



EFFECT OF MAMMOGRAPHY IMAGING PROCEDURE ON SERUM INFLAMMATORY AND/OR TUMOR MARKER LEVELS

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SUMMARY – Mammography is one of the gold standard screening tests for breast cancer. The effects of mammography procedure on blood parameters are not known. This study aimed to investigate whether the procedure-associated breast compression affects the widely and simultaneously performed blood measurements of C-reactive protein (CRP), carcinoembryonic antigen (CEA), and cancer antigen (CA) 15-3. According to breast ultrasound examination results, participants were divided into 3 groups as follows: group 1 (participants with breast mass size ≥ 20.0 mm, n=48); group 2 (participants with breast mass size < 20.0 mm, n=17); and group 3 (participants with no breast mass, n=23). In groups 1 and 2, on the day of the mammographic imaging study, serum CRP, CEA, and CA 15-3 levels were measured before and after the imaging study. Participants in group 3 had their blood parameters measured without mammography and/or any breast compression. Post-mammography blood measurements displayed a significant increase in serum CRP levels, and a significant decrease in serum CEA and CA 15-3 levels in group 1 (in comparison with the same day pre-mammography blood sampling levels; $p < 0.05$ all). Although pre-mammography serum CEA levels in group 1 participants were significantly higher than those in group 2 and 3 participants, this significant elevation became nonsignificant at post-mammography measurements ($p < 0.05$ and $p > 0.05$, respectively). On the day of the mammographic imaging study, the optimal time of blood sampling for testing CRP, CEA and CA 15-3 levels in persons with a breast mass is before, but not after the mammographic imaging procedure. This issue requires additional detailed studies.

Key words: *Breast cancer; Blood tests; Breast compression; Mammography; C-reactive protein; Tumor markers*

Introduction

Breast cancer (BC) is the leading cause of cancer related deaths in women. The majority of BC cases are diagnosed upon detection of abnormal results on

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screening¹. One of these screening tests of paramount importance is mammography^{2,3}. This imaging test starts by positioning and compressing the breast between two clear plates. Compression of the breast during the mammography procedure helps improve the image quality and decreases the amount of irradiation needed. The plates are attached to a highly specialized camera, which takes two pictures of the breast from two different directions. Some patients feel pain during this mandatory compression stage^{2,4}. Besides mammography, some blood tests may also guide the physician in the diagnosis and/or determination of BC prognosis. The well-known inflammatory marker C-reactive protein (CRP) is widely used in daily practice. It is elevated in BC related inflammation and in infection(s) as well. It also could predict prognosis of this malignancy⁵. Tumor markers such as cancer antigen (CA) 15-3, and carcinoembryonic antigen (CEA) may help in diagnosis, but more importantly, they help determine metastasis, prognosis, response to treatment, and recurrence of the disease⁶⁻⁸. There is no precaution in terms of the timing of blood sampling for these biomarkers and no strong evidence for diurnal variation in their levels. However, sampling during the menstruation period may lead to a false elevation in CA 15-3 levels. In daily practice, fasting sampling is not mandatory for such blood tests⁹. It is known that breast compression during mammography procedure does not cause shedding of circulating tumor cells to the peripheral venous blood¹⁰. As far as we know, whether compression of the breast during mammography procedure could alter blood levels of the above-mentioned biomarkers has not been studied yet. So, we tried to investigate this issue in our study.

Subjects and Methods

This prospective study was approved by the Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee and conducted according to the Declaration of Helsinki (Decision no. 20-19-03). Written consent was obtained from the participants. All procedures carried out in the research with participation of humans were in compliance with the ethical standards of the National Research Ethics Committee and with the Helsinki Declaration of 1964 and its subsequent changes or with comparable ethics standards.

