Current Women's Health Review, 2024, *20*, e200123212949

RESEARCH ARTICLE

Cosmetics Use and Mammographic Breast Density (MBD) in Iranian Women: A Cross-Sectional Study

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Abstract: ***Background*:** Since breast cancer is increasing worldwide and previous risk factors cannot justify such an increasing trend, investigating new environmental factors is necessary for each population. Mammographic breast density (MBD) is a strong risk factor for breast cancer as well as a biomarker for the effect of chemicals on breast tissue.

***Objective*:** Given limited data about the association between breast density and cosmetic products containing endocrine-disrupting chemicals (EDCs), the purpose of this study was to evaluate the effects of cosmetic products on MBD in Iranian women.

***Methods*:** In this cross-sectional study, women who attended two university hospitals for breast screening mammography and who had been living in the capital city of Iran for the last 3 years or more were recruited. We asked women to fill out a questionnaire containing two parts; the first part was about the women's characteristics and medical history and the second part consisted of cosmetic use. The frequency of cosmetic use was measured using the Likert scale in four scales. One expert radiologist in each center reported the MBD on a four-category scale.

***Results*:** The mean age of 813 participants was 50.16 ± 7.65. Three hundred-seven (37.8%) women had low breast density and 506 (62.2%) had high breast density. Based on our results, heavy use of moisturizers, sunscreen, nail polish, eye products, makeup products, and lipstick was associated with increased breast density. In multivariable analysis after adjusting for menopause, excessive use of nail polish, sunscreen, and moisturizing cream was associated with increased MBD.

***Conclusion*:** Our study shows a probability of an increased MBD with the excessive use of cosmetic products. Since a small increase in the risk of breast cancer may lead to a considerable public health impact, thus further studies are needed to find new prevention strategies.

ARTICLE HISTORY

Received: June 15, 2022
Revised: November 21, 2022
Accepted: December 01, 2022

DOI:
10.2174/1573404819666230120114004

Keywords: Breast, density, cosmetics, endocrine, disrupting chemicals, cross-sectional study, mammography.

1. INTRODUCTION

Breast cancer (BC) is the most common cancer and a leading cause of cancer death in women, which imposes a considerable burden on public health. According to GLOBOCAN 2012 project, the number of new cases in Iran will be nearly 2 times in 2035 compared to 2012 [1]. Since common risk factors cannot explain the increasing trend of BC, researchers focus on investigating new risk factors such as environmental chemicals. Finding new risk factors for BC can provide important clues for preventive strategies.

Several lines of evidence have shown that endocrine-disrupting chemicals (EDCs) with estrogenic properties are potentially linked to an increased rate of breast cancer [2]. These estrogen mimic are known as xenoestrogens, which comprise a variety of chemicals such as phthalates, parabens, phenols, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), and bisphenol A (BPA) [2]. Other chemicals called Metalloestrogens (such as aluminum, lead, cadmium, mercury, chromium) are a class of inorganic xenoestrogens with the capability of binding to cellular estrogen receptors and mimicking actions of physiological estrogens [3]. Breast tissue is indirectly exposed to these compounds *via* different routes such as food, water, and air; then, due to their lipophilic properties, they can accumulate in breast fat [4]. However, these xenoestrogens are

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1875-6581/24 $65.00+.00

also found in many products, including cosmetics; therefore, a more direct breast tissue exposure can occur through the application of cosmetics, and continued use may increase the absorption of EDCs and heavy metals through dermal absorption or swallowing [5].

Breast cancer occurs in young Iranian women and the age of diagnosis is about one decade earlier than in western countries [6]. On the other hand, the use of cosmetic products is increasing in Iran [7] and Iran is the third biggest consumer in Middle East countries [8]. In a recent study of female students, about 70% of them started using cosmetic products before 20 years of age, and 50% of the participants were using cosmetic products on a daily basis [9]. Several studies have been performed to evaluate the level of exogenous compounds in cosmetic products such as lipstick, eye shadow, eye pencil, and hair dyes in Iran [8-11]. These lines of evidence support the high level of some chemicals in cosmetics, especially in some of the brands, and confirm that high and continuous use of these cosmetics can increase the absorption of the substances and consequently increase their harmful effects. Therefore, it is hypothesized that perhaps one of the reasons for the increasing incidence of breast cancer is the excessive use of cosmetic products. According to the National Cancer Institute (NCI), given the widespread use of cosmetic products, even a small increase in risk may lead to a considerable public health impact [12] and thus may necessitate new strategies for the prevention of breast cancer.

A variety of studies show that cosmetics comprising EDCs can cause hormone-related complications such as breast cancer [13-21]. However, numerous controversies surround increased breast cancer risk and cosmetic products. These findings raise an important question regarding the potential impacts of EDCs on breast tissue.

Mammographic breast density (MBD) is one of the strongest risk factors of breast cancer and could be used as a marker for the effects of various exposures on breast tissue [22]. Limited studies evaluate the effect of environmental chemicals and breast density [23-25]. Two of these studies focused on chemical exposure during adolescence when the breast tissue has great susceptibility to carcinogens [24, 25].

Based on the food and drug administration (FDA) report, the available data about the association of cosmetics and cancer have significant bias and lack supporting information such as demographic data, medical history, and other influential variables [26]. Therefore, any conclusion regarding the impact of cosmetics on cancer, specifically breast cancer that is affected by many reproductive and other factors needs broader studies and more complete reporting, and multifaceted researches. For the evaluation of the effects of cosmetics on breast cancer, long-term cohort studies with accurate recording of cosmetics and their brands are needed. Since the design and implementation of a cohort study are costly and time-consuming and are not feasible in all countries due to insufficient resources, it seems that the study of possible intermediate mechanisms of the effect of cosmetics on breast tissue is more effective than the long-term follow-up of women until breast cancer occurs.

