Original article

The Association between Soy Food and Breast Cancer; a Multicenter Cross-Sectional Study at Taif City, Saudi Arabia

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Abstract

Background: Breast cancer (BC) has a high incidence rate among females (3 to 8 per 1000) and is one of the most common causes of cancer-related death. Diet is considered one of the risk factors in BC. Phytoestrogens are chemical components similar to estrogen in structure. An isoflavone is a major group of phytoestrogens, and it is found in food like soy products. *Aim:* Our study investigates the association between soy food intake, BC development and mammogram density among women in Taif City, Saudi Arabia. *Methods:* A descriptive cross-sectional study was conducted in three hospitals in Taif City, Saudi Arabia. The data was gathered using a questionnaire created by the authors. Phone interviews were conducted with female patients who visited breast/general surgery clinics from January to July 2020. *Results:* A total of 194 patients participated in this study. We observed that only two female patients (1.03%) had a history of high soya intake, and both developed BC (p = 0.011). One-third (33.5%) showed scattered areas of fibro-glandular densities in a mammogram. *Conclusion:* We found that a large amount of soy food intake was significantly associated with a higher risk of BC. There is no relationship between mammogram density and age based on soya intake. More prospective studies with larger sample sizes in different cities of Saudi Arabia are needed to confirm this association.

Keywords: Soy Food, Phytoestrogens, Isoflavones, Mammogram Density, Breast Cancer.

Introduction

Breast cancer (BC) is considered the most common cancer diagnosed among women and is the leading cause of death from cancer [1]. The incidence of BC among Saudi female patients ranged between 3 to 8 confirmed BC cases per 1000 patients from 2010 to 2017, with the highest incidence rate in 2017 [2]. Additionally, BC can affect men and is not limited to women [3]. Many risk factors can induce BC, such as race, ethnicity, oral contraceptive use, age at first menstruation, menopausal age, age at first childbirth, and diet [4].

Phytoestrogens are natural compounds chemically similar to estrogens and found mainly in plants such as soybeans, fruits, vegetables, and whole grains [5,6]. Furthermore, they have three main classes, among which are the isoflavones [7]. Isoflavones have three forms (genistein, daidzein, and glycitein) found in soy products, beans, peas, and nuts [7]. Food that contains soybean is widely consumed in Western countries (including flour, oil, milk, yogurt, cheese, sausages, and vegetarian burgers), containing many folds more isoflavones than Asian soy products[8].

The chemical structure of genistein is very similar to the ovarian estrogen, estradiol (E2) [9], as well as binding and activating both estrogen receptors (ERα and ERβ) [10]. The function of ERα was to mediate the proliferative effects of estrogens, while ERβ binds to ERα and inhibits its effect [10,11]. Additionally, genistein binds more strongly to ERβ than to ERα [12] and activates ERα equally as well as E2 [13]. The action of genistein on both ERs depends on the developmental stage of the breast: ERβ is expressed

at a higher level than ERα during early development while in the breast tumor, ERα expression is more elevated than ERβ expression [14]. Soy products are considered a natural alternative to hormone replacement therapy (HRT) because these phytoestrogens do not involve any risk similar to HRT [15].

The relationship between soy food and BC has remained confusing over the past years. A review article reported that several previous studies found that BC in Asian people was lower than other populations because they consume high levels of isoflavones as a part of their usual diet [4]. Many similar studies have shown that regular and high consumption of soy foods, including isoflavones, reduced the risk of BC [16-18]. In contrast, others found that genistein stimulates the growth of existing estrogen-dependent tumors [19,20].

A mammogram is considered an X-ray photograph of the breast and is known as a biomarker for BC. Several studies demonstrate the effect of soy intake on mammogram density inform of increased percent mammographic density (PMD) [21-23]. Furthermore, another research found that lower PMD was associated with high soy intake [23]. On the other hand, a review article showed no overall effect of isoflavones intake on PMD in postmenopausal women but might cause a small increase in breast density in premenopausal women [24].

