Available online at www.sciencedirect.com

ScienceDirect

www.nrjournal.com

The Western dietary pattern is associated with increased serum concentrations of free estradiol in postmenopausal women: implications for breast cancer prevention

Luisa María Sánchez-Zamorano[a], *Lourdes Flores-Luna*[a], *Angélica Angeles-Llerenas*[a], *Carolina Ortega-Olvera*[a], *Eduardo Lazcano-Ponce*[a], *Isabelle Romieu*[b], *Fernando Mainero-Ratchelous*[c], *Gabriela Torres-Mejía*[a,*]

[a] *Population Health Research Center, National Institute of Public Health, Cuernavaca, Mor, Mexico, Av. Universidad 655, Col. Sta. Ma. Ahuacatitlán CP 62100*

[b] *International Agency for Research on Cancer (IARC), 150 cours Albert Thomas 69372, Lyon, Cedex, 08, France*

[c] *Mexican Institute of Social Security, Dr. Luis Castelazo Ayala Hospital for Gynecology and Obstetrics # 4, Mexico City, Mexico*

ARTICLE INFO

Article history:
Received 20 November 2015
Revised 18 April 2016
Accepted 20 April 2016

Keywords:
Serum sex hormones
Western dietary pattern
Postmenopausal women
Testosterone
Estradiol
Red meat
Chicken eggs

ABSTRACT

Little is known about the possible influence of food consumption on the serum concentrations of endogenous sex hormones in postmenopausal women. We evaluated the relationships of the Western dietary pattern with serum concentrations of free estradiol and testosterone of postmenopausal women to test the hypothesis that a highly Western dietary pattern is associated with high serum concentrations of these hormones. We used data from a representative subsample of 305 women from the control group of a population-based case-control study conducted in Mexico from 2004 to 2007. A Western dietary pattern index value was compared with log natural serum concentrations of testosterone and estradiol using multiple linear regression models. The median values of serum concentrations of free estradiol and testosterone were 0.26 pg/mL (interquartile range, 0.14-0.43) and 0.40 pg/mL (interquartile range, 0.30-0.70), respectively. A multiple linear regression model showed that for each unit increase in the Western dietary pattern index, there was a 16.2% increase in the serum concentrations of free estradiol (β = 0.15; 95% confidence interval [CI], 0.01-0.29); for each additional serving per week of chicken eggs, the increase was 31.0% (β = 0.27; 95% CI, 0.106-0.441); for each additional serving per week of red meat, the increase was 64.9% (β = 0.50; 95% CI, 0.01-1.01). There was no relationship found between dietary patterns and serum concentrations of free testosterone. The present findings suggest that intake of a Western diet, particularly of chicken eggs and meat, increases serum concentrations of free estradiol; these results have implications for breast cancer prevention.

Abbreviations: AHEI, Alternate Healthy Eating Index; BMI, body mass index; CI, confidence interval; IQR, interquartile range; SHBG, sex hormone binding globulin.

* *Corresponding author at:* Dirección de Enfermedades Crónicas, Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública, Av. Universidad 655, Col. Sta. Ma. Ahuacatitlán, Cuernavaca, Mor., México, CP 62100. Tel.: +52 777 311 1960.
E-mail address: gtorres@insp.mx (G. Torres-Mejía).

http://dx.doi.org/10.1016/j.nutres.2016.04.008
0271-5317/

1. Introduction

High serum concentrations of free estradiol and testosterone have been associated with an increased risk of breast cancer in postmenopausal women [1] and other diseases such as cardiovascular disease, increased triglyceride concentrations and insulin resistance [2]. High serum concentrations of estradiol have been considered mutagenic for breast duct cell DNA [3]. In postmenopausal women, the synthesis of 17β-estradiol is produced from the aromatization of adrenal androgens, which are derived from cholesterol [4,5]. Adipose tissue is the primary storage site of the enzymes (aromatase and 17-hydroxysteroid dehydrogenases) that catalyze the synthesis of estrone, testosterone, and estradiol [6]. Testosterone may have an effect on breast cancer risk through estrogen synthesis or by a direct effect on breast tissue [2]. During postmenopause, women secrete more testosterone; therefore, serum concentrations of this hormone are higher in this period than during premenopause [4].

Dietary patterns have been used to assess the effects of a variety of foods on the risk of chronic diseases, including breast cancer [7–10]. Research on the association between individual foods or nutrients and several diseases has been difficult to interpret because of the strong correlations among them [7]. The consumption of meat and processed meat has been associated with the risk of colorectal cancer [11,12], and it has been suggested that diets high in tuna fish and processed meats increase the risk of breast cancer among Hispanic women, particularly in those with estrogen receptor–positive tumors [13]. Using dietary patterns reduces collinearity, and there is evidence of the synergistic and interactive effects of a variety of foods on the risk of chronic diseases, including cancer [7–10]. It has been shown that the Western dietary pattern increases the risk of breast cancer [14], and a higher estrogenic dietary pattern score has also been associated with an increased risk [15]. There is evidence that "prudent or healthy" dietary patterns have a protective effect on breast cancer; this is mainly attributed to the high content of fiber and antioxidants and fewer animal fats, carbohydrates, preservatives, and additives [14,16–18].

Little is known about the possible influence of food on the concentration of endogenous sex hormones in postmenopausal women. It has been observed that a high fiber intake [19,20] and a Mediterranean dietary pattern [21] are associated with lower serum concentrations of estradiol; in contrast, milk consumption has been associated with higher serum concentrations [22,23]. A dietary pattern known as *estrogenic food* with a high component of meat was positively correlated with serum estradiol [24]. In the Nurses' Health Study, it was found that in overweight postmenopausal women, the Alternate Healthy Eating Index (AHEI-2010) was associated with lower serum concentrations of estradiol; the authors suggested that there may be other combinations of foods that could have stronger associations [25]. The AHEI-2010 was proposed as a more accurate measure of diet quality and is based on high intakes, for example, vegetables, fruit, whole grains, nuts and legumes, and long-chain omega-3 fatty acids, among others [26,27]. Fung et al (2007) [25] compared the fifth and first quintiles of the AHEI score, and the geometric means of free estradiol were 0.08 and 0.12 pg/mL, respectively (P for trend < .0001). Regarding testosterone, in men, it has been observed that energy restriction in the diet lowers serum concentrations of free testosterone [28].

The association between Western dietary patterns and the risk of breast cancer could be explained, in part, by the correlation between this dietary pattern and serum concentrations of sex hormones. The hypothesis for this study was that a highly Western dietary pattern is associated with high serum concentrations of free estradiol and testosterone. In this context, the aim of this study was to assess the association of the Western dietary pattern with serum concentrations of free testosterone and estradiol in postmenopausal women.