Given prior literature supporting an association between EDC exposure and breast cancer risk and limited data about the association between breast density and EDC, in this study, we aim to find any relation between cosmetic products and breast density in Iranian women.

2. MATERIALS AND METHODS

2.1. Study Design and Populations

This cross-sectional study was approved by the Institutional Research Board (No. 47974) and Ethics committee (IR.TUMS.IKHC.REC.1399.132) of Tehran University of Medical Sciences. This study was conducted according to the principles of the Declaration of Helsinki for medical research involving human subjects. All participants signed informed consent before filling out the questionnaire. Participants of this study include women who attended Imam Khomeini Hospital and Arash Women's Hospital of Tehran University of Medical Sciences for breast screening mammography from February 2020 to August 2021. In order to eliminate the possible effect of environmental risk factors, the criteria for inclusion consisted of women who had been living in Tehran, the capital city of Iran, for the recent last 3 years or more. All participants had the capability of writing and reading. We asked women to fill a questionnaire containing demographic characteristics, reproductive history, family history of breast and ovarian cancer, smoking status, height, and weight. Furthermore, we asked about cosmetic use such as hair dye and oxidant, moisturizers, body lotions, sunscreen cream, nail polish, underarm deodorant/ antiperspirant, and make-up products (cream powder), eye products (eye pencils, eye shadow, and mascara), and lipstick. The frequency of cosmetic use was measured using the Likert scale in four scales (Always, often, sometimes, and never). For hair dye and other products four scale categories were defined as always (more than 1 time in a month), often (5-12 times per year), sometimes (1-4 times per year), and never. The Likert scale for other cosmetic products was categorized as always (every day), often (2-3 times per week), sometimes (irregular use), and never use.

In order to evaluate the agreement between the radiologists' reports, the third independent radiologist was rated the mammographic breast density of the same cases. Breast density was reported according to the American College of Radiology (ACR) breast imaging-reporting and data system (BI-RADS) four-category density scale (1 = almost entirely fatty, 2 = scattered fibroglandular densities, 3 = heterogeneously dense, and 4 = extremely dense (27). Mammographic density was finally classified into two categories, low density (1 and 2) and high density (3 and 4).

For sample size calculation, since the results of studies about an association between MBD and cosmetics have inconsistent results, we estimated that 30% of women with low breast density would be cosmetic users and with an assumed odds ratio (OR) equal to 1.5, about 850 samples would be required to find any possible association between cosmetics and MBD with a power of 80 and α =0.05 by using the Epi Info website (www.cdc.gov/epiinfo).

2.2. Statistical Analysis

Data are presented in mean and standard deviation for continuous variables and number and percentage in categor-

ical variables. Cohen's kappa (κ) was run to determine if there was an agreement between two radiologists on breast density in the reports of the same case. Odds ratios (ORs) and 95% confidence interval (CI) were estimated by logistic regression analysis to estimate the associations between breast density and cosmetic products. In a multivariable model, we used a backward selection process, whereby potential confounders were selected a priori and omitted based on the *P*-value (less than 0.10). MBD (high density and low density) was considered as a dependent variable and adjusting for other effective variables such as age, body mass index (BMI), parity, smoking, history of oral contraceptive (OCP) use, and menopausal status was performed. These variables were entered into the models based on a previous and current association of these variables with breast density. Finally, from the sum of the numbers 1 to 4 (never to always) assigned to the use of each cosmetic according to the Likert scale of each person, a variable called the overall use of cosmetics was created. Since we had eight categories of cosmetics, the sum score range was from 8 to 32. Then sum numbers were categorized considering quartiles into less than 25 percentile, Interquartile range (25-75 percentile), and more than 75 percentile. At last, overall cosmetic use was entered into the model to find an association with breast density. A *P*-value less than 0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS 26 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp).

3. RESULTS

After the exclusion of the incomplete questionnaires (n = 35), the final analysis was performed on 813 women who completed all steps and questionnaires. The mean age of participants was 50.16 ± 7.65 (range: 32-80). Table **1** shows the characteristics of the total population. About half of the women were premenopausal (50.1%) and half were postmenopausal (49.9%). Three hundred-seven (37.8%) women had low breast density and 506 (62.2%) had high breast density. There was almost perfect agreement between the radiologists' report, κ = 0.98 (95% CI: 0.97-0.99; *P* <0.001). Table **2** presents a comparison of variables in low and high breast density groups. The association between breast density and cosmetic products is presented in Table **3**. Based on this table data, in the univariate analysis, heavy users of moisturizers, sunscreen, nail polish, eye products, makeup products, and lipstick have an increased breast

Table 1. Total characteristics of study population (n = 813).

Variables	-
Age (yrs)	50.16 ± 7.65
BMI (Kg/m^2)	28.16 ± 4.81
Parity (n)	2.19 ± 1.47
Age of menarche (yrs)	13.56 ± 1.52
History of OCP use	306 (37.6%)
Menopause	
Post-menopause	406 (49.9%)
Pre-menopause	407 (50.1%)
History of HRT	30 (3.7%)
History of BC and OC in relatives	
Yes	245 (30.1%)
No	555 (68.3%)
Missed data	13 (1.6%)
History of breast disease	
No	629 (77.4%)
Breast Cancer	88 (10.8%)
Benign Breast Disease	96 (11.8%)
Breast Composition	
1	107 (13.2%)
2	200 (24.6%)
3	465 (57.2%)
4	41 (5%)

Abbreviations: BMI= Body Mass Index; OCP=Oral Contraceptive Pills; HRT= Hormone Replacement Therapy; BC= Breast Cancer; OC=Ovarian Cancer.