Nowadays, soy consumption is widespread among people in Saudi Arabia. During the previous 25 years, many studies worldwide have investigated the connection between soy-containing food and BC. However, there are insufficient studies on this subject in Saudi Arabia. This study, aimed to assess the association between soy consumption and BC and its effect on mammogram density among women in Taif City, Saudi Arabia.

Method

A random cross-sectional study was conducted in three hospitals in Taif City, Saudi Arabia, from July 2020 to October 2020. We obtained ethical approval from the Taif ethical committee.

The sample size was 973 patients. Of these, 336 did not answer the phone or their cell-phones were turned off, and 443 did not meet our inclusion criteria, so the sample size became 194 participants. Inclusion criteria: All female patients who visited breast/general surgery clinics from January to July 2020 and have a mammogram done during the past two years. The included hospitals are Alhada Armed Forces Hospital, King Abdulaziz Specialist Hospital and King Faisal Specialist Hospital, at Taif city, Saudi Arabia. Exclusion criteria: Male patients with BC.

The data was collected through a questionnaire designed by the authors except for the food assessment section. Phone interviews were conducted with the participants. The questionnaire included the demographic data (e.g., gender, age, nationality, and social status), risk factors of BC (previous history of BC or family history, HRT, radiation, oral contraceptive, age of menarche, menopause, and age of first pregnancy), and a yes/no question to assess the previous surgery or chemotherapy. For the food assessment section of the questionnaire, we used a validated semi-quantitative food frequency questionnaire (FFQ) and the food items taken from American references [25]. However, we deleted food that is not sold in our country and added the nutrients that contain soy, available in Saudi Arabia. Mammogram density results were classified based on BIRAD Lexicon into four categories: A, the breasts are almost entirely fatty; B, there are scattered areas of fibro-glandular densities; C, the breasts are heterogeneously dense; and D, the breasts are extremely dense.

The data collected were analyzed using SPSS version 23 (IBM Corp. Chicago, USA). The normality of the main continuous variable was tested for normality and found to be normally distributed (Shapiro-Wilk test, $p > 0.05$). Continuous variables were expressed using mean and standard deviations and categorical variables using frequencies and percentages. Pearson's Chi-square test was used to evaluate the statistical relationship between categorical variables. A multivariate analysis was run for some of the related variables to gain a greater understanding of correlations. A p-value of ≤ 0.05 was considered statistically significant.

Results

A total of 194 patients participated in this study. The majority of the participants were Saudis, 97.4% (n = 189), and only 2.6% (n = 5) were non-Saudis. The percentage of females who had breast cancer in our study was found to be 23.7% (n = 46). There was no significant association observed with socio-demographic characteristics of the participants except with education. Participants with no primary education showed a higher prevalence of breast cancer (35%) than graduated (20.3%), and high secondary school participants (17.3%) (P = 0.043) [**Table 1**].

When we compared the reported prevalence of BC according to BMI, it was found that 20.8% of obese and 22.2% of overweight participants had BC, but there was no statistically significant association (P = 0.684). In participants who did regular physical activities or exercise, 23.1% had BC, whereas this proportion was 24.7% in those who did not do regular physical activities or exercise (P = 0.798). There was no significant difference seen in BC prevalence between tobacco smokers (38.5%) and non-smokers (22.7%) (P = 0.195). Female patients who reported a positive family history of BC showed a greater incidence of BC (34.5%) than those who did not have a family history (19.4%), which showed a statistically significant association (P = 0.026). In this study, 10.3% (n = 20) had reported a family history of ovarian cancer (OC). Among them, 40% (n = 8) had BC, whereas this proportion was 21.5% (n = 38) among those who did not have a family history of OC (P = 0.071). The incidence of BC was 31.4% in females who had HRT and 22.5% in females who used hormonal contraceptives. Neither of these factors had a statistically significant association with BC. There was no statistical difference in the incidence of BC seen between females who had induced pregnancy (20.7%) and had normal pregnancy (24.2%) (P = 0.678). There was no statistically significant association of incidence of BC observed with early menarche (P = 0.328) and late menopause (P = 0.914). The percentage of females who had first pregnancy at late age was 7.2% (n = 14), and the incidence of BC among these was found to be 21.4%, whereas it was 23.9% in the female patients who had their first pregnancy at an earlier age (P = 0.835) [**Table 2**].

