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Association of Oral Contraceptives use with Breast Cancer and Hormone Receptor Status in Iraqi Women

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Abstract

BACKGROUND: Worldwide, there is a significant concern regarding the association of breast cancer risk and oral contraceptives use. Differences in demographical and pathological breast cancer characteristics in Iraqi patients have been reported compared to other western countries; however, studies addressing the risk of breast cancer among oral contraceptive users in Iraq and subsequent correlation with hormonal receptor status are lacking.

AIM: The aim of the study was to evaluate association of breast cancer risk and oral contraceptives use in patients visiting tertiary oncology center and to correlate hormone receptor status with history of oral contraception use in breast cancer patients.

PATIENTS AND METHODS: Two hundred women with breast cancer were compared regarding patterns of oral contraceptives use with 300 age-matched healthy female controls by personal interview and questionnaire. Patient's records were reviewed for hormone receptor status.

RESULTS: A significantly higher proportion (49%) of women with breast cancer reported a positive history of combined oral contraceptives use as compared with (35.7%) healthy controls. Ever oral contraceptives users had a significantly increased risk of breast cancer (odds ratio [OR] = 1.73; 95%, confidence interval = 1.2–2.5, p = 0.003), with the highest risk was seen in early use before the age of 20 (OR = 6.62, p = 0.02); whereas increased duration of use did not significantly increase the risk of breast cancer. There was no significant association between estrogen and progesterone receptors expression profile in breast cancer patients and combined oral contraceptive use.

CONCLUSION: In Iraqi women, the risk of breast cancer increases with oral contraceptives intake particularly when starts early before the age of 20 years. The hormonal receptor status of breast cancer patients is not significantly affected by combined oral contraceptives use.

Introduction

Breast cancer is the most common cancer worldwide. In Iraq, breast cancer tops cancers for the past 30 years, accounting for 19% of all and 33.5% of female newly diagnosed cancer cases with incidence rate of about 25.8 per 100,000 female population in 2010. It is the leading cause (22.3%) of female cancer related deaths and the second cause (11.3%) of all cancer-related deaths [1].

The association between breast cancer and exogenous hormonal intake has been a research focus for decades. The use of exogenous estrogen in the forms of postmenopausal hormone replacement therapy (estrogens alone or combined with progestins), premenopausal oral contraceptive pills, contraceptive injections, or implants has been repeatedly reported as possible risk factors of breast cancer, and they were shown to have a relative risk (RR) of <2 [2], [3]. In 1996, ever oral contraception (OC) users showed a small but significant increase risk of breast cancer (RR = 1.07; confidence interval [CI], 1.02–1.13) that was unrelated to the duration, dose or type of the preparation used and a slightly more risk among current users (RR = 1.24; CI, 1.15–1.33), which continues 10 years after stopping OC (RR = 1.01; CI, 0.96–1.05) [4].

Depending on more than 10 cohort studies and 60 case–control studies published up to 2005, International Agency of Research on Cancer (IARC) concluded in a monograph published in 2007 that the best evidence suggested an increase in risk for breast cancer among current and recent OC users with more increase are seen among females younger than 35 years of age who started taking OC when they were teenagers and that "OC are carcinogenic to humans" [5]. More recently, breast cancer incidence was shown to be significantly increased in ever users (odds ratio [OR], 1.08; CI, 1.00–1.17) with a higher risk among recent OC use up to 5 years (OR, 1.21; CI, 1.04–1.41) [6].

Furthermore, association between OC use and hormone receptors status which is considered important prognostic and predictive markers of breast cancer has been proposed since 1987 [7]. Studies results, however, varied between strong association with ER, PR negative cancers [8], [9] to little or no association [10], [11]. More

importantly, none of these studies has been done in Middle East region, the population of which may differ in their contraceptive prevalence and breast cancer biological behavior, hence, may not typically reflect the condition in Iraq. Therefore, the current study aims to find the association between breast cancer risk and OC use among Iraqi females and examine the association OC use and ER and PR expression in breast cancer patients.