2. Methods and materials

2.1. Design and study population

This study used data from the control group of a population-based case-control study conducted from 2004 to 2007 in Mexico City, Monterrey, and Veracruz, with a total of 1000 cases and 1074 controls [29]. The cases were patients with a new histologically confirmed diagnosis of breast cancer, with no previous treatment, such as radiotherapy, chemotherapy, or antiestrogens such as tamoxifen, during the previous 6 months. Controls were selected based on a probabilistic multistage sampling design and were frequency-matched to cases on 5-year age groups, health care system, and region. Of 1074 controls, 598 were postmenopausal women, and 305 had diet information and serum hormone determinations (Fig. 1). Briefly, all participants signed an informed consent letter. A nurse performed an in-person interview to obtain sociodemographic information as well as data on physical activity, diet, and health. In addition, anthropometric measurements (weight, height, and waist circumference) and blood samples for biochemical determinations were taken. The response rate for controls was 90.1% for Monterrey, 87.4% for Mexico City, and 97.6% for Veracruz. The study was approved by the National Institute of Public Health Institutional Review Board as well as by the equivalent committees from each of the participating hospitals [29].

In the present study, *postmenopausal women* were defined as those experiencing natural menopause (12 months or more since their last period), women with induced menopause (bilateral oophorectomy), and women with a history of hysterectomy who did not know if their ovaries had been removed but were older than 48 years, taking into consideration that the mean age at menopause in Mexico is 48 years [29–31].

2.2. Analysis of dietary patterns

Dietary data were obtained using a semiquantitative food-frequency questionnaire of 104 food components with 10 multiple-choice consumption frequency categories, as described by Willett [32] and adapted to the Mexican population [33].

To determine dietary patterns [34], all 104 foods included in the questionnaire were classified into groups according to their composition, with reference to tables of the Mexican system of food equivalents [35]. Seventeen food groups were obtained as a result (Supplemental Table 1). Subsequently, a

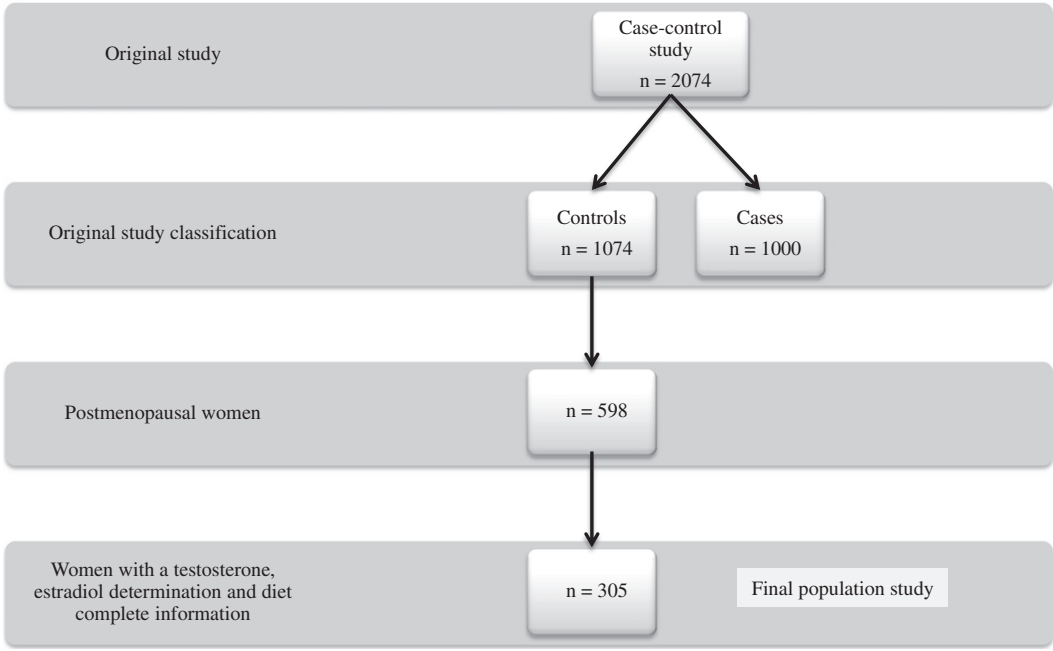

Fig. 1 – Study population diagram according to availability of information about free estradiol, testosterone, and diet in postmenopausal women. Flowchart describing study population.

cluster analysis was performed by aggregating individuals based on differences in their food-frequency consumption using a correlation coefficient similarity value among the frequencies of food consumption for each cluster of ≥60% as a cutoff point for each group (Supplemental Table 2) [7,9,36]. After obtaining the clusters, variables were generated to represent each of them. Principal component factor analysis with varimax rotation [37] was performed, determining 3 patterns reported previously (Western, fruits and cereals, prudent) [38,39] and 1 pattern that could be specific for the Mexican population (traditional) [14]. Foods and food groups whose proportion of explained variance (communality) was less than 0.10 were excluded (Supplemental Table 3).

2.3. *Blood withdrawal and determination of serum concentrations of free estradiol and testosterone*

Trained nurses obtained blood samples from each woman by venipuncture after at least 8 hours of fasting. The samples were centrifuged at 698.8*g* (2500 rpm) for 10 minutes at room temperature [40]; subsequently, the serum was separated and aliquoted into cryovials that were stored between –20°C and –70°C at the hospital where they were obtained. Within a period of no longer than 3 weeks, the samples were shipped from the participating hospitals to the National Institute of Public Health, where they were stored in deep freezers at –70°C until analysis [41]. The measurements of serum concentrations of free estradiol and testosterone were performed at the National Institute of Medical Sciences and Nutrition Salvador Zubiran in Mexico City using liquid chromatography coupled with mass spectrometry [41] (variation coefficient of 9.5%) and radioimmunoassay (variation coefficient of 8.1%), respectively [42].

2.4. *Statistical analyses*

A descriptive analysis of the study population was conducted, and medians and interquartile ranges (IQRs) were determined. For comparison, we used an equality-of-populations rank test and the Spearman correlation. To evaluate the association between dietary patterns and serum concentrations of free estradiol and testosterone, 2 multiple linear regression models were constructed where these variables were transformed to their natural log value (Ln) to meet the assumptions of the goodness of fit of the models [43]. The following variables were considered as potential confounders: age in 5-year periods, body mass index (BMI) (kg/m^2), alcohol consumption (g/d), physical activity (moderate and vigorous intensity, hours/day); total kilojoules intake (kJ/d), free testosterone (pg/mL, when assessing free estradiol), and free estradiol (pg/mL, when assessing free testosterone). For each multiple model, a statistical power analysis comparing the actual model vs the reduced model was performed according to Cohen (1988) [44]. Interpretation of the coefficients of the linear regression models with the natural log dependent variable was performed according to the methodology proposed by Cornell University, in which an increase of 1 unit in *X* would result in "$(e^{\beta_1}-1)*100$" percentage change in *Y* [45–48].