Table 2. Comparison of variables in low and high breast density.

Variables	Low Density (n = 307)	High Density (n = 506)	*P*-value
Age (yrs)	53.29 ± 8.33	48.27 ± 6.51	<0.001
BMI (kg/m^2)	29.83 ± 5.29	27.15 ± 4.19	<0.001
Parity (n)	2.58 ± 1.59	1.96 ± 1.33	<0.001
Breastfeeding (m)	35.11 ± 32.25	32.65 ± 29.19	0.26
Age of menarche (yrs)	13.60 ± 1.58	13.53 ± 1.48	0.56
Menopause			
Yes	212 (69.1)	194 (38.3)	<0.001
No	95 (30.9)	312 (61.7)	
Smoking			
Yes	40 (13)	37 (7.3)	0.007
No	267 (87)	469 (92.7)	
History of OCP use			
Yes	143 (46.6)	163 (32.2)	<0.001
No	164 (53.4)	343 (67.8)	
BCOC in relatives			
Yes	100 (32.6)	145 (28.7)	0.49
No	202 (65.8)	353 (69.8)	
Missing data	5 (1.6)	8 (1.6)	

Table 3. Comparison of cosmetic use in low and high mammographic breast density.

Cosmetic Products	Category	Low Density (n = 307)	High Density (n = 506)	*P*-value
*Hair products	Never	21 (6.8)	26 (5.1)	0.03
	Sometimes	168 (54.7)	272 (53.8)	
	Often	81 (26.4)	171 (33.8)	
	Always	37 (12.1)	37 (7.3)	
Moisturizers	Never	55 (17.9)	72 (14.2)	0.002
	Sometimes	111 (36.2)	133 (26.3)	
	Often	44 (14.3)	83 (16.4)	
	Always	97 (31.6)	218 (43.1)	
Sunscreen	Never	110 (35.8)	144 (28.5)	0.01
	Sometimes	107 (34.9)	158 (31.2)	
	Often	15 (4.9)	27 (5.3)	
	Always	75 (24.4)	177 (35)	
Nail polish	Never	217 (70.7)	326 (64.4)	0.03
	Sometimes	71 (23.1)	120 (23.7)	
	Often	9 (2.9)	17 (3.4)	
	Always	10 (3.3)	43 (8.5)	

(Table 3) Contd….

Cosmetic Products	Category	Low Density (n= 307)	High Density (n= 506)	*P*-value
Eye products	Never	145 (47.2)	192 (37.9)	0.02
	Sometimes	111 (36.2)	188 (37.2)	
	Often	14 (4.6)	34 (6.7)	
	Always	37 (12.1)	92 (18.2)	
Makeup products	Never	164 (53.4)	227 (44.9)	0.04
	Sometimes	102 (33.2)	186 (36.8)	
	Often	18 (5.9)	29 (5.7)	
	Always	23 (7.5)	64 (12.6)	
Underarm Deodorant /Antiperspirant	Never	163 (53.1)	254 (50.2)	0.19
	Sometimes	63 (20.5)	107 (21.1)	
	Often	24 (7.8)	26 (5.1)	
	Always	57 (18.6)	119 (23.5)	
Lipstick	Never	97 (31.6)	139 (27.5)	0.13
	Sometimes	132 (43)	200 (39.5)	
	Often	25 (8.1)	48 (9.5)	
	Always	53 (17.3)	119 (23.5)	

Note: *Hair dye and other products were defined as always (more than 1 time in a month), often (5-12 times per year), sometimes (1-4 times per year), and never. ** Other cosmetic products was categorized as always (every day), often (2-3 times per week), sometimes (irregular use), and never use.

density; the odds ratio shows that increasing cosmetics use is associated with a rising trend in breast density. In multivariable analysis after adjusting for menopause, excessive use of nail polish (OR = 2.16, 95% CI: 1.03-4.49) and sunscreen (OR = 1.52, 95% CI: 1.04-2.23) were associated with increased MBD. However, after adjusting for age, BMI, parity, OCP usage, history of smoking, and menopause (Table **4**), these effects disappeared. Only in underarm products, a reverse association was shown in women who often use underarm products compared with those who never use them (OR = 0.41, 95% CI: 0.21-0.78, *p*-value=0.007). Univariate analysis in three categories of the sum of the cosmetic use manifested a positive association with high breast density in the interquartile range (OR = 1.49, 95% CI: 1.05-2.10) and higher than 75 percentile (OR = 2.11, 95% CI: 1.36-3.25) categories in compared with the reference group (less than 25 percentile). However, these associations were not statistically significant after the confounding variables adjustment (Table **4**).

4. DISCUSSION

This study was performed to find a possible association between cosmetic products usage and breast density as an important biomarker for the effects of various exposures on breast tissue. Our result shows that excessive sunscreen cream, moisturizers, lipstick, make-up products, nail polish, and eye products are associated with higher breast density compared to never usage. However, after adjusting for the variables affecting the density (age, BMI, parity, OCP usage, smoking, and menopause), no clear statistical relationship was observed between breast density and cosmetic product use. The following sections discuss the impacts of the cosmetic product individually on the breast.

4.1. Hair Dye and Other Related Products

A review study about the use of hair dye and its implications for human health represented that hair dye and its ingredients have moderate to low acute toxicity and some hair dye components are reported to be carcinogenic in animals [27, 28]. A recent meta-analysis in 2018 also indicated that hair dye users have an 18.8% increased risk of future development of breast cancer [14]. Our study didn't find any association between the use of hair dye or related products such as oxidants, straightener or perm and breast density, neither in univariate nor in multivariable analysis.