Materials and Methods

This is a hospital-based case–control study carried out in the Oncology Teaching Hospital in Baghdad Medical City during the period from January 1, 2018, to June 1, 2018. The study was approved by Oncology Teaching Hospital Ethical Committee and conformed to the principles of the Declaration of Helsinki of 1975. Informed written consent from study participants was secured. The interview was performed in a private setting.

Study groups

A total sample size of 500 was calculated to be sufficient to detect a statistically significant difference of <0.05 between cases/controls and the relative frequency of using OC implying an alpha error of 0.05 and a study power (1-beta) of 0.95.

The study groups included 200 female patients with an established diagnosis of breast cancer (positive histopathology and receiving systemic therapy) with no positive family history of breast cancer and 300 age-matched control selected from the first-degree relatives of the cases with no previous personal history of non-invasive breast tumors or benign proliferative breast diseases and no previous history of radiation therapy to match the genetic and environmental confounders. More than one control subjects were invited from each case when possible or available to overcome unavailability of relative controls for some cases. Participants with history of injectable or hormonal loaded intrauterine contraceptive device were excluded from the study.

A custom made close ended questionnaire form was filled by the participants who were personally interviewed gathering data about: Age, marital status, number of children, menstrual status, use of OC, type, duration of use, and time since first and last use. Hospital records were reviewed to obtain data about tumor site, histopathological type, stage, and hormonal receptors status.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS) software version 21 in association with Microsoft Excel 2013. All continuous data were presented as mean and standard deviation. OR and 95% CIs was used to measure the strength of association between two categorical variables. t-test or Chi-square was used to compare between groups when appropriate. Binary logistic regression analysis performed to assess the relationship between different variables if one or both of them follow normal distribution. $p < 0.05$ was considered statistically significant.

Results

Patient demographics

The mean age of breast cancer patient and aged-matched healthy control participants was 48.5 (27–85) and 46 (20–79) years, respectively, which showed no statistical difference; almost half of them were postmenopausal as shown in Table 1.

Table 1: Study groups demographics and characteristics

Variable	Healthy controls		Breast cancer patients		
	n	%	n	%	p-value
Age group (years)					0.15 [NS]
Young (<45)	125	41.7	60	30	
Average (45–64)	153	51	126	63	
Older (≥65+)	22	7.3	14	7	
Postmenopausal compared to menopausal					0.68 [NS]
Reproductive age (premenopausal)	181	60.3	117	58.5	
Postmenopausal	119	39.7	83	41.5	
Parous compared to nulliparous					0.001
Nulliparous	20	6.7	31	15.5	
Parous	280	93.3	169	84.5	
Tumor type					
Invasive ductal carcinoma	-		191	95	
Invasive lobular carcinoma	-		9	5	
Tumor stage					
I-II	-		74	37	
III-IV	-		126	63	

NS: Non-significant.

The parity status was significantly different between the cases and controls ($p = 0.001$) with 15% of the cases were nulliparous women compared to only 6.7% of the controls (Table 1).

Breast cancer risk and OC

As shown in Table 2, a significantly higher proportion (49%) of breast cancer patients gave a positive history of OC use compared to healthy controls

Table 2: Breast cancer risk in OC users according to the age of first use

Variable	Healthy control		Breast cancer patients			95% CI	p-value
	n	%	n	%	OR		
Age of first use of OC							
Non-users	193	64.3	102	51.0			
<20	2	0.7	7	3.5	6.62	(1.35–32.48)	0.02
20–24	17	5.7	12	6.0	1.34	(0.61–2.9)	0.465 [NS]
25–29	19	6.3	18	9.0	1.79	(0.9–3.57)	0.096 [NS]
30–39	52	17.3	46	23.0	1.67	(1.05–2.66)	0.029
≥40	17	5.7	15	7.5	1.67	(0.8–3.48)	0.171 [NS]
Age of first use of OC ≥20 years							
Non-user	193	64.3	102	51			
<20	2	0.7	7	3.5	6.62	(1.35–32.48)	0.02
≥20	105	35	91	45.5	1.64	(1.13–2.37)	0.009

NS: Non-significant, OC: Oral contraception, OR: Odds ratio, CI: Confidence interval.