3. Results

The median age of the study population was 56.6 years (IQR, 51.6-61.4), whereas the median age at natural menopause was 47.0 years (IQR, 41.0-50.0). The median time since menopause to the age of the interview was 10.3 years (IQR, 4.6-16.1). The median serum concentrations of free estradiol and testosterone

Table 1 – Distribution of serum concentrations of free estradiol and testosterone according to characteristics

Characteristics		Distribution [a] n = 305 [b]	Free estradiol [c]	P [d]	Free testosterone [c]	P [d]
Age (y)						
<40		2.0	1.03 (0.74-1.86)	<.01	0.50 (0.30-1.00)	.59
40-44		2.6	1.30 (0.23-1.60)		0.32 (0.20-0.50)	
45-49		13.8	0.23 (0.14-0.46)		0.45 (0.30-0.60)	
50-54		23.6	0.22 (0.12-0.44)		0.34 (0.20-0.65)	
55-59		25.3	0.29 (0.13-0.43)		0.50 (0.30-0.74)	
60-64		22.3	0.24 (0.15-0.32)		0.40 (0.30-0.60)	
≥65		10.5	0.26 (0.14-0.42)		0.40 (0.22-0.75)	
State of residence						
Mexico City		54.1	0.25 (0.13-0.41)	.04	0.50 (0.30-0.74)	.01
Monterrey		31.0	0.30 (0.20-0.53)		0.30 (0.30-0.60)	
Veracruz		14.9	0.22 (0.12-0.39)		0.34 (0.20-0.59)	
Alcohol consumption (g/d)						
No		45.5	0.27 (0.17-0.44)	.33	0.36 (0.20-0.63)	.32
<1		44.2	0.25 (0.13-0.43)		0.40 (0.30-0.70)	
≥1		10.2	0.14 (0.11-0.15)		0.40 (0.30-1.30)	
History of smoking						
No		81.5	0.25 (0.13-0.41)	.02	0.40 (0.20-0.62)	.09
Yes		18.5	0.29 (0.21-0.62)		0.50 (0.30-0.70)	
Benign breast disease						
No		96.0	0.26 (0.14-0.44)	.85	0.40 (0.28-0.70)	.99
Yes		4.0	0.30 (0.09-0.39)		0.40 (0.30-0.60)	
Family history of breast cancer						
No		98.0	0.26 (0.14-0.43)	.28	0.40 (0.30-0.70)	.46
Yes		2.0	0.29 (0.25-0.50)		0.30 (0.20-0.50)	
Physical activity (h/wk)						
0-3		29.4	0.22 (0.13-0.45)	.19	0.40 (0.30-0.70)	.27
3.5-14		31.4	0.28 (0.18-0.44)		0.40 (0.30-0.70)	
14.5 to max		39.3	0.26 (0.14-0.41)		0.40 (0.20-0.61)	
BMI (kg/m^2)						
Obese		58.4	0.28 (0.17-0.46)	.09	0.40 (0.30-0.70)	.40
Overweight		31.8	0.21 (0.13-0.36)		0.40 (0.25-0.60)	
Normal		9.8	0.24 (0.11-0.48)		0.32 (0.20-0.60)	
Western dietary pattern [e]						
T1	(0.10-1.37)	32.9	0.22 (0.13-0.39)	.03	0.40 (0.30-0.70)	.77
T2	(1.38-2.15)	33.2	0.26 (0.14-0.41)		0.40 (0.20-0.70)	
T3	(2.16-7.43)	33.9	0.28 (0.17-0.55)		0.40 (0.30-0.60)	
Pattern of fruits and whole cereals						
T1	(0.0-1.64)	32.2	0.26 (0.13-0.35)	.26	0.32 (0.20-0.60)	.32
T2	(1.65-3.19)	33.2	0.27 (0.16-0.48)		0.40 (0.26-0.60)	
T3	(3.20-24.48)	34.6	0.25 (0.15-0.46)		0.40 (0.30-0.70)	
"Prudent" pattern of vegetables and fresh fish [e]						
T1	(0.15-1.46)	32.2	0.26 (0.15-0.39)	.93	0.40 (0.30-0.60)	.10
T2	(1.47-2.24)	32.9	0.26 (0.14-0.42)		0.40 (0.20-0.60)	
T3	(2.25-14.68)	34.9	0.26 (0.13-0.49)		0.50 (0.30-0.80)	
"Traditional" pattern [e]						
T1	(0.06-1.77)	32.6	0.26 (0.14-0.41)	.76	0.40 (0.26-0.60)	.15
T2	(1.78-2.89)	33.2	0.26 (0.14-0.41)		0.50 (0.30-0.80)	
T3	(2.90-7.43)	34.2	0.26 (0.14-0.48)		0.40 (0.30-0.60)	

[a] Values are expressed as percentages.
[b] Sample size =305 postmenopausal women.
[c] Values are expressed in pg/mL and medians (IQRs).
[d] Kruskal-Wallis test was used to compare categories.
[e] Values are expressed as ranges.

were 0.26 pg/mL (IQR, 0.14-0.43) and 0.40 pg/mL (IQR, 0.30-0.70), respectively. Table 1 shows the distribution of the median testosterone and estradiol concentrations according to the different characteristics of the study population. Women in the highest tertile of the Western dietary pattern had a median serum free fraction of estradiol concentrations of 0.28 pg/mL (IQR, 0.17-0.55), and the women in the lowest tertile had 0.22 pg/mL (IQR, 0.13-0.39) (P = .034). In contrast, no statistically significantly differences were observed for testosterone (P = .776). The concentrations of free estradiol decreased with the increasing age of the women (P = .002), whereas this correlation was not observed with testosterone concentrations (P = .599). Regarding

free estradiol, it was observed that the serum concentrations of this hormone were higher in women living in Monterrey than in those living in Veracruz and Mexico City ($P = .035$); regarding free testosterone, serum concentrations of this hormone were higher in women living in Mexico City than in those living in Veracruz and Monterrey ($P = .011$). Women who reported a history of smoking had higher serum concentrations of free estradiol than those who reported not smoking ($P = .018$). Regarding both hormones, no other differences were found among other variable categories. Fig. 2 shows the correlations of Western dietary pattern, chicken egg, and red meat intake with the natural logarithm of serum concentrations of free estradiol.

We constructed 4 dietary patterns: "Western," "fruits and whole cereals," "prudent," and "traditional." Of all the dietary patterns, only the Western was statistically significantly associated with serum concentrations of free estradiol (Table 2); for an increase of 1 unit in the Western dietary pattern index, serum free estradiol increased by 16.2% (95% CI, 1.0-33.6) ($\beta = 0.15$; 95% CI, 0.01-0.29). An inverse association was also found between 5-year age categories and the concentrations of this hormone (P for trend = .007). In addition, regarding moderate- and vigorous-intensity physical activity, it was observed that compared with women who reported performing between 0 and 3 hours per week, serum concentrations of this hormone increased by 35.0% (95% CI 5.1-73.3%) ($\beta = 0.30$; 95% CI, 0.05-0.55) in those who reported performing physical activity for 3.5 to 14 hours per week ($P = .016$).

