2005; Cilt: 2 Sayı: 4 Sayfa: 311-315

HİSTORY OF CONTRACEPTİVE USE AND AFFECT ON MAMMOGRAPHIC PATTERNS

Sitki GÜLHAN*, Burcu Dilek, Nurdan BARCA***, Saffet DİLEK******

*Mersin Üniversitesi Tıp Fakültesi Radyoloji AD. Mersin
** Mersin Devlet Hastanesi, Radyoloji Kliniği, Mersin
*** Ankara Numune Eğitim ve Araştırma Hastanesi Radyoloji Kliniği, Ankara
**** Mersin Üniversitesi Tıp Fakültesi Kadın Hastalıkları ve Doğum AD, Mersin

SUMMARY

Objective: *To investigate the affect of previous combined oral contraceptives use on mammographic density in the postmenopausal asymptomatic women.*

Design: ***Retrospective cross-sectional trial***

Setting: *Tertiary training and education hospital, mammography unit*

Patients: *Study population consisted from 219 women who had history of combined oral contraceptive (COC) use and exposed or group included 200 women had no history of COC.*

Intervention: *Screening mammography*

Main Outcome Patterns: *mammographic breast patterns according to Wolfe Classification*

Results: *Twenty-two percent of exposed (48) and 20 % (40) of unexposed groups had high-risk mammographic pattern. Increased breast density such as P2 and Dy (Wolfe classification) was higher in the exposed group, however this difference was not statistically significant (p=0.66). Odds ratio for having high-risk mammograms of subjects who had previous history of COC's was 1.14 (95 % CI: 0.62-2.09). Only BMI were related with mammographic density (p=0.01 and Pearson co-efficient= -0.407).*

Conclusions: *Previous history oral contraceptive use is most likely only making a small and statistically non-significant contribution to mammographic breast density.*

Key words: *combined oral contraceptives, mammographic density, menopause, screening mammography, wolfe classification*

ÖZET

Asemptomatik Postmenapozal Kadınlarda Kombine Oral KontrAseptiflerin (KOK) Mamografik Dansite üzerine etkisi

Objektif: *Asemptomatik postmenapozal kadınlarda kombine oral kontraseptiflerin (KOK) mamografik dansite üzerine etkisini araştırmak.*

Planlama: *Retrospektif kesitsel çalışma*

Ortam: *Üçüncü basamak araştırma ve eğitim hastanesi, mamografik ünitesi,*

Hastalar: *Çalışma grubu geçmişte kombine oral kontraseptif kullanma öyküsü olan 219 kadından, kontrol grubu ise kombine oral kontraseptif kullanım öyküsü olmayan 200 postmenapozal kadından meydana gelmekte idi.*

Girişim: *Tarama mamografisi.*

Değerlendirme Parametreleri: *Wolfe sınıflamasına göre mamografik meme dansitesi.*

Corresponding Author: Burcu DİLEK. Adonis Sitesi Selvi F Blok No:20, Mezitli-MERSİN, TURKEY
Tel: 0532 301 43 14
e.mail:burcudilek1974@yahoo.co.uk
Alındığı tarih: 04. 08. 2005, kabul tarihi: 27. 09. 2005

Sonuç: *KOK kullanım öyküsü olan kadınların % 22' sinde (n=48) ve kontrol grubundaki kadınların % 20' sinde (n=40) yüksek riskli mamografik patern (Wolfe P2 ve Dy) izlendi. Artmış veya yüksek riskli meme paterni KOK kullanan grupta daha fazla olmasına rağmen aradaki fark istatistiksel olarak olarak anlamlı değildi (p=0.66). KOK kullanım öyküsü olan kadınlarda yüksek riskli mamografik patern için odds ratio 1.14 (% 95 güven aralığında 0.62-2.09) idi. Sadece vücut kitle indeksi mamografik dansite ile ilişkili bulundu (p=0.01 and Pearson katsayısı= -0.407).*

Yorum: *Geçmişte kombine oral kontraseptif kullanım öyküsü meme dansitesinde istatistiksel olarak anlamlı olmayan bir artışa yol açmaktadır.*

Anahtar kelimeler: *kombine oral kontraseptifler, mamografik dansite, menapoz, tarama mamografisi, wolfe klasifikasyonu*