Our study observed that only two females (1.03%) had high soya intake, and both developed BC (P = 0.011), which is a statistically significant difference [**Table 3**]. The mammogram findings showed that 13.9% showed extremely dense breast, 15.5% showed entirely fatty type, 33.5% showed scattered areas of fibro-glandular densities, and 37.1% heterogeneously dense type [**Figure 1**]. When we ran a multivariate analysis to assess the relationship of mammogram findings with age based on soya intake, we found no statistically significant difference between the different age groups for soya intake (P > 0.05) [**Table 4**]. The prevalence of BC was more remarkable in females who had high soya intake among patients aged 35–44 years old, but this did not reach statistical significance (P = 0.060) [**Table 5**]

Table 1: Socio-demographic data and Breast cancer

		Breast cancer		Total	X^2 value	P value
		No	Yes			
Nationality	Saudi	144	45	189	0.039	0.843
		76.2%	23.8%	100.0%		
	Non-Saudi	4	1	5		
		80.0%	20.0%	100.0%		
Social status	Single	7	3	10	3.568	0.312
		70.0%	30.0%	100.0%		
	Married	127	35	162		
		78.4%	21.6%	100.0%		
	Divorced	8	3	11		
		72.7%	27.3%	100.0%		
	Widow	6	5	11		
		54.5%	45.5%	100.0%		
Education	Graduated/ Post-graduate	47	12	59	6.248	0.043
		79.7%	20.3%	100.0%		
	High secondary school or less	62	13	75		
		82.7%	17.3%	100.0%		
	No primary education	39	21	60		
		65.0%	35.0%	100.0%		
Age	<24 years	3	1	4	2.644	0.450
		75.0%	25.0%	100.0%		
	25-34 years	51	10	61		
		83.6%	16.4%	100.0%		
	35-44 years	86	32	118		
		72.9%	27.1%	100.0%		
	>45 years	8	3	11		
		72.7%	27.3%	100.0%		

Table 2: Relationship between breast cancer and other risk factors

		Breast Cancer		Total	X^2 Value	P value
		No	Yes			
Body Mass Index	Under-weight	5	2	7	1.494	0.684
		71.4%	28.6%	100.0%		
	Normal	33	14	47		
		70.2%	29.8%	100.0%		
	Overweight	49	14	63		
		77.8%	22.2%	100.0%		
	Obese	61	16	77		
		79.2%	20.8%	100.0%		
Regular Exercise	No	58	19	77	0.066	0.798
		75.3%	24.7%	100.0%		
	Yes	90	27	117		
		76.9%	23.1%	100.0%		
Smoking	No	140	41	181	1.676	0.195
		77.3%	22.7%	100.0%		
	Yes	8	5	13		
		61.5%	38.5%	100.0%		
Family History Breast Cancer	No	112	27	139	4.981	0.026
		80.6%	19.4%	100.0%		
	Yes	36	19	55		
		65.5%	34.5%	100.0%		
Family History Ovarian Cancer	No	136	38	174	3.271	0.071
		78.2%	21.8%	100.0%		
	Yes	12	8	20		
		60.0%	40.0%	100.0%		
Hormonal Replacement Therapy	No	124	35	159	1.406	0.236
		78.0%	22.0%	100.0%		
	Yes	24	11	35		
		68.6%	31.4%	100.0%		