A large retrospective population-based case-control study in Finland showed that the odds of breast cancer increased 23% among women who used hair dye compared to those who did not [21]. Llanos *et al.* studied in white and African American US women reported a higher risk of breast cancer in African American women who used dark hair dye (OR = 1.51, 95% CI: 1.20-1.90) and in white women with dual-use of relaxer and hair dyes (OR = 2.40, 95% CI: 1.35-4.27) [16].

Two studies in Iran that evaluated the effect of hair dye usage and breast cancer had equivocal results [18, 29]. A case-control study showed that hair coloring on a regular basis was significantly associated with the risk of breast cancer (OR= 1.93, 95% CI: 1.41-2.62, *P*=0.001) [18]. However, another study by Dehghan *et al.* didn't confirm any relation between cosmetic usages such as hair dye and breast cancer [29]. It seems that the type of hair dye also may affect the results; but this has not been addressed in any of the studies. Khalili *et al.* measured the concentration of 10 heavy metals in different hair dyes in our market. They reported that among the investigated hair dyes, the ones made in Iran and the dark brown color had the higher level of risk [11].

Table 4. Association between cosmetic products and breast mammographic density in univariate and multivariable models.

-	-	*Model 1		**Model 2		***Model 3	
Cosmetics	**Category**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
****Hair products	Never	Ref		Ref		Ref	
	Sometimes	1.31 (0.71-2.40)	0.39	1.20 (0.64-2.27)	0.58	0.83 (0.40-1.73)	0.62
	Often	1.71 (0.91-3.21)	0.10	1.62 (0.84-3.15)	0.15	1.14 (0.53-2.44)	0.74
	Always	0.81 (0.39-1.68)	0.57	0.71 (0.33-1.54)	0.39	0.45 (0.19-1.08)	0.08
Moisturizers	Never	Ref		Ref		Ref	
	Sometimes	0.92 (0.59-1.41)	0.69	0.80 (0.51-1.26)	0.34	0.66 (0.40-1.08)	0.10
	Often	1.44 (0.87-2.39)	0.16	1.21 (0.71-2.06)	0.48	0.84 (0.47-1.49)	0.55
	Always	1.72 (1.12-2.63)	0.01	1.46 (0.94-2.28)	0.09	1.03 (0.63-1.68)	0.91
Sunscreen	Never	Ref		Ref		Ref	
	Sometimes	1.13 (0.80-1.60)	0.50	1 (0.69-1.44)	0.99	0.84 (0.56-1.25)	0.39
	Often	1.38 (0.70-2.71)	0.36	1.35 (0.66-2.73)	0.41	0.86 (0.40-1.86)	0.71
	Always	1.80 (1.25-2.60)	0.002	1.52 (1.04-2.23)	0.03	1.09 (0.72-1.65)	0.69
Nail polish	Never	Ref		Ref		Ref	
	Sometimes	1.13 (0.80-1.58)	0.50	0.96 (0.67-1.38)	0.84	0.74 (0.50-1.09)	0.13
	Often	1.26 (0.55-2.87)	0.59	0.92 (0.39-2.19)	0.85	0.77 (0.31-1.90)	0.57
	Always	2.86 (1.41-5.82)	0.004	2.16 (1.03-4.49)	0.04	1.83 (0.84-4)	0.13
Eye products	Never	Ref		Ref		Ref	
	Sometimes	1.28 (0.93-1.76)	0.13	1.02 (0.73-1.43)	0.90	0.77 (0.53-1.12)	0.17
	Often	1.83 (0.95-3.54)	0.07	1.50 (0.76-2.99)	0.24	1.20 (0.58-2.51)	0.62
	Always	1.88 (1.21-2.91)	0.005	1.30 (0.82-2.06)	0.27	0.95 (0.57-1.57)	0.83
Makeup products	Never	Ref		Ref		Ref	
	Sometimes	1.32 (0.96-1.80)	0.09	1.13 (0.81-1.57)	0.47	0.94 (0.66-1.34)	0.73
	Often	1.16 (0.63-2.17)	0.63	0.90 (0.47-1.73)	0.75	0.86 (0.43-1.73)	0.67
	Always	2.01 (1.20-3.37)	0.008	1.50 (0.87-2.57)	0.14	1.20 (0.67-2.15)	0.53
Overall cosmetic use	<25 percentile	Ref		Ref		Ref	
	IQR	1.49 (1.05-2.10)	0.024	1.15 (0.80-1.65)	0.46	0.85 (0.56-1.27)	0.42
	>75 percentile	2.11 (1.36- 3.25)	0.001	1.44 (0.91-2.28)	0.12	0.95 (0.57-1.57)	0.84

Note: *Univariate analysis. ** Multivariable models adjusted for menopause. ***Multivariable models adjusted for age, BMI, parity, menopause, smoking, and history of OCP use. ****Hair products including hair dye, oxidant, chemicals to curl or straighten hair, and miscellaneous. OR= Odds Ratio, CI= Confidence Interval.

A recent study in 2020 by Eberle *et al.* represented that black women who used permanent dye were at a 45% increased risk of breast cancer [15]. Two concerns mentioned by the researchers were that they believed the harmful effect of cosmetic products was related to early use in adolescence and to the frequency of use. Therefore White *et al.* evaluated the risk of breast cancer during premenopausal and postmenopausal periods in women who used hair dye, straighteners/relaxers, and perms at ages 10-13 years in the Sister Study [19]. They found that frequent use of straighteners and perms was associated with a higher risk of premenopausal breast cancer in those participants [19].