INTRODUCTION

Breast cancer screening is undertaken routinely in many communities in the prosperous world for early diagnosis. In the Turkey, there is no national breast cancer screening program however, opportunistic screening is performed. High-risk mammographic patterns represent an increased risk of contracting breast cancer and may be used as a surrogate endpoint for the disease in research concerning the etiology and prevention of breast cancer[1, 2]. Epidemiological studies have repeatedly shown that mammographic patterns or densities are influenced by hormonal factors [3]. Breast cancer risk factors such as age at menarche, parity, and age at first birth have been found to be independently associated with mammographic patterns [4]. High breast density on mammography is associated with a four to six-fold increased risk of breast cancer [3, 5]. A review of eight cohort studies concluded that women with the highest breast density using Wolfe's method of classification compared with the lowest density have a relative risk of 5.2 (CI=3.6–7.5) for breast cancer[6]. Increased density is also a problem because it impairs the detection of breast masses (microcalcifications are less obscured by surrounding dense tissue than masses)[7]. A failure to detect masses because of high density would cause an increase in interval cancers (cancers that present between mammographic screenings)[1, 2]. Difficulties in reading high density mammograms also produce false positive recalls[2]. Breast density gives information about exogenous hormones, of which the most widely used, are combined oral contraception (COC) and hormone replacement therapy (HRT). There is little information in the literature about density and COC, and an extensive literature about density and HRT. The relationship between oral contraceptive (COC) use and the risk of breast cancer have been controversial for several decades[1, 8, 9]. According to national data, only 5-6 % of women prefer the COC as a contraceptive method (by Ministry of Health). However, prevalence of COC use is increasing. In this study, we investigated the affect of previous combined oral contraceptives use on mammographic density in the postmenopausal asymptomatic women.

MATERIALS AND METHODS

This study was carried out January 2002-May 2002 period. Total 419 women who admitted to mammography unit for screening mammograms were enrolled in this study. All women attending the mammography unit got invited to take a part in the study and only who carried inclusion and exclusion criteria were selected. Following this, standard questionnaire was answered by every subject before the mammographic examination. Exposed group was consisted from 219 subjects who had previous history of combined oral contraceptive (COC) use. The unexposed group composed from 200 subjects who had no history of COC use. All subjects were postmenopausal (At least 12 month of amenorrhea). Exclusion criteria included known or suspected breast cancer or history of this disease, surgical menopause, and previous history of breast surgery. Also women who had history or ongoing hormone replacement therapy were excluded. As baseline characteristics the age, parity, body mass index (BMI), age of menopause, age of menarche, maternal age at first delivery, total duration of lactation was recorded. Also, whether they had history of previous COC use were asked and cumulative time of COC use (for women who started and stopped taking COC) was recorded. For the women who received COC in the several occasions during the reproductive age, total (cumulative) duration of drug use was recorded. Only

combined oral contraceptives were included in the study and patients who received progestin only pill were excluded. Weight (kg) and height (cm) were measured before mammographic examination and BMI (kg/m^2) was calculated. Following this all subjects underwent mammographic evaluation by Elscint MAM 22 S mammography system. Mediolateral oblique and craniocaudal images from both breasts were obtained. The mammograms visually evaluated by two radiologists who were blinded about clinical features of each subject. Breast density was determined by Wolfe classification[10].

N1: Parenchyma composed primarily of fat, with at most small amounts of dysplasia. No ducts visible.

P1: Parenchyma chiefly fat, with prominent ducts in the anterior portion of up to one quarter of the volume of the breast. Also can be a thin band of ducts extending into a quadrant.

P2: Severe involvement, with prominent duct pattern occupying more than one quarter of the volume of the breast.

DY: Severe involvement with dysplasia. Often obscures an underlying prominent duct pattern.

Statistical analysis was done by SPSS 11.5 (Statistical Package for Social Sciences). Continues variables such as age, parity, BMI, total duration of lactation, maternal age at first delivery, age of menarche and age of menopause were compared by Mann-Whitney U test due to they did not distribute normally. Only BMI shows normal distribution. Therefore; Student's- t test was used for comparison between the two groups for BMI. As a categorical variable, breast density was compared by Chi-Square test between the exposed and unexposed groups. Factors which affecting breast pattern were evaluated by multiple logistic regression analysis. P value less than 0.05 was accepted statistically significant.

RESULTS

Four-hundred and nineteen women were included in the study. Baseline characteristics of the exposed and unexposed groups are shown in Table I. The age, body mass index, age of first delivery and total duration of lactation was not statistically between the two groups (p>0.05). In the exposed group 29 patients (13.49 %) had family history of breast cancer and 24 patients (12 %) had family history of endometrial, ovarian or colorectal adenocarcinoma in the first or second degree relatives. However; 17 (8 %) and 13 of controls (6.35 %) had family history of breast and other adenocarcinoma. In the exposed group, median time of COC use was 41.48 month (6-144 month range).