(35.7%). The type of OC used was combined pills, none of the patients or control have had used progesterone only pills. The risk of having breast cancer was significantly increased by 73% in subjects with a positive history of OC use compared to those who never used OC. When age at first use of OC was considered, OC use at the youngest age (<20 years) associated with the highest increase in the risk of having breast cancer (6.62 times, p = 0.02, Table 3) compared to non-users. The increased risk of having breast cancer for the remaining age groups in terms of first OC use ranged between 34% and 79% (Table 2). In addition, being older than 20 years at first OC use increased the risk of having breast cancer by 64% (p = 0.009) compared to non-users (Table 2).

Table 3: Breast cancer risk in OC users according to the duration of OC use and total OC exposure time

Variable	Healthy controls		Cases (Breast Ca)			95% CI OR	p-value
	n	%	n	%	OR		
Duration of OC use (years)							
Never user	193	64.3	102	51			
<1	11	3.7	24	12	4.13	(1.94–8.77)	<0.001
1–4 years	49	16.3	35	17.5	1.35	(0.82–2.22)	0.234 [NS]
≥5 years	47	15.7	39	19.5	1.57	(0.96–2.56)	0.07 [NS]
Total	300	100	200	100			
Total exposure time (OC use + quit time)							
None users	193	64.3	102	51.0			
<5	20	6.7	17	8.5	1.61	(0.81–3.21)	0.177 [NS]
5–14	48	16.0	28	14.0	1.10	(0.65–1.86)	0.712 [NS]
15–24	23	7.7	23	11.5	1.89	(1.01–3.54)	0.046
≥25	16	5.3	30	15.0	3.55	(1.85–6.82)	<0.001
Total	300	100.0	200	100.0			

NS: Non-significant, OC: Oral contraception, OR: Odds ratio, CI: Confidence interval.

The short duration of OC use of <1 year was associated with an exceptionally higher risk of having breast cancer (OR = 4.13) compared to non-users. This may be attributed to recall bias. The short duration of use (1–4 years) marginally and non-significantly increase the risk by 35%, while, 5 years or longer duration of OC use showed further increase numerically but was statically not significant.

In addition, the total OC exposure time which was calculated by adding the duration of using OC and the discontinuation time together was assessed against the risk of having breast cancer. The longer exposure time showed the highest risk to have breast cancer; exposure time of 15–24 years was associated with 89% increased risk (p = 0.046) compared to non-users while, 25 years of exposure or more was associate with OR of 3.55 (p < 0.001), Table 3. There was no correlation between OC use and cancer type or stage.

Hormonal receptors status of breast cancer patients and OC use

ER and/or PR positive cases were 150 (75%) and 50 (25%) were receptor negative. The association between the risk of having positive hormone receptors among breast cancer cases and age of first OC use, ever OC use, duration of OC use, and total exposure time are shown in Table 4. There was no obvious or statistically significant association.

Discussion

The association between exogenous steroid hormones and breast cancer development was the focus of research in the developed countries for the past 3 decades, yet the association of OC intake and breast cancer in some developing countries in particular Iraq has not been well addressed. Several studies have pointed out differences in demographical and pathological breast cancer characteristics in Iraqi patients compared to other western countries [12], [13]. Moreover the age of starting OC intake differs from other countries due to cultural and social factors prompting studying this potential risk factor in Iraqi population.

Table 4: The risk of having positive hormonal receptor by selected explanatory variables among breast cancer cases