Although most of the studies suggested a higher risk of breast cancer in hair dye users; further studies are needed to clarify potential mechanisms considering the type and brand of hair dye and other related products. Since the diversity of hair dye and related products is very high in our market, it was not possible to gather accurate information about these cosmetic products in this study. It seems that the increased risk of breast cancer in hair product users is not through the mechanism of effect on breast density.

4.2. Underarm Products

There are limited studies evaluating the possible relation between underarm cosmetic product use and the risk of breast cancer [30-34]. The present study results didn't show a significant association between underarm product use and breast density. Only in the multivariate model, a reverse association was found in women who often use underarm products compared with those who never used them (OR = 0.39, 95% CI: 0.20-0.75, *P* =0.005). The aluminum salts are the active ingredients of the underarm products and these

ingredients act as metalloestrogens that have the ability to interfere with estrogens. Therefore, they may be associated with an increased risk of breast cancer.

Darbre *et al.* discussed the role of underarm products and the risk of breast cancer. They mentioned since the prevalence of breast cancer in the upper out quadrant is higher than in the other area and the parallel increasing the use of cosmetics in the underarm area was seen, that possibly is a risk factor of breast cancer [35].

On the other hand, the existing limited evidence showed no association between the use of antiperspirants or deodorants and the risk of breast cancer [31, 32]. A systematic review in 2016 [33] evaluated the results of two previous studies; one of which reported an inverse association [31], and the other a small increase in risk of breast cancer development [32] in association with deodorant use. In a pooled analysis, they reported no relation between underarm cosmetic products and breast cancer. However, in none of these studies did they adjust important variables such as age, BMI, and reproductive factors such as menopausal status. In addition, they considered underarm products used as users and non-users, and the level of usage was not considered. One study in 2003 reported that frequency and earlier onset of antiperspirant/deodorant usage with underarm shaving were associated with an earlier age of breast cancer diagnosis [34]. This study suggested the dose-response relation of exogenous compounds at a young age which was consistent with the pattern of breast development [4].

A published hospital-based case-control study by Linhart and colleagues in 2017 reported that the risk of breast cancer increased by an odds ratio of 3.88 (95% CI: 1.03-14.66) in women who self-reported the use of underarm products from before the age of 30 for several times daily [17]. They hypothesized that the association was due to the aluminum-based compounds in underarm cosmetic products.

Since in some of the studies comparison was performed between users and non-users cosmetic products; in the present study, we also evaluated breast density in underarm products users and non-users. Analysis between users and non-users didn't reveal any differences in breast density between the two groups (data not shown in the Tables).

4.3. Moisturizers

In a cancer-related report attributed to cosmetic products by the Center for Food Safety and Applied Nutrition's Adverse Event Reporting System (CAERS) of the FDA, 5% of breast cancers were attributed to topical moisturizers [26]. These products consisted of parabens and phthalate, which are EDCs. One study showed that paraben alone or in combination is present in human breast tissue with sufficient concentration to stimulate the proliferation of MCF-7 cells *in vitro* [36]. The result of an age-matched case-control study in Mexican women reported a urinary phthalate compound that was associated with breast cancer risk [37]. Another study showed that urinary paraben compounds were associated with an increased risk of breast cancer [38].

Two studies that evaluated the association between skincare products and breast cancer risk had contradictory results [20, 39]. Taylor *et al*. study concluded that the association between skin products and breast cancer was stronger in postmenopausal women than premenopausal [20]. However, based on the results of the other study, heavy use of skin products up to three times per day during midlife did not increase the risk of breast cancer [39]. Both studies considered the menopausal status of participants.

For the first study in Iran, measurement of urinary paraben compounds in adolescents showed although the estimated daily intake of the parabens was lower than the Acceptable Daily Intake, it was higher than those reported in other countries and this result confirms the widespread exposure of Iranian adolescents to the paraben compounds [40].

4.4. Sunscreen

To our knowledge, there is no research about the possible effect of sunscreen creams use and breast density or breast cancer. Sunscreen creams contain oxybenzone that belongs to aromatic ketones known as benzophenones; its systematic absorption and endocrine-disrupting properties have raised major concerns [41]. Based on a review study, different *in vitro* studies reported increased estrogenic activity of oxybenzone metabolites in breast cancer cells [41]. Considering our result, it seems that daily usage of sunscreen creams is related to higher breast density. However, this relationship was not statistically significant in multivariate analysis. Since sunscreens protect against the known carcinogenic effects of UV radiation, a possible effect of sunscreens on breast tissue and breast cancer should be carefully stated.

4.5. Other Cosmetic Products

All the above-mentioned cosmetics are applied on the skin, which can prevent the entry of many chemicals as a barrier. However, cosmetics used in some areas, such as lips and eyes can cause high exposure. Ghaderpoor and colleagues selected 11 studies that had measured the heavy metals in products including lipstick, eye shadow, eye pencil, powder, and cream in Iran [10]. Based on their results, eye pencil has the highest concentration of heavy metals, and cream contains a high amount of lead (Pb). Therefore, these cosmetics products may increase the risk of breast cancer. Our results show the daily use of makeup creams and eye products is associated with a high density of breast tissue before adjustment of confounding variables.

Finally, our results represented that the heavy use of cosmetic products was accompanied by a higher breast density as a marker of breast cancer. However, after adjustment of effective variables, no statistically significant associations were found.