Table I: *Baseline characteristics of study and control groups.*

	Exposed Group**	Unexposed Group**	p
Age (years)	54.82±6.83	57.56±6.82	0.015*
Parity	3.17±1.34	2.52±1.48	0.01*
Body Mass Index (kg/m2)	29.02±5.48	29.65±6.19	0.570
Age of first menses (years)	14.00±1.30	13.28±1.35	0.014*
Age of first delivery (years)	20.40±4.76	20.50±4.40	0.890
Total duration of lactation (month)	34.76±27.03	30.76±20.47	0.272

**P<0.05 was statistically significant*

*** Values expressed as median ± standard deviation except BMI*

However, patients who had previous history of oral contraceptives had higher parity, higher BMI and lower age of menarche (p=0.01, p=0.042 and p=0.014 respectively). Subjects of exposed group had higher total duration of lactation, however, there is no statistically significant difference between the unexposed and exposed group (p=0.272). P2 and Dy pattern was higher in the exposed group, however this difference between the exposed and unexposed group was not statistically significant (p=0.66). Twenty-two percent of exposed[48] and 20 % (40) of unexposed group had high-risk mammographic pattern. Odds ratio for having high-risk mammograms of subjects who had previous history of COC's was 1.14 (95 % CI: 0.62-2.09). Distribution of mammograms of both unexposed and exposed groups' subjects was shown Table II. In the exposed group, subjects reclassified by cumulative COC use as 12 month and less, 13-60 month and 61 month and more. Cumulative duration of COC use is not found a statistically significant parameter to effect mammographic density (p=0.745).

Table II: *Distribution of Mammographic Breast Density* in the Study and Control Groups*

	N1	P1	P2	Dy	Total
Exposed Group (n=219)	58	113	41	7	219
Unexposed Group (n=200)	20	140	27	13	200
Total	78	253	68	20	419

**: Evaluation was performed by Wolfe classification.*

(Table III). In the logistic regression analysis, there was no relationship between the mammographic density and age (p=0.237), age of menopause (p=0.164) and lactation (p=0.514), parity (p=0.362), history of COC use (p=0.632) and age of menarche (p=0.362). However; only BMI were related with mammographic density (p=0.01 and Pearson co-efficient= -0.407).

Table III: *Distribution of mammographic breast density according to cumulative COC use in the exposed group.*

Duration of COC Use	N1	P1	P2	Dy	Total
1-12 month	28	33	17	4	82
13-60 month	21	49	19	2	91
61 month and more	9	31	5	1	46
Total	58	113	41	7	219

DISCUSSSION

Screening mammography significantly reduces the rate of mortality from breast cancer in women 50 years of age or older. HRT may increase the mammographic density of breast tissue and impair the ability to detect early signs of breast cancer[11-13] Major impact of sex steroids on breast tissue is induced densities mimicking that of breast disease and association of dens breasts with increased risk of malignant breast tumors. In this study, we found slightly higher rate of Wolfe P2 and Dy pattern in the women who had previous COC use than unexposed group however this difference was not statistically significant. Odds ratio for previous COC use was 1.14. Women who had used COC's previously were 14 % more likely to have high-risk pattern mammograms (Wolfe P2 and Dy) than unexposed group. We did not detect any relationship between the cumulative duration of COC use and breast density. BMI was the only statistically significant covariate that affecting mammographic density. Relationship between the mammographic density and exogenous sex steroids is well-known association. There is now on extensive literature about interplay between the postmenopausal HRT and breast density. HRT causes increase in mammographic density in up to 25 % of women and continuous combined HRT most likely to cause increased breast density than estrogen only preparations and tibolone[14]. Prolonged use and initiation before the menopause are more likely associated with increased breast density[4]. The relationship between the mammographic density and previous COC use is unclear. Most studies reported that previous COC use is not associated with increased breast cancer risk[15]. Funkhouser et al[8] reported that positive association between OC use and high-risk patterns. Gram et al,[9] reported that women who reported ever having used COC's were 20 % more likely to have high risk mammographic patterns compared with never having used COC's in a population-based screening study in Norway. Also in this study; nulliparous women who had previous history of COC were four times more likely to have high risk patterns in the mammograms[9].