Hormonal Contraceptive	No	48	17	65	0.322	0.570
		73.8%	26.2%	100.0%		
	Yes	100	29	129		
		77.5%	22.5%	100.0%		
Induced Pregnancy	No	125	40	165	0.172	0.678
		75.8%	24.2%	100.0%		
	Yes	23	6	29		
		79.3%	20.7%	100.0%		
Early menarche	No	125	36	161	0.955	0.328
		77.6%	22.4%	100.0%		
	Yes	23	10	33		
		69.7%	30.3%	100.0%		
Late menopause	No	141	44	185	0.012	0.914
		76.2%	23.8%	100.0%		
	Yes	7	2	9		
		77.8%	22.2%	100.0%		
Late age of first pregnancy	No	137	43	180	0.043	0.835
		76.1%	23.9%	100.0%		
	Yes	11	3	14		
		78.6%	21.4%	100.0%		

Table 3: Relationship of Soya intake and Breast cancer

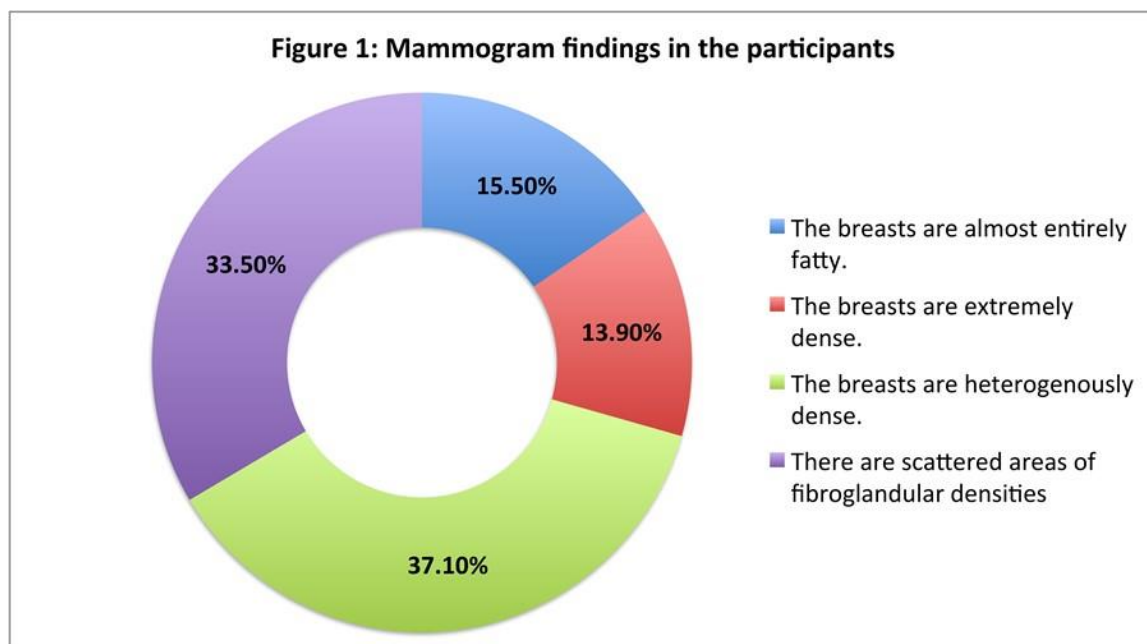|		Breast Cancer		Total	X^2 Value	P value
		No	Yes			
Soya intake/ per week	Low	148	44	192	6.502	0.011*
		77.1%	22.9%	100.0%		
	High	0	2	2		
		0.0%	100.0%	100.0%		

Figure 1: Mammogram findings in the participants

- 15.50% The breasts are almost entirely fatty.
- 13.90% The breasts are extremely dense.
- 37.10% The breasts are heterogenously dense.
- 33.50% There are scattered areas of fibroglandular densities

Table 4: A multivariate analysis of mammogram findings and age of the patients based on soya intake