Based on our knowledge three studies evaluated the effect of EDCs on breast density [23-25]. Sprague *et al.* showed that postmenopausal women with a high serum level of BPA and phthalate had elevated MBD [23]. Another study suggested that the developing breast tissue is susceptible to EDCs during childhood and adolescence [25]. Only one study by McDonald and colleagues evaluated the effect of cosmetics on breast density, and their results are consistent with ours; suggesting that exposure to EDCs through hair products in early life may affect breast cancer risk through a mechanism distinct from breast density [24].

This study has some advantages. First, this is the first study that evaluated the effects of various cosmetic products on MBD by considering the main confounding factors. Second, for the first time, habitual use of cosmetics in recent years has been evaluated on MBD; this is important because the half-life of some chemicals is very short and usage habits may represent the current and long-term use of cosmetics. Although the habit of using cosmetics and fashion trends may change over a period of time.

This study had some limitations. Women use a variety of cosmetic products and the content of chemical substances in cosmetics is not well defined. The important point is that in order to carefully examine the effects of these cosmetics, the brand and type of cosmetics should be considered. The best way to assess the effects of these contaminants is by measuring contaminant levels in the blood and specifically in breast adipose tissue. However, the latter is not acceptable and feasible as it requires an invasive procedure. Therefore, the above-mentioned issues make conducting such studies difficult.

It is important to note that most of the sampling in this study coincided with the worldwide onset of the COVID-19 pandemic and contrary to our expectation, sample collection was very time-consuming; so we performed the final analysis with 813 samples. Since, in the COVID-19 pandemic period women with higher risk or lower economic status have been likely screened in public hospitals, the generalizability of the study is questionable.

CONCLUSION

In conclusion, our study shows a probability of an increased MBD with the excessive use of cosmetic products; however, this effect disappeared when confounding variables were considered in further analysis. Given the widespread use of cosmetic products and the increasing worldwide risk of breast cancer, further studies are needed to find the accurate association and risk among various products. These kinds of studies may provide important insights into behavioral patterns and growing perceptions about cosmetic product risk and breast cancer prevention.

LIST OF ABBREVIATIONS

ACR	=	American Collage of Radiology
BC	=	Breast Cancer
BI-RADS	=	Breast Imaging-Reporting And Data System
BMI	=	Body Mass Index
BPA	=	Bisphenol A
CI	=	Confidence Interval
EDCs	=	Endocrine-Disrupting Chemicals
FDA	=	Food and Drug Administration
MBD	=	Mammographic Breast Density
NCI	=	National Cancer Institute
OCP	=	Oral Contraceptive
OR	=	Odds Ratio
PBDEs	=	Polybrominated Diphenyl Ethers
PCBs	=	Polychlorinated Biphenyls

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This cross-sectional study was approved by the Institutional Research Board (No. 47974) and Ethics committee (IR.TUMS.IKHC.REC.1399.132) of Tehran University of Medical Sciences.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All participants signed informed consent before filling out the questionnaire.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors would like to thank Zohre Samadi, Mina Mahmoodi, and Afsaneh Teimoori for their assistance in collecting women samples, which made this project possible.

REFERENCES

[1] Valipour, A.A.; Mohammadian, M.; Ghafari, M.; Mohammadian-Hafshejani, A. Predict the future incidence and mortality of breast cancer in Iran from 2012-2035. *Iran. J. Public Health,* **2017**, *46*(4), 579-580.
PMID: 28540280

[2] Wan, M.L.Y.; Co, V.A.; El-Nezami, H. Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. *Crit. Rev. Food Sci. Nutr.,* **2021**, *62*(24), 6549-6576.
PMID: 33819127

[3] Darbre, P.D. Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. *J. Appl. Toxicol.,* **2006**, *26*(3), 191-197.
http://dx.doi.org/10.1002/jat.1135 PMID: 16489580

[4] Darbre, P.D. Environmental oestrogens, cosmetics and breast cancer. *Best Pract. Res. Clin. Endocrinol. Metab.,* **2006**, *20*(1), 121-143.
http://dx.doi.org/10.1016/j.beem.2005.09.007 PMID: 16522524

[5] Konduracka, E.; Krzemieniecki, K.; Gajos, G. Relationship between everyday use cosmetics and female breast cancer. *Polish Arch. Inter. Med.,* **2014**, *124*(5), 264-269.

http://dx.doi.org/10.20452/pamw.2257 PMID: 24694726

[6] Mousavi, S.M.; Montazeri, A.; Mohagheghi, M.A.; Jarrahi, A.M.; Harirchi, I.; Najafi, M.; Ebrahimi, M. Breast cancer in Iran: an epidemiological review. *Breast J.,* **2007**, *13*(4), 383-391. http://dx.doi.org/10.1111/j.1524-4741.2007.00446.x PMID: 17593043

[7] Hosseini, S.N.; Mari, A.; Jouybari, T.A.; Salehi, I.; Vahidinia, A.A.; Emdadi, S. Cosmetic products use intention among iranian female college students. *Int. Sci. Index.,* **2014**, *7*, 669-672.