Regarding the free fraction of testosterone (Table 3), for each unit change in serum concentrations of free estradiol, serum concentrations of free testosterone increased by 24.6% (95% CI, 8.3-43.3%) ($\beta = 0.22$; 95% CI, 0.08-0.36) ($P = .002$); it was also observed that compared with women who reported no alcohol consumption, those who reported consuming 1 g or more of alcohol per day had a 32.3% increase in serum concentrations of free testosterone (95% CI, 5.1-68.2%) ($\beta = 0.28$; 95% CI, 0.05-0.52) ($P = .017$).

When the same analysis was performed replacing the Western dietary pattern with each of its component foods (data not shown), there was a significant relationship between chicken egg consumption and serum concentrations of free estradiol ($\beta = 0.27$; 95% CI, 0.106-0.441; $R^2 = 0.1092$); that is, for each unit change in 1 egg consumption, an increase of 31.0% was observed. A similar figure was observed for red meat consumption ($\beta = 0.50$; 95% CI, 0.01-1.01; $R^2 = 0.092$); that is, for each unit change in 1 red meat serving consumption, an increase of 64.9% was observed in serum concentrations of free estradiol ($P = .048$).

4. Discussion

A Western dietary pattern, specifically the consumption of red meat and chicken eggs, was associated with higher serum concentrations of free estradiol, whereas no association was observed with serum concentrations of free testosterone. Thus, our hypothesis that a high Western dietary pattern is associated with high serum concentrations of free estradiol is supported by the results of the present study. The association between the consumption of these foods and serum concentrations of free estradiol can be explained, in part, because Western dietary component foods are a source of cholesterol. After menopause, cholesterol is a precursor of endogenous estrogens from androgen aromatization that takes place mostly in the adrenal gland [41,49–51].

Chicken eggs and red meat are at the top of the list of foods high in cholesterol (548 mg/100 g and 47 to 90 mg/100 g, respectively) [52]. In Mexico, egg consumption is approximately 24.8 kg per person per year [53], representing a daily intake of 68.0 g, equivalent to 372 mg of cholesterol consumption, whereas in the last decade, the average red meat consumption per capita was 18 kg per year [54], 49 g consumed per day, representing a daily beef cholesterol contribution of 44 mg. The level of consumption of these 2 foods is above the recommendations of the 2010 Dietary Guidelines for Americans [55] and the National Cholesterol Education Program Adult Treatment Panel III [56], which recommend a daily intake of less than 300 mg of cholesterol per day for healthy adults. Although the 2015-2020 Dietary Guidelines for Americans do not establish a limit of dietary cholesterol intake per day, it is implicit in their recommendation in favor of a healthy eating pattern, which includes foods with low concentrations of cholesterol [57], a more easily adoptable recommendation than daily milligrams cholesterol intake.

Another source of estrogenic activity is the exposure to zeranol contained in food mainly of animal origin. Zeranol is an estrogenic compound derived from fungi of the Fusarium family and is used as a growth promoter in cattle in many countries, including Canada, Australia, New Zealand, South Africa, Mexico, Chile, Japan, and the United States. Zeranol is a known estrogen agonist, and its estrogenicity has been found to be comparable to that of natural estradiol [58–62]. It has been documented that meat can contain residues of hormonal components used in the growth and fattening of cattle, which are associated with higher concentrations of estradiol, estrone, progesterone, and testosterone in animals [63]. In addition, it has been suggested that sex hormones acquired in the body by food consumption have the same biological activity as endogenously produced hormones [63].

Worldwide, nutrition habits have changed over the years. It has been explained as a so-called nutritional transition, which includes shifts in dietary intake and energy expenditure that are influenced by ongoing simultaneous interactions among economic, demographic, environmental, psychosocial, and cultural factors occurring in society [64]. Dietary patterns have moved from a traditional diet based on cereals, corn, roots, tubers, and legumes to a diet based on simple carbohydrates, saturated and vegetable fats, red meat [65], and a Western dietary pattern [66]. The Food and Agriculture Organization reported an increase of diet energy in approximately 879 kJ per person per day from 1990 to 2010, higher in developing (kJ per person per day) than in developed countries (360 kJ per person per day) [67]. The United States, Europe, and Mexico are 3 different regions with diverse characteristics, yet they have experienced coincidental changes in dietary patterns that include a high intake of meat, simple carbohydrates, and total fat [65,68–70].

The association between certain dietary components and serum concentrations of free estradiol found in this study is consistent with findings in other studies. Since 1990, diet has been evaluated as one of the factors affecting the concentrations of estradiol and other serum biomarkers [71], showing that the change from a standard diet, based mainly on red