During a 3-month period (from November 1, 2019 to February 1, 2020), women who were referred

by their physicians to the radiology department for mammography imaging were asked to participate in this study. Decision on the referral to mammography imaging was made according to the known national and international guidelines, and the investigators had no influence on this mammography indication and/or request^{1,11}. Those who accepted to participate were allocated to two groups according to their ultrasound examination for breast mass size to group 1 that included participants with a breast mass size ≥ 20.0 mm and group 2 including participants with a breast mass size < 20 mm. Group 3 consisted of age-matched volunteer women with no history of BC and/or breast mass who presented to the Internal Medicine outpatient clinics of the Hospital.

The inclusion criteria were age > 30 years (all groups) and presence of an indication for mammography imaging study (groups 1 and 2). The exclusion criteria were inability to give written consent (all groups), presence of breast operation history (all groups), presence of a breast mass of any size on ultrasonographic examination (group 3), having a mammography imaging investigation within the previous month (all groups), having menstruation and/or blood sampling at the time of mammography (all groups).

A total of 90 participants were enrolled in this study. Group 1 consisted of 48, group 2 of 19 participants, and group 3 of 23 participants. Subsequently, two subjects from group 2 were excluded from the study. One of these two subjects was excluded because the pre-mammography laboratory measurements were not available, and the other was excluded because she could not complete her mammography imaging procedure (due to the sense of fainting that occurred during the procedure). Therefore, final analysis was performed for a total of 88 participants (group 1, $n=48$; group 2, $n=17$; and group 3, $n=23$).

Timeline of blood sampling and mammography procedures

Venous blood samples for determination of the CRP, CEA and CA15-3 parameters were obtained from group 1, 2 and 3 participants at 08:00 a.m. under fasting conditions of at least 10 hours. Subsequently, the group 1 and 2 participants underwent mammographic imaging study at 10:00-11:00 a.m. Another blood sample for the above-mentioned study parameters was obtained 2 hours after completing the imaging study (at 12:00-13:00 a.m.). Group 3 participants

did not undergo mammographic imaging study but underwent second blood sampling at 12:00-13:00 a.m. All participants were allowed to take a snack 1 hour before the second blood sampling. Hereafter, the above-mentioned 2 blood measurements of CRP, CEA, and CA 15-3 will be referred to as the 1st and 2nd measurements, respectively.

Mammographic imaging study

Routine craniocaudal and mediolateral oblique views were obtained for each breast. Digital mammography images were obtained using a Hologic Selenia Dimension system (Hologic, Bedford, MA, USA) and dedicated digital mammography (Hologic, Selenia Dimensions) with standard screening automatic exposure control. To obtain similar compression techniques in all patients, the same technician who had 10 years of experience in performing mammography, performed all examinations. Compression was finished when blenching occurred on the breast or the participant could not bear more.

Measurement of blood inflammatory and tumor markers

These measurements were done at the Hospital accredited central laboratory with standardized internal quality control and external quality assurance measures. Venous blood samples were collected into Vacutainer® Plus serum tubes (Becton Dickinson, UK). The venous blood samples were centrifuged for 10 min at 1500 rpm. The measurements of CRP, CEA and CA 15-3 were performed using Beckman Coulter Kit (Beckman Coulter, Brea, CA, USA) and Beckman Coulter UniCel DXI 800 analyzer (Beckman Coulter, Brea, CA, USA). All tests were performed within 1 hour of blood collection. CEA and CA 15-3 assays were two-step immunoenzymatic (sandwich) assays. The lowest detectable level of CEA distinguishable from zero with 95% confidence level is 0.1 ng/mL. The lowest detectable level of CA 15-3 antigen is distinguishable from zero (Access BR Monitor Calibrator S0) with a 95% confidence level is <0.5 U/mL. CRP was measured by immunoturbidimetric method; the expected value for adults is <5 mg/dL.

The primary aims of the study were to assess the effect of breast compression elicited during mammography procedure on the parameters of CRP, CA 15-3, and CEA measured, and to compare this effect between the groups.

The secondary aims of the study were to compare blood inflammatory markers and tumor markers

measured before and after mammography breast compression procedure with those of the participants who did not undergo mammographic imaging study