[8] Nourmoradi, H.; Foroghi, M.; Farhadkhani, M.; Vahid Dastjerdi, M. Assessment of lead and cadmium levels in frequently used cosmetic products in Iran. *J. Environ. Public Health,* **2013**, *2013*, 1-5. http://dx.doi.org/10.1155/2013/962727 PMID: 24174937

[9] Parizi, M.G.; Sedaghat, Z.; Mazloomi, M.; Fararouei, M. Serum level of lead and cadmium is linked to facial cosmetics use among Iranian young women. *Environ. Sci. Pollut. Res. Int.,* **2021**, *28*(11), 13913-13918. http://dx.doi.org/10.1007/s11356-020-11618-x PMID: 33201504

[10] Ghaderpoori, M.; Kamarehie, B.; Jafari, A.; Alinejad, A.A.; Hashempour, Y.; Saghi, M.H.; Yousefi, M.; Oliveri Conti, G.; Mohammadi, A.A.; Ghaderpoury, A.; Ferrante, M.; Mohammadi, A.A.; Ghaderpoury, A.; Ferrante, M. Health risk assessment of heavy metals in cosmetic products sold in Iran: the Monte Carlo simulation. *Environ. Sci. Pollut. Res. Int.,* **2020**, *27*(7), 7588-7595. http://dx.doi.org/10.1007/s11356-019-07423-w PMID: 31885066

[11] Khalili, F.; Mahvi, A.H.; Nasseri, S.; Yunesian, M.; Yaseri, M.; Djahed, B. Health risk assessment of dermal exposure to heavy metals content of chemical hair dyes. *Iran. J. Public Health,* **2019**, *48*(5), 902-911. http://dx.doi.org/10.18502/ijph.v48i5.1807 PMID: 31523647

[12] Fillon, M. Examining the link between hair chemicals and cancer. *J. Natl. Cancer Inst.,* **2017**, *109*(9), 2-5. http://dx.doi.org/10.1093/jnci/djx202 PMID: 28954289

[13] Gore, A.C.; Cohn, B. Endocrine-disrupting chemicals in cosmetics. *JAMA Dermatol.,* **2020**, *156*(5), 603-604. http://dx.doi.org/10.1001/jamadermatol.2020.0301 PMID: 32186657

[14] Gera, R.; Mokbel, R.; Igor, I.; Mokbel, K. Does the use of hair dyes increase the risk of developing breast cancer? A meta-analysis and review of the literature. *Anticancer Res.,* **2018**, *38*(2), 707-716. PMID: 29374694

[15] Eberle, C.E.; Sandler, D.P.; Taylor, K.W.; White, A.J. Hair dye and chemical straightener use and breast cancer risk in a large US population of black and white women. *Int. J. Cancer,* **2020**, *147*(2), 383-391. http://dx.doi.org/10.1002/ijc.32738 PMID: 31797377

[16] Llanos, A.A.M.; Rabkin, A.; Bandera, E.V.; Zirpoli, G.; Gonzalez, B.D.; Xing, C.Y.; Qin, B.; Lin, Y.; Hong, C.C.; Demissie, K.; Ambrosone, C.B. Hair product use and breast cancer risk among African American and White women. *Carcinogenesis,* **2017**, *38*(9), 883-892. http://dx.doi.org/10.1093/carcin/bgx060 PMID: 28605409

[17] Linhart, C.; Talasz, H.; Morandi, E.M.; Exley, C.; Lindner, H.H.; Taucher, S.; Egle, D.; Hubalek, M.; Concin, N.; Ulmer, H. Use of underarm cosmetic products in relation to risk of breast cancer: a case-control study. *EBioMedicine,* **2017**, *21*, 79-85. http://dx.doi.org/10.1016/j.ebiom.2017.06.005 PMID: 28629908

[18] Dianatinasab, M.; Fararouei, M.; Mohammadianpanah, M.; Zarebandamiri, M.; Rezaianzadeh, A. Hair coloring, stress, and smoking increase the risk of breast cancer: a case-control study. *Clin. Breast Cancer,* **2017**, *17*(8), 650-659. http://dx.doi.org/10.1016/j.clbc.2017.04.012 PMID: 28549689

[19] White, A.J.; Gregoire, A.M.; Taylor, K.W.; Eberle, C.; Gaston, S.; O'Brien, K.M.; Jackson, C.L.; Sandler, D.P. Adolescent use of hair dyes, straighteners and perms in relation to breast cancer risk. *Int. J. Cancer,* **2021**, *148*(9), 2255-2263. http://dx.doi.org/10.1002/ijc.33413 PMID: 33252833

[20] Taylor, K.W.; Troester, M.A.; Herring, A.H.; Engel, L.S.; Nichols, H.B.; Sandler, D.P.; Baird, D.D. Associations between personal care product use patterns and breast Cancer risk among white and black women in the sister study. *Environ. Health Perspect.,* **2018**, *126*(2), 027011. http://dx.doi.org/10.1289/EHP1480 PMID: 29467107

[21] Heikkinen, S.; Pitkäniemi, J.; Sarkeala, T.; Malila, N.; Koskenvuo, M. Does hair dye use increase the risk of breast cancer? A population-based case-control study of Finnish women. *PLoS One,* **2015**, *10*(8), e0135190. http://dx.doi.org/10.1371/journal.pone.0135190 PMID: 26263013

[22] Boyd, N.F.; Martin, L.J.; Bronskill, M.; Yaffe, M.J.; Duric, N.; Minkin, S. Breast tissue composition and susceptibility to breast cancer. *J. Natl. Cancer Inst.,* **2010**, *102*(16), 1224-1237. http://dx.doi.org/10.1093/jnci/djq239 PMID: 20616353

[23] Sprague, B.L.; Trentham-Dietz, A.; Hedman, C.J.; Wang, J.; Hemming, J.D.C.; Hampton, J.M.; Buist, D.S.M.; Aiello Bowles, E.J.; Sisney, G.S.; Burnside, E.S. Circulating serum xenoestrogens and mammographic breast density. *Breast Cancer Res.,* **2013**, *15*(3), R45. http://dx.doi.org/10.1186/bcr3432 PMID: 23710608

[24] McDonald, J.A.; Tehranifar, P.; Flom, J.D.; Terry, M.B.; James-Todd, T. Hair product use, age at menarche and mammographic breast density in multiethnic urban women. *Environ. Health,* **2018**, *17*(1), 1-8. http://dx.doi.org/10.1186/s12940-017-0345-y PMID: 29301538