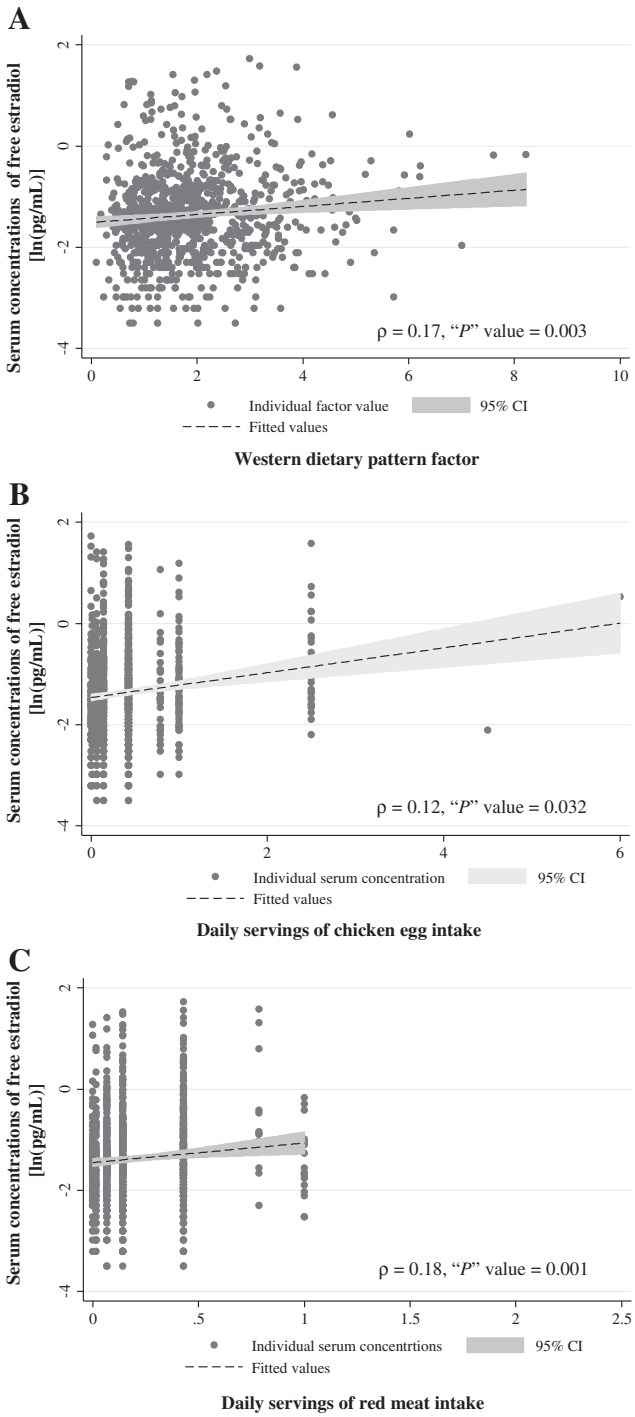

Fig. 2 – Distribution of serum concentrations of free estradiol in relation with Western dietary pattern, chicken egg, and red meat intake in postmenopausal women. This figure shows the relationship of the Western dietary pattern factor, daily servings of chicken egg, and red meat intake with the natural logarithm of the serum concentrations of free estradiol.

meat and animal fat, to a vegetarian diet significantly decreased serum free estradiol, total estradiol, and sex hormone binding globulin (SHBG). In a population of American women, Fung et al (2012) [24] observed that the dietary pattern known as *estrogenic food*, composed of red meat, legumes, and pizza but with a low consumption of coffee and whole grains, was modestly but significantly positively correlated with plasma concentrations of estradiol. However, in their study, Iwasaki et al (2011) [72] highlighted that diet is related to serum concentrations of free estradiol and that it differs according to the place of residence of the study population. They compared serum concentrations of estradiol in postmenopausal Japanese women, Japanese women living in Brazil, and Brazilian women and observed that Japanese women living in Brazil had higher concentrations of free estradiol compared with Japanese women living in Japan, indicating that

Table 2 – Association between dietary patterns and serum concentrations of free estradiol

Characteristics	Unadjusted [a]						Adjusted [b]					
					P						P	
Pattern of fruits and whole cereals	0.006	(−0.05	, 0.06	)	.81	−0.0031	−0.02	(−0.07	, 0.03	)	.47	0.1068
Pattern of vegetables and fresh fish	0.02	(−0.08	, 0.12	)	.70	−0.0028	−0.01	(−0.11	, 0.08	)	.72	0.1055
Traditional pattern	0.002	(−0.08	, 0.09	)	.96	−0.0033	−0.02	(−0.11	, 0.07	)	.72	0.1056
Western pattern	0.16	(0.07	, 0.26	)	<.01	0.0326	0.15	(0.01	, 0.29	)	.03	0.1199
Age (y)												
<40	Ref.					0.0286	Ref.					
40-44	−0.61	(−1.51	, 0.29	)	.18		−0.53	(−1.42	, 0.36	)	.25	
45-49	−1.49	(−2.22	, −0.76	)	<.01		−1.42	(−2.15	, −0.70	)	<.01	
50-54	−1.62	(−2.33	, −0.91	)	<.01		−1.57	(−2.27	, −0.86	)	<.01	
55-59	−1.57	(−2.28	, −0.87	)	<.01		−1.51	(−2.21	, −0.80	)	<.01	
60-64	−1.64	(−2.35	, −0.92	)	<.01		−1.51	(−2.22	, −0.80	)	<.01	
≥65	−1.59	(−2.33	, −0.84	)	<.01		−1.45	(−2.2	, −0.71	)	<.01	
Trend test					<.01						<.01	
BMI (kg/m^2)												
Obesity	Ref.					−0.001	Ref.					
Overweight	−0.14	(−0.36	, 0.08	)	.19		0.12	(−0.16	, 0.41	)	.40	
Normal	−0.08	(−0.43	, 0.26	)	.63		0.26	(−0.24	, 0.77	)	.31	
Trend test					.31						.29	
Free testosterone	0.13	(−0.07	, 0.33	)	.19	0.002	0.13	(−0.05	, 0.32	)	.17	
Alcohol consumption (g/d)												
No	Ref.					−0.004	Ref.					
<1 g	−0.09	(−0.29	, 0.12	)	.40		−0.11	(−0.32	, 0.09	)	.27	
≥1 g	−0.03	(−0.82	, 0.76	)	.94		−0.06	(−0.36	, 0.24	)	.69	
Trend test					.44						.65	
Physical activity (h/wk)												
0-3	Ref.					0.008	Ref.					
3.5-14	0.25	(−0.01	, 0.51	)	.05		0.30	(0.05	, 0.55	)	.01	
14.5 to max	0.04	(−0.20	, 0.29	)	.72		0.09	(−0.14	, 0.32	)	.45	
Trend test					.92						.88	
Constant	–	–	–		–		−0.36	(−1.16	, 0.42	)	.36	

[a] Multiple linear regression unadjusted model. Values are expressed as β, 95% CI, P value, and adjusted R^2. Interpretation of the coefficients with the natural log dependent variable was performed according to the methodology proposed by Cornell University, in which an increase of 1 unit in X would result in "$(e^{\beta_1}-1)*100$" percentage change in Y [46–48].

[b] Multiple linear regression adjusted model. Values are expressed as β, 95% CI, P value, and adjusted R^2. Each dietary pattern was adjusted for energy intake (kJ/d) and all variables in the table except other dietary patterns. β values from the covariates correspond to the Western pattern model, and values are expressed as in a.

the different diet may explain their findings [72]. Another study in postmenopausal Japanese women showed that a high-fat diet was associated with elevated serum concentrations of estrone and dehydroepiandrosterone sulfate [73], results that were similar to those found in American women in the study conducted by Newcomb et al (1994) [74].

Serum and plasma concentrations of estradiol are biomarkers that may represent an important mechanism for breast cancer risk [3,75,76]. Circulating estrogens are important because they stimulate the proliferation, growth, and development of tumor cells (mitogenic activity) [77], and it has also been postulated that estrogens have genotoxic activity [78].

Regarding potential limitations, our sample study was representative of the controls obtained from a population-based case-control study [29]. Regarding selection bias, there were no statistically significant differences among general characteristics between all postmenopausal controls and the subsample (ie, age, BMI, state of residence, history of smoking, alcohol consumption, and family history of breast cancer). To avoid information inaccuracies, standardized study personnel interviewed controls to obtain information about their health, physical activity, and diet. The questionnaire used for the present study was previously validated only for the population in Mexico City and not for other states; therefore, a variety of Mexican dishes were not included [33]. To avoid confounding, multiple models were adjusted for potential confounders. Although the SHBG was not measured in this study, the free fractions of serum estradiol and testosterone were determined directly. Furthermore, the models were adjusted for BMI, energy intake, Western dietary pattern, and physical activity, variables that have been indirectly correlated to serum SHBG [79–81]; because the models were adjusted for these variables, we indirectly adjusted for the serum concentration of SHBG.

