgroup. Furthermore, the stringent criteria adopted in the statistical analysis allowed us to identify only the genes differentially expressed in response to DER.

CONCLUSION

The findings indicate that, in addition to the advantages described in the original article,[11] which include: a significant weight reduction (−7.0 ± 2.3 kg), a decreased level of some recognized circulating biomarkers associated with the risk of breast cancer such as leptin, total and low-density lipoprotein cholesterol, and triglycerides, and the changes in the expression of the genes involved in lipid metabolism and glycolytic pathways, DER may downregulate the *local* expression of some genes pivotally involved in the production of biologically active estrogens, thus contributing to preventing the estrogen-dependent initiation of breast cancer.

CONFLICTS OF INTEREST

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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