[25] Binder, A.M.; Corvalan, C.; Pereira, A.; Calafat, A.M.; Ye, X.; Shepherd, J.; Michels, K.B. Prepubertal and pubertal endocrine-disrupting chemical exposure and breast density among Chilean adolescents. *Cancer Epidemiol. Biomarkers Prev.,* **2018**, *27*(12), 1491-1499. http://dx.doi.org/10.1158/1055-9965.EPI-17-0813 PMID: 30158279

[26] Jacob, S.L.; Cornell, E.; Kwa, M.; Funk, W.E.; Xu, S. Cosmetics and cancer: Adverse event reports submitted to the Food and Drug Administration. *JNCI Cancer Spectr.,* **2018**, *2*(2), pky012. http://dx.doi.org/10.1093/jncics/pky012 PMID: 31360845

[27] Sickles, E.; d'Orsi, C.; Bassett, L.; Appleton, C.; Berg, W.; Burnside, E. ACR BI-RADS Mammography. In: *ACR BI-RADS Atlas, Breast Imaging Reporting and Data System, 5th Edition, American College of Radiology*, Reston, VA, pp. 134-136.

[28] Kim, K.H.; Kabir, E.; Jahan, S.A. The use of personal hair dye and its implications for human health. *Environ. Int.,* **2016**, *89-90*, 222-227. http://dx.doi.org/10.1016/j.envint.2016.01.018 PMID: 26895479

[29] Dehghan, M.; Baniasadi, H.; Moghadam, R.F.; Salehi, M. Cosmetic products don't increase the risk of breast cancer: A retrospective case-control study in Southern Iran. World. J. Cancer. *Res. WCRJ.,* **2020**, *7*, e1572.

[30] Darbre, P.D. Underarm cosmetics and breast cancer. *J. Appl. Toxicol.,* **2003**, *23*(2), 89-95. http://dx.doi.org/10.1002/jat.899 PMID: 12666152

[31] Fakri, S.; Al-Azzawi, A.; Al-Tawil, N. Antiperspirant use as a risk factor for breast cancer in Iraq. *East. Mediterr. Health J.,* **2006**, *12*(3-4), 478-482. PMID: 17037719

[32] Mirick, D.K.; Davis, S.; Thomas, D.B. Antiperspirant use and the risk of breast cancer. *J. Natl. Cancer Inst.,* **2002**, *94*(20), 1578-1580. http://dx.doi.org/10.1093/jnci/94.20.1578 PMID: 12381712

[33] Allam, M.F. Breast cancer and deodorants/antiperspirants: a systematic review. *Cent. Eur. J. Public Health,* **2016**, *24*(3), 245-247. http://dx.doi.org/10.21101/cejph.a4475 PMID: 27755864

[34] McGrath, K.G. An earlier age of breast cancer diagnosis related to more frequent use of antiperspirants/deodorants and underarm shaving. *Eur. J. Cancer Prev.,* **2003**, *12*(6), 479-485. http://dx.doi.org/10.1097/00008469-200312000-00006 PMID: 14639125

[35] Darbre, P.D. Underarm antiperspirants/deodorants and breast cancer. *Breast Cancer Res.,* **2009**, *11*(S3), S5. http://dx.doi.org/10.1186/bcr2424 PMID: 20030880

[36] Charles, A.K.; Darbre, P.D. Combinations of parabens at concentrations measured in human breast tissue can increase proliferation

of MCF-7 human breast cancer cells. *J. Appl. Toxicol.,* **2013**, *33*(5), 390-398.
http://dx.doi.org/10.1002/jat.2850 PMID: 23364952

[37] López-Carrillo, L.; Hernández-Ramírez, R.U.; Calafat, A.M.; Torres-Sánchez, L.; Galván-Portillo, M.; Needham, L.L.; Ruiz-Ramos, R.; Cebrián, M.E. Exposure to phthalates and breast cancer risk in Northern Mexico. *Environ. Health Perspect.,* **2010**, *118*(4), 539-544.
http://dx.doi.org/10.1289/ehp.0901091 PMID: 20368132

[38] Parada, H., Jr; Gammon, M.D.; Ettore, H.L.; Chen, J.; Calafat, A.M.; Neugut, A.I.; Santella, R.M.; Wolff, M.S.; Teitelbaum, S.L. Urinary concentrations of environmental phenols and their associations with breast cancer incidence and mortality following breast cancer. *Environ. Int.,* **2019**, *130*, 104890.
http://dx.doi.org/10.1016/j.envint.2019.05.084 PMID: 31228785

[39] Rylander, C.; Veierød, M.B.; Weiderpass, E.; Lund, E.; Sandanger, T.M. Use of skincare products and risk of cancer of the breast and endometrium: a prospective cohort study. *Environ. Health,* **2019**, *18*(1), 105.
http://dx.doi.org/10.1186/s12940-019-0547-6 PMID: 31796030

[40] Kiani Feizabadi, G.; Hajizadeh, Y.; Feizi, A.; Ebrahimpour, K. Urinary concentrations of parabens in a population of Iranian adolescent and their association with sociodemographic indicators. *Arch. Environ. Contam. Toxicol.,* **2020**, *79*(2), 195-207.
http://dx.doi.org/10.1007/s00244-020-00746-7 PMID: 32572517

[41] Burnett, M.E.; Wang, S.Q. Current sunscreen controversies: a critical review. *Photodermatol. Photoimmunol. Photomed.,* **2011**, *27*(2), 58-67.
http://dx.doi.org/10.1111/j.1600-0781.2011.00557.x PMID: 21392107