	Soya intake		Age				Total	P value
			<25 years	25-34 years	35-44 years	>45 years		
The breasts are almost entirely fatty.	Low	N	1	6	22	1	30	NA*
		%	3.3%	20.0%	73.3%	3.3%	100.0%	
	High	N	0	0	0	0	0	
		%	0.0%	0.0%	0.0%	0.0%	0.0%	
The breasts are extremely dense.	Low	N	1	13	12	1	27	NA*
		%	3.7%	48.1%	44.4%	3.7%	100.0%	
	High	N	0	0	0	0	0	
		%	0.0%	0.0%	0.0%	0.0%	0.0%	

The breasts are heterogeneously dense.	Low	N	0	30	39	2	71	0.667
		%	0.0%	42.3%	54.9%	2.8%	100.0%	
	High	N	0	0	1	0	1	
		%	0.0%	0.0%	100.0%	0.0%	100.0%	
There are scattered areas of fibro-glandular densities	Low	N	2	12	43	7	64	0.922
		%	3.1%	18.8%	67.2%	10.9%	100.0%	
	High	N	0	0	1	0	1	
		%	0.0%	0.0%	100.0%	0.0%	100.0%	

* NA: Not Applicable.

Table 5: A multivariate analysis of prevalence of breast cancer based on age and soya intake

Age	Soya intake		BREAST CANCER		Total	P value
			No	Yes		
<25 years	Low	n	3	1	4	NA*
		%	75.0%	25.0%	100.0%	
	High	n	0	0	0	
		%	0.0%	0.0%	0.0%	
25-34 years	Low	n	51	10	61	NA*
		%	83.6%	16.4%	100.0%	
	High	n	0	0	0	
		%	0.0%	0.0%	0.0%	
35-44 years	Low	n	75	41	116	0.060
		%	64.7%	35.3%	100.0%	
	High	n	0	2	2	
		%	0.0%	100.0%	100.0%	
>45 years	Low	n	10	1	11	NA*
		%	90.9%	9.1%	100.0%	
	High	n	0	0	0	
		%	0.0%	0.0%	0.0%	

*NA: Not Applicable.

Discussion

BC was diagnosed in over 2.3 million women, was responsible for 685,000 deaths worldwide in 2020, and is considered the most prevalent cancer globally [26]. Our study found that there was a significant association between soy food and BC. This result is similar to previous studies that have reported that soy proteins were shown to stimulate existing estrogen-dependent tumors [27,28]. In contrast, various studies found no association between soy products and BC [29-31]. Explanation for these outcomes includes differences in ethnicity, age, amount of soy consumption, and other environmental factors among women.

Unlike the western region, the soy intake was low in all age groups in our study except in 35-44 year-olds, with two patients with high consumption. This could be due to dietary culture in our society, which depends mainly on non-soy products.

According to age group, BC prevalence was 25% among those less than 25 years old, 16.4% in 25–34 years-year-olds, 27.1% in 35-44 year-olds, and 27.3% in women older than 45 years old. This result is the opposite of a study done in 2019, which shows low-risk ER+ of BC in premenopausal and early menopausal women with soy supplements intake. This is consistent with the hypothesis that isoflavones' effects differ according to the estrogen milieu and have a weak estrogenic or anti-estrogenic action on low estrogen levels [31].

Regarding the mammogram density (MD), the heterogeneously dense breast was the most common type in our participants, accounting for 37.1%, then scattered area of fibro-glandular densities (33.5%), entirely fatty type (15.5%), and extremely dense breast (13.9%). This result is similar to a Chinese study [32], which showed that about 50% of MD was

heterogeneously dense, followed by scattered fibro-glandular densities (37%), almost entirely fat (11%), and extremely dense (3%). Both studies applied to women with a high risk of BC. Our study found no significant difference between mammogram density and consumption of soy food, which is consistent with many studies [33-36]. On the other hand, a review article reported that soya intake in premenopausal women increases PMD [33]. Our research covered a small sample size and used BIRAD Lexicon to classify MD rather than PMD, which may explain this difference.