Variable	Hormone positive Breast Ca				OR	95% CI OR	p-value
	Both ER/PR negative		Positive ER and/or PR				
	n	%	n	%			
Age of first use of OC (20+ years)							
Non-user	26	52.0	76	50.7			
<20	1	2.0	6	4.0	2.05	(0.24–17.87)	0.515 [NS]
20+	23	46.0	68	45.3	1.01	(0.53–1.94)	0.973 [NS]
Total	50	100.0	150	100.0			
Parity							
Parous	44	88.0	125	83.3			
Nullipara	6	12.0	25	16.7	1.47	(0.56–3.81)	0.432 [NS]
Total	50	100.0	150	100.0			
History of ever using OC							
Negative	26	52.0	76	50.7			
Positive	24	48.0	74	49.3	1.05	(0.56–2)	0.87 [NS]
Total	50	100.0	150	100.0			
Duration of OC use (years)-categories four							
Never used	26	52.0	76	50.7			
<1	6	12.0	18	12.0	1.03	(0.37–2.86)	0.96 [NS]
1–5 years	10	20.0	25	16.7	0.86	(0.36–2.02)	0.721 [NS]
5+ years	8	16.0	31	20.7	1.33	(0.54–3.25)	0.537 [NS]
Total	50	100.0	150	100.0			
Total exposure time (OC use + quit time)-categories							
None users	26	52.0	76	50.7			
<5	6	12.0	11	7.3	0.63	(0.21–1.87)	0.401 [NS]
5-14	5	10.0	23	15.3	1.57	(0.54–4.56)	0.404 [NS]
15–24	7	14.0	16	10.7	0.78	(0.29–2.11)	0.628 [NS]
25+	6	12.0	24	16.0	1.37	(0.5–3.72)	0.538 [NS]
Total	50	100.0	150	100.0			

NS: Non-significant, OC: Oral contraception, OR: Odds ratio, CI: Confidence interval.

Reviewing literature showed variability in calculating the RR of OC use. This was in part, due to selecting bias resulting in difficulties in controlling cofounders. In this study, we selected the control group from the first-degree relatives of patients excluding women with past personal of breast cancer, to overcome the difficulty of determining the genetic predisposition of breast cancer and to reduce the ethnic, social and environmental variations between cases and controls to the minimum. We also excluded women with history of the previous radiation therapy, breast proliferative diseases and non-invasive tumors, and we age-matched both patient and control groups, as all these factors known to increase risk of breast cancer to a greater extent than OC use [3].

Nulliparity was rated to increase risk of the breast cancer with (OR 1.67–1.9) [3]. In Iraqi society, OC is predominantly used by married fertile women with very little exceptions of some unmarried or infertile married women who use OC for stopping bleeding or menstrual cycles during limited periods like the fasting month (Ramadan) or pilgrimage when women should stop worship during the days of cycle, if not stopped by medications. This reduces the confounding chance of nulliparity as all the nulliparous participants, in this study, did not use OC during their lives.

The association between specific OC formulations and breast cancer risk remains uncertain. Few studies have looked into this, the largest compared 38 OC formulations and failed to detect a specific OC formulation that increase breast cancer risk in a greater extent than other formulations [14]. While other study done in a younger age group has detected an increased risk in current users of triphasic regimens only [15], which is not marketed in Iraq according to the data of IARC monograph [5], [16]. Combined OC are the most commonly used pills by Iraqi women; however, most of the participants in the current study were uncertain of the OC formulation they had used and some used more than one formulation. This fact made the analysis of risk association of specific formulation difficult in addition to recall bias.

In the present study, ever users have increased risk of breast cancer by 73%, this was consistent with the extensive evidence of OC association with breast cancer stated in IARC monograph, 2007 [16], and the more recent systemic review of Gierisch *et al*. [6]. Several case–control studies conducted in the neighboring countries, which share relatively similar demographic and cultural factors, have shown wide variation in results [17], [18]. Consistent with a Turkish and an Iranian studies [17], [19], we has shown a significant increase risk of breast cancer among OC users. Interestingly, the effect of early use of OC before age of 20 years further increased the risk of breast cancer among Iraqi females irrespective of duration of use and time since the last use. This is important in the view of the trend toward early marriage in Iraqi society and the WHO documented estimation of using contraception by 21% of young Iraqi females aged 15–19 years [20]. This finding may explain the stronger effect of larger total exposure time (time since first use) more than 15 years on breast cancer among Iraqi females. Consistent with IARC pooled study which concluded an increase in RR in the subgroup of women <50 years of age at diagnosis who had begun using OC when they were teenagers [21]. Conversely, Collaborative Group study in 1996 had found an increased risk of breast cancer in current users continued to 10 years after stopping OC (RR = 1.07; CI, 1.02–1.13) but disappear then after [4]. All the previously mentioned studies failed to detect a time-dependent association of breast cancer with duration of OC use, except a cohort study of Van Hoften *et al*. [22] which showed an increased risk but only for more than 10 years-use in women older than 55 years (RR = 2.1; CI, 1.1–4.0) [22]. In the present study, trend of positive association between duration of OC use and breast cancer risk was noted; however, that was statically not significant. The short use for <1 year has shown significant increase of cancer the risk, but this may be attributed to the recall bias of old short interval life events by the control group.