Nulliparity is well-known risk factor for breast cancer independent from history of COC use and nulliparous women are more likely to have high-risk patterns than multiparas. In this study, we did not detect any relationship between parity and high risk mammograms. Although, number of nulliparous women were small in comparison to multiparous women. BMI was inversely correlated with mammographic breast density in both groups as previously reported[4]. In our study, median duration of COC use was 41 month and this period is relatively short in comparison to studies of Gram et al[9] and Meirik et al[16]. A Swedish-Norwegian case-control study showed a fourfold statistically significant increased risk for breast cancer among nulliparous women who had used COC's for 8 years or more[9]. Major handicaps of published studies to assess impact of COC on breast density are older COC's formulations, which had contained higher amount estrogen and progesterone than currently used low dose formulations. We also, lack information about formula dosage however, most women in our study stopped taking pill many years before their mammograms. Rutter CM et al[17] reported that following the withdrawal of HRT, mammographic density changes related with HRT diminishes within 3 weeks after stopping[17]. Probably, increased breast density related with COC's could be reversed following the stopping COC's. Also, period between the stopping drug and screening mammography is relatively long in comparison to postmenopausal HRT.

As a conclusion, in this study we evaluated the relationship between previous history of COC's and mammographic density. We detected small and statistically non-significant increase in the breast density according to Wolfe classification and inverse correlation between the breast density and BMI. Oral contraceptive

use might be responsible from only small contribution to increased breast density. Small sample size and lack information about formula dosage and interval between the cessation of COC' use and screening mammography were major handicaps of study. Also another issue which should be clarified is time period between the cessation of taking pill and baseline mammograms to reversal of mammographic changes. We need further studies to evaluate whether increased risk of breast cancer related with COC's and effect on mammographic screening sensitivity especially low dose formulas which prescribed since early 1980' s.

REFERENCES

1. Warren R. Hormones and mammographic breast density. Maturitas 2004;49:67-78.
2. Speroff L. The meaning of mammographic breast density in users of postmenopausal hormone replacement therapy. Maturitas 2002;41:171-175.
3. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause statusm. J Natl Cancer Inst 1995;87:1622–1629.
4. Sala E, Warren R, McCann J, Duffy S, Luben R, Day N. High-risk mammographic parenchymal patterns and hormone replacement therapy: a case control study. Int J Epidemiol 2000;29:629-636.
5. Byng JW, Yaffe MJ, Jong RA, Shumak RS, Lockwood GA, Tritchler DL et al. Analysis of mammographic density and breast cancer risk from digitized mammograms. Radiographics 1998;18:1587-1598.
6. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. Cancer Detect Prev 1992; 16:67-72.
7. Freedman M, San Martin J, O'Gorman J, Eckert S, Lippman ME, Lo SC et al. Digitized mammography: a clinical trial of postmenopausal women randomly assigned to receive raloxifene, estrogen, or placebo. J Natl Cancer Inst 2001;93:51-56.
8. Funkhouser E, Waterbor JW, Cole P, Rubin E. Mammographic patterns and breast cancer risk factors among women having elective screening. S Med J 1993;86:177-180.
9. Gram IT, Funkhouser E, Nordgard L, Tabar L, Ursin G. Oral contraceptive use and mammographic patterns. Eur J Cancer Preven 2002;11:265-270.
10. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol 1976;126:1130-1139.
11. Leung w, Goldberg F, Zee B, Sterns F. Mammographic density in women on postmenopausal hormone replacement therapy. Surgery 1997;122:669-674.
12. Laya MB, Larson EB, Taplin SH, White E. Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography. J Natl Cancer Inst 1996;88:643-649.
13. Litherland JC, Stallard S, Hole D, Cordiner C. The effect of hormone replacement therapy on the sensitivity of screening mammograms. Clin Radiol 1999; 54:284-288.
14. Lundstrom E, Christow A, Kersemaekers W, Swane G, Azavedo E, Soderqvist G et al.<Effects of tibolone and continuous combined hormone replacement therapy on mammographic breast density. Am J Obstet Gynecol 2002;186:717-722.
15. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53.297 women with breast cancer and 100.239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713-1727.
16. Meirik O, Farley TM, Lund E. Adami HO, Christofferson T, Bergsjo P. Breast cancer and oral contraceptives: patterns of risk among parous and nulliparous women-further analysis of the Swedish –Norwegian material. Contraception 1989;39: 471-475.
17. Rutter CM, Mandelson MT, Laya MB, Seger DJ, Taplin S. Changes in breast density associated with initiation, discontinuation and continuing use of hormone replacement therapy. JAMA 2001;285:171-176.