The multiple linear models showed that physical activity was positively associated with serum concentrations of free estradiol. Contrary to our results, McTiernan et al (2004) [82] showed a negative relationship, but this relation could be mediated by body fat (Neilson et al, 2014) [83]. We found a negative association only in women within a normal category of BMI but not in overweight or obese women (P for interaction = .029) (data not shown).

In conclusion, the Western dietary pattern showed positive associations with serum concentrations of free estradiol; within the components of this Western pattern, chicken eggs and red

Table 3 – Association between dietary patterns and serum concentrations of free testosterone

Characteristics	Unadjusted [a]					Adjusted [b]				
				P					P	
Pattern of fruits and whole cereals	0.01	(−0.02	0.05)	.51	−0.0018	0.01	(−0.03	0.05)	.63	0.0334
Pattern of vegetables and fresh fish	0.07	(0.0001	0.15)	.05	0.0094	0.06	(−0.01	0.14)	.12	0.0407
Traditional pattern	−0.04	(−0.11	0.02)	.17	0.0028	−0.05	(−0.12	0.01)	.15	0.0395
Western pattern	−0.001	(−0.076	0.07)	.96	−0.0033	−0.04	(−0.15	0.06)	.42	0.0348
Age (y)										
<40	Ref.					Ref.				
40-44	−0.45	(−1.16	0.27)	.22	−0.0027	−0.03	(−1.08	0.33)	.30	
45-49	−0.21	(−0.79	0.37)	.47		0.02	(−0.56	0.61)	.94	
50-54	−0.28	(−0.84	0.29)	.34		−0.02	(−0.59	0.55)	.94	
55-59	−0.09	(−0.65	0.47)	.75		0.14	(−0.42	0.72)	.61	
60-64	−0.26	(−0.83	0.3)	.36		−0.03	(−0.61	0.53)	.89	
≥65	−0.20	(−0.79	0.39)	.50		0.01	(−0.59	0.61)	.98	
Trend test				.87					.74	
BMI (kg/m^2)										
Obesity	Ref.				−0.0005	Ref.				
Overweight	−0.05	(−0.22	0.12)	.56		−0.09	(−0.32	0.14)	.44	
Normal	−0.18	(−0.44	0.09)	.19		−0.23	(−0.64	0.17)	.26	
Trend test				.20					.27	
Free estradiol	0.20	(0.07	0.33)	<.01	0.0245	0.22	(0.08	0.36)	<.01	
Alcohol consumption (g/d)										
No	Ref.				0.0021	Ref.				
<1 g	0.10	(−0.05	0.26)	.19		0.05	(−0.11	0.21)	.52	
≥1 g	0.35	(−0.26	0.95)	.26		0.28	(0.05	0.52)	.02	
Trend test				.12					.03	
Physical activity (h/wk) [c]										
0-3	Ref.				−0.0001	Ref.				
3.5-14	−0.05	(−0.25	0.15)	.61		−0.11	(−0.31	0.07)	.23	
14.5 to max	−0.13	(−0.32	0.06)	.17		−0.16	(−0.34	0.02)	.88	
Trend test				.16					.12	
Constant	–	–	–	–		−1.07	(−1.71	−0.43)	<.01	

[a] Multiple linear regression unadjusted model. Values are expressed as β, 95% CI, P value, and adjusted R^2. Interpretation of the coefficients with the natural log dependent variable was performed according to the methodology proposed by Cornell University, in which an increase of 1 unit in X would result in "$(e^{\beta_1}-1)*100$" percentage change in Y [46–48].

[b] Multiple linear regression adjusted model. Values are expressed as β, 95% CI, P value, and adjusted R^2. Each dietary pattern was adjusted for energy intake (kJ/d) and all variables in the table except other dietary patterns. β values from the covariates correspond to the Western pattern model, and values are expressed as in a.

[c] Hours of moderate- and vigorous-intensity physical activity.

meat were the only foods associated with this biomarker. Additional study of the mechanisms that sustain the association observed in this study is needed to propose mechanisms for improving the quality of food intake. In the meantime, a healthier diet should be recommended to the population.

Conflicts of interest

None.

Acknowledgment

We acknowledge the support of the following physicians from participating hospitals: Germán Castelazo (IMSS, Mexico City, DF), Sinuhé Barroso Bravo (IMSS, Mexico City, DF), Joaquín Zarco Mendez (ISSSTE, Mexico City, DF), Edelmiro Pérez Rodríguez (University Hospital, Monterrey, Nuevo León), Jesus Pablo Cano Esparza (IMSS, Monterrey, Nuevo León), Heriberto Fabela (IMSS, Monterrey, Nuevo León), Fausto Hernández Morales (ISSSTE, Veracruz, Veracruz), Pedro Coronel Brizio (CECAN SS, Xalapa, Veracruz), and Vicente A. Quiroz Saldaña (IMSS, Veracruz, Veracruz).

This work was funded by the National Council of Science and Technology (grant CONACyT-SALUD-2002 C01-7462) and DGPOP 2011, Dirección General de Programación Organización y Presupuesto, Ejercicio fiscal 2011, Ramo 12 Salud.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nutres.2016.04.008.

REFERENCES

[1] Tworoger SS, Missmer SA, Barbieri RL, Willett WC, Colditz GA, Hankinson SE. Plasma sex hormone concentrations and subsequent risk of breast cancer among women using postmenopausal hormones. J Natl Cancer Inst 2005;97:595–602.