The current study findings show that 23.7% of the females had a history of BC, which demonstrates that it is one of the most common malignancies in Saudi women, as reported in multiple studies in Saudi Arabia [37-39]. The current findings show that the prevalence is increasing dramatically. In 2018, Alotaibi et al. had reported that the prevalence of BC is 21.8%, where 13.08% of the deaths among women were attributable to BC [40]. GLOBOCAN reported that approximately 34.2% of new cancer diagnoses in women were BC, and about 24.9% of deaths in the Middle East are related to this malignancy [41]. Our study findings did not show any difference in the prevalence of BC with marital status. However, it was reported that divorced, separated, or widowed women tend to lead an unhealthy lifestyle due to intense suffering in their personal and social life, which may increase the risk of BC [42]. A recent population-based study done by Zhai et al. had reported that married and single BC patients had a better prognosis than divorced, separated, or widowed patients [43]. Our study found that BC was significantly more common in women who had no primary education than in educated patients. Breast self-examination (BSE) is crucial for the early detection of BC, and earlier studies indicate that education and socioeconomic status could influence the diagnosis and treatment of BC [44,45]. Thus, it can be postulated that

higher educational levels among women may positively affect BSE, which may help identify BC at its initial stages, leading to a better prognosis. Age is a risk factor for BC that is considered independent. A recent report showed that approximately 99.3% and 71.2% of all BC-associated deaths were in women over 40 and 60 years old, respectively [46]. Another recent study done in Saudi Arabia had reported that the average age for women who have been diagnosed with invasive BC is 51 years [47]. Thus, it is necessary to mammography screen all women after 40 years.

In addition, we reported that there was a clear association between high BMI and increased risk of BC in our participants. Similarly, a literature review found a greater risk for BC in women who gain weight in adulthood and overweight postmenopausal women than lean women [48]. We believe that obesity and metabolic syndrome are linked to the inflammatory environment that promotes BC tumor formation. Also, whole grains, vegetables and fruits, and fish lead to reduced inflammation, which reduces the risk of BC [48]. We found that a quarter of women with BC had a positive family history of breast or ovarian cancer. A similar study in Iran reported that BC risk was significantly greater in women with a positive family history of BC [49]. A positive family history of the disease is a substantial risk factor for BC at a young age. A young demographic structure and a combination of older age at menarche and younger age at first birth are both protective in later life [49]. Additionally, in our participants, there was no association between BC and other factors like smoking and HRT. A similar study found no statistically significant association between smoking and the risk of BC [50].

Conclusion

Consumption of a large amount of soy is considered a risk factor for BC in this study, especially among the 35–44 age group. This result supports the importance of awareness of the impact of soy consumption on the etiology and prevention of BC. There is no relationship between mammogram density and age based on soya intake. Further prospective studies to evaluate the exact amount and duration of soy intake are recommended to be conducted with a larger sample size in multiple cities in Saudi Arabia.

Strength and limitation

This research is one of a few studies carried out in Saudi Arabia to assess the association between soy food, BC risk and breast density. The small sample size limits our study. Also, no source in the Middle East shows the type of food containing soy protein (isoflavone) in our region, and different systems in the three included hospitals led to difficulty in collecting the mammogram density reports. However, we overcome this by using the BIRAD Scoring System. More studies are needed to evaluate a larger sample size, including the exact quantities and duration of soy food consumption. We recommend dietitians study and publish lists of food that contains soy that is available in Saudi Arabia and nearby.

Abbreviations

BC: Breast Cancer
HRT: Hormone Replacement Therapy
PMD: Percent Mammographic Density
FFQ: Food Frequency Questionnaire
MD: Mammogram Density
BSE: Breast Self-Examination

Conflict of interest

The authors declare that they have no competing interests.

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