The relationship between hormone receptors status and known risk factors of breast cancers, including OC use, has been studied previously but in a lesser extent comparing to other breast cancer risk factors and summarized in Supplementary Table 1.

In our cohort, and consistent with many other studies [23], [24], [25], [26], [27], no significant association was found between the hormone receptor status and the ever OC users, age at first OC use, duration of use, age at diagnosis, or parity.

Conversely, some studies reported a significant increase in risk of ER/PR –ve breast cancers among OC users [28], [29], two of which recruited African American women only [8], [29], and other studies included only young aged women [28]. A recent large study from UK showed that this association is seen only among OC users for more than 5 years [30]. A single Indian study depicted a significant association of hormone positive (ER/PR +ve) breast cancers and pre and postmenopausal OC users which was confounded by the low prevalence of OC use in India [9].

Conclusion

Oral contraceptives use increases the risk of breast cancer among Iraqi females, especially with the early use before age of 20 years and those with longer exposure time and showed no association with hormone receptor status.

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Supplementary Table

Supplementary Table 1: Summary of studies which addressed the risk of hormone status in OC users

Authors	Country	Year	n	OR	p-value
Elwood *et al.*	UK	1980	735	0.83	NS
Lesser *et al.*	USA	1981	784	NA	NS
McTiernan *et al.*	USA	1986	240	1.2+	NS
				0.8−	NS
Stanford *et al.*	USA	1987	458	0.8+	NS
				1.2−	NS
Cooper *et al.*	USA	1989	380	0.88+	NS
				1.33−	NS
Huang *et al.*	USA	2000	783	1.5+	NS
				1.2−	NS
Britton *et al.**	USA	2002	1212	1.2+	NS
				1.5−	S
McCredie *et al.**	Australia	2003	618	1.1+	NS
				0.9−	NS
Cotterchio *et al.*	Canada	2003	3276	0.9+	NS
				1.3−	NS
Althuis *et al.**	USA	2003	1375	1.6+	NS
				3.1−	S
Tewari *et al.*	India	2007	300	2.5 + pre	S
				2.4 + post	S
Lumachi *et al.*	Italia	2008	NA	R=0.22	S
Kwan *et al.*	USA	2009	2280	Luminal B 0.73	S
				TN 0.97	NS
Rosenberg *et al.***	USA	2010	789	1.11+	NS
				1.65–	S
				0.9±	NS
Ma *et al.*	USA	2010	1197	NA	NS any subtype
Phipps *et al.*	USA	2011	2610+ 307−	NA	NS any subtype
Islam *et al.*	Japan	2011	706	0.82 luminal B 069 TN	NS any subtype
Turkoz *et al.*	USA	2013	1884	NA	NS any subtype
Ritte *et al.*	Europe	2013	3567+ 998−	0.9+ 1.09−	NS NS
Work *et al.*	UK	2014	4011	0.83+> 5 years	S
				1.35 - >5 years	S
Beaber *et al.**	USA	2014	985	Age 20–39 years 3.5 - >5 years current	S
				3.7 TN >5 years current	S
Bethea *et al.***	USA	2015	1848+ 1043− 494 TN	1.15+ 1.24− 1.14TN	S S NS

*The study included only young aged patients; **Studies included African Americans; HR+: Hormonal receptors ER or PR expressed breast cancers; HR: Breast cancer lacking both ER and PR; Users: OC users; NA: This data is not accessible; NS: Non-significant; S: Significant; Pre: Premenopausal patients; Post.: Postmenopausal patients; TN: Triple Negative breast cancers.