[2] Yasui T, Matsui S, Tani A, Kunimi K, Yamamoto S, Irahara M. Androgen in postmenopausal women. J Med Invest 2012;59: 12–27.
[3] Bernstein L, Ross RK. Endogenous hormones and breast cancer risk. Epidemiol Rev 1993;15:48–65.
[4] Speroff L, Glass RH, Kase NG. The breast. Clinical gynecologic endocrinology and infertility. Lippincott Williams & Wilkins; 1999 595–604[12–33].
[5] Ganong W. Fisiología Médica: manual Moderno; 2002.
[6] Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002;346:340–52.
[7] Randall E, Marshall JR, Graham S, Brasure J. Patterns in food use and their associations with nutrient intakes. Am J Clin Nutr 1990;52:739–45.
[8] Wirfalt AK, Jeffery RW. Using cluster analysis to examine dietary patterns: nutrient intakes, gender, and weight status differ across food pattern clusters. J Am Diet Assoc 1997;97: 272–9.
[9] Randall E, Marshall JR, Brasure J, Graham S. Dietary patterns and colon cancer in western New York. Nutr Cancer 1992;18: 265–76.
[10] Willett WC. Diet and health: what should we eat? Science 1994;264:532–7.
[11] Blackadar CB. Historical review of the causes of cancer. World J Clin Oncol 2016;7:54–86.
[12] Stepien MCV, Romieu I. The role of diet in cancer: the epidemiologic link. Salud Publica Mex 2016;58:261–73.
[13] Kim AE, Lundgreen A, Wolff RK, Fejerman L, John EM, Torres-Mejia G, et al. Red meat, poultry, and fish intake and breast cancer risk among Hispanic and non-Hispanic white women: the breast cancer health disparities study. Cancer Causes Control 2016.
[14] Sanchez-Zamorano LM, Flores-Luna L, Angeles-Llerenas A, Romieu I, Lazcano-Ponce E, Miranda-Hernandez H, et al. Healthy lifestyle on the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2011;20:912–22.
[15] Harris HR, Bergkvist L, Wolk A. An estrogen-associated dietary pattern and breast cancer risk in the Swedish mammography cohort. Int J Cancer 2015;137:2149–54.
[16] Brennan SF, Cantwell MM, Cardwell CR, Velentzis LS, Woodside JV. Dietary patterns and breast cancer risk: a systematic review and meta-analysis. Am J Clin Nutr 2010;91: 1294–302.
[17] Cottet V, Touvier M, Fournier A, Touillaud MS, Lafay L, Clavel-Chapelon F, et al. Postmenopausal breast cancer risk and dietary patterns in the E3N-EPIC prospective cohort study. Am J Epidemiol 2009;170:1257–67.
[18] Albuquerque RC, Baltar VT, Marchioni DM. Breast cancer and dietary patterns: a systematic review. Nutr Rev 2014;72:1–17.
[19] Fowke JH, Longcope C, Hebert JR. Macronutrient intake and estrogen metabolism in healthy postmenopausal women. Breast Cancer Res Treat 2001;65:1–10.
[20] Monroe KR, Murphy SP, Henderson BE, Kolonel LN, Stanczyk FZ, Adlercreutz H, et al. Dietary fiber intake and endogenous serum hormone levels in naturally postmenopausal Mexican American women: the multiethnic cohort study. Nutr Cancer 2007;58:127–35.
[21] Carruba G, Granata OM, Pala V, Campisi I, Agostara B, Cusimano R, et al. A traditional Mediterranean diet decreases endogenous estrogens in healthy postmenopausal women. Nutr Cancer 2006;56:253–9.
[22] Brinkman MT, Baglietto L, Krishnan K, English DR, Severi G, Morris HA, et al. Consumption of animal products, their nutrient components and postmenopausal circulating steroid hormone concentrations. Eur J Clin Nutr 2010;64:176–83.
[23] Troisi R, Ganmaa D, dos Santos SI, Davaalkham D, Rosenberg PS, Rich-Edwards J, et al. The role of hormones in the differences in the incidence of breast cancer between Mongolia and the United Kingdom. PLoS One 2014;9:e114455.
[24] Fung TT, Schulze MB, Hu FB, Hankinson SE, Holmes MD. A dietary pattern derived to correlate with estrogens and risk of postmenopausal breast cancer. Breast Cancer Res Treat 2012; 132:1157–62.
[25] Fung TT, Hu FB, Barbieri RL, Willett WC, Hankinson SE. Dietary patterns, the alternate healthy eating index and plasma sex hormone concentrations in postmenopausal women. Int J Cancer 2007;121:803–9.
[26] Varraso R, Chiuve SE, Fung TT, Barr RG, Hu FB, Willett WC, et al. Alternate healthy eating index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study. BMJ 2015;350:h286.
[27] Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–18.
[28] Henning PC, Margolis LM, McClung JP, Young AJ, Pasiakos SM. High protein diets do not attenuate decrements in testosterone and IGF-I during energy deficit. Metabolism 2014;63: 628–32.
[29] Angeles-Llerenas A, Ortega-Olvera C, Perez-Rodriguez E, Esparza-Cano JP, Lazcano-Ponce E, Romieu I, et al. Moderate physical activity and breast cancer risk: the effect of menopausal status. Cancer Causes Control 2010;21:577–86.
[30] Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, Escudero-De los Rios P, Salmeron-Castro J, Hernandez-Avila M. Reproductive factors of ovarian and endometrial cancer risk in a high fertility population in Mexico. Cancer Res 1999; 59:3658–62.
[31] Mayagoitia S. La edad de la menopausia en México. Rev Endocrinol Nutr 2006;14:4.
[32] Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998.
[33] Hernandez-Avila M, Romieu I, Parra S, Hernandez-Avila J, Madrigal H, Willett W. Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City. Salud Publica Mex 1998;40:133–40.
[34] Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr 1999;69:243–9.
[35] Rodríguez-Ramírez S, M-R V, Jiménez-Aguilar A, Shamah-Levy T. Methodology for the analysis of dietary data from the Mexican National Health and Nutrition Survey 2006. Salud Publica Mex 2006.
[36] Agriculture UDo. A series of systematic reviews on the relationship between dietary patterns and health outcomes. USDA; 2014.
[37] Milan L, aWJ. Application of the parametric bootstrap to models that incorporate a singular value decomposition. Appl Stat 1995;42:19.
[38] Ronco AL, De Stefani E, Boffetta P, Deneo-Pellegrini H, Acosta G, Mendilaharsu M. Food patterns and risk of breast cancer: a factor analysis study in Uruguay. Int J Cancer 2006;119:1672–8.
[39] Hu FB, Rimm EB, Stampfer MJ, Ascherio A, Spiegelman D, Willett WC. Prospective study of major dietary patterns and risk of coronary heart disease in men. Am J Clin Nutr 2000;72:912–21.
[40] SO M. A review on centrifugation in the pharmaceutical industry. Am J Biomed Eng 2015;5:12.
[41] Blair IA. Analysis of estrogens in serum and plasma from postmenopausal women: past present, and future. Steroids 2010;75:297–306.
[42] Janse F, Eijkemans MJ, Goverde AJ, Lentjes EG, Hoek A, Lambalk CB, et al. Assessment of androgen concentration in women: liquid chromatography–tandem mass spectrometry and extraction RIA show comparable results. Eur J Endocrinol 2011;165:925–33.
[43] Montgomery DCPE, Vining GG. Introduction to linear regression analysis. 3rd ed. New York: John Willey & Sons, Inc.; 2001.

[44] Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Lawrence Erlbaum Associates; 1988.
[45] Reznikov A. Hormonal impact on tumor growth and progression. Exp Oncol 2015;37:162–72.
[46] Keene ON. The log transformation is special. Stat Med 1995; 14:811–9.
[47] Feng C, Wang H, Lu N, Chen T, He H, Lu Y, et al. Log-transformation and its implications for data analysis. Shanghai Arch Psychiatry 2014;26:105–9.
[48] Kim CM, Park YG. Interpreting the results of statistical analysis of serum hormone data: comment on the article by Hussain et al. Arthritis Rheumatol 2015;67:315.
[49] Simpson E, RG, Clyne C, Robertson K, O'Donnell L, Jones M, et al. The role of local estrogen biosynthesis in males and females. Trends Endocrinol Metab 2000;11:184–8.
[50] Cóppola F, N J, Aguirre R. Metabolismo de los estrógenos endógenos y cáncer de mama. Rev Med Urug 2004;21:15–22.
[51] Ackerman GE, Smith ME, Mendelson CR, MacDonald PC, Simpson ER. Aromatization of androstenedione by human adipose tissue stromal cells in monolayer culture. J Clin Endocrinol Metab 1981;53:412–7.
[52] Chávez-Villasana AP-GRF, Mendóza-Martínez E, Castañeda-López J, Calvo J, Castro-González I, Sánchez-Castillo C, et al. Los alimentos y sus nutrientes: Tablas de valor Nutritivo de Alimentos. McGrawHill; 2002.
[53] R. V-D. Registra un crecimiento de 1.7% la industria avícola en 2013. Unión Nacional de Avicultores; 2014.
[54] Monografía de Carne de Bovino. Dirección Ejecutiva de Análisis Sectorial, Dirección General Adjunta de Planeación Estratégica y Análisis Sectorial; 2012.
[55] U.S. Departement of Agriculture USDoHaHS. In: USDA U, editor. Dietary guidelines for Americans 2010. 7th ed. U.S. Goverment Printing Office; 2010.
[56] Third report of the National Cholesterol Education Program. Expert panel on detection, evaluation, treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report; 2002. p. C1.
[57] Department of Health and Humans Services USDoA. In: U.S. D.A. HaHS, editor. Dietary guidelines for Americans 2015-2020; 2015. p. 201.
[58] Leffers H, Naesby M, Vendelbo B, Skakkebaek NE, Jorgensen M. Oestrogenic potencies of zeranol, oestradiol, diethylstilboestrol, bisphenol-a and genistein: implications for exposure assessment of potential endocrine disrupters. Hum Reprod 2001;16:1037–45.
[59] Liu S, Lin YC. Transformation of MCF-10A human breast epithelial cells by zeranol and estradiol-17beta. Breast J 2004; 10:514–21.
[60] Mukherjee D, Royce SG, Alexander JA, Buckley B, Isukapalli SS, Bandera EV, et al. Physiologically-based toxicokinetic modeling of zearalenone and its metabolites: application to the Jersey girl study. PLoS One 2014;9:e113632.
[61] Wang H, Camargo Rodriguez O, Memili E. Mycotoxin alpha-zearalenol impairs the quality of preimplantation porcine embryos. J Reprod Dev 2012;58:338–43.
[62] Johnson JH, C.E. The U.S.-EU beef hormone dispute. In: Congress CRf, editor. CRS report for Congress; 2012. p. 1–22.
[63] Andersson AM, Skakkebaek NE. Exposure to exogenous estrogens in food: possible impact on human development and health. Eur J Endocrinol 1999;140:477–85.
[64] Barria RM, Amigo H. Nutrition transition: a review of Latin American profile. Arch Latinoam Nutr 2006;56:3–11.
[65] Moreno-Altamirano L, Silberman M, Hernandez-Montoya D, Capraro S, Soto-Estrada G, Garcia-Garcia JJ, et al. Type 2 diabetes and dietary patterns 1961 to 2009: some social determinants in Mexico. Gac Med Mex 2015;151:354–68.
[66] Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9.
[67] l'agriculture OdNUplae. El estado d ela inseguridad alimentaria en el mundo. Rome, Italia: Organización de las Naciones Unidas para la Alimentacón y Agricultura; 2012.
[68] EN M. American food habits in historical perspective1st ed.; 1995.
[69] Elmadfa I, Meyer AL. Trends in nutrition in Europe. Acta Aliment Hung 2009;38:153–9.
[70] Nettleton JA, Villalpando S, Cassani RS, Elmadfa I. Health significance of fat quality in the diet. Ann Nutr Metab 2013;63: 96–102.
[71] Bennett FC, Ingram DM. Diet and female sex hormone concentrations: an intervention study for the type of fat consumed. Am J Clin Nutr 1990;52:808–12.
[72] Iwasaki M, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, et al. Comparison of postmenopausal endogenous sex hormones among Japanese, Japanese Brazilians, and non-Japanese Brazilians. BMC Med 2011;9:16.
[73] Nagata C, Nagao Y, Shibuya C, Kashiki Y, Shimizu H. Fat intake is associated with serum estrogen and androgen concentrations in postmenopausal Japanese women. J Nutr 2005;135:2862–5.
[74] Newcomb PA, Klein R, Klein BE, Haffner S, Mares-Perlman J, Cruickshanks KJ, et al. Association of dietary and life-style factors with sex hormones in postmenopausal women. Epidemiology 1995;6:318–21.
[75] Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. J Natl Cancer Inst 2007;99:1178–87.
[76] Zeleniuch-Jacquotte A, Shore RE, Koenig KL, Akhmedkhanov A, Afanasyeva Y, Kato I, et al. Postmenopausal levels of oestrogen, androgen, and SHBG and breast cancer: long-term results of a prospective study. Br J Cancer 2004;90:153–9.
[77] Fishman J, Osborne MP, Telang NT. The role of estrogen in mammary carcinogenesis. Ann N Y Acad Sci 1995;768:91–100.
[78] Liehr JG. Genotoxicity of the steroidal oestrogens oestrone and oestradiol: possible mechanism of uterine and mammary cancer development. Hum Reprod Update 2001;7: 273–81.
[79] McTiernan A, Wu L, Chen C, Chlebowski R, Mossavar-Rahmani Y, Modugno F, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity (Silver Spring) 2006;14:1662–77.
[80] Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, et al. Reduced-calorie dietary weight loss, exercise, and sex hormones in postmenopausal women: randomized controlled trial. J Clin Oncol 2012;30: 2314–26.
[81] Fabian CJ, Kimler BF, Donnelly JE, Sullivan DK, Klemp JR, Petroff BK, et al. Favorable modulation of benign breast tissue and serum risk biomarkers is associated with >10% weight loss in postmenopausal women. Breast Cancer Res Treat 2013;142:119–32.
[82] McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004;64:2923–8.
[83] Neilson HK, Conroy SM, Friedenreich CM. The influence of energetic factors on biomarkers of postmenopausal breast cancer risk. Curr Nutr Rep 2014;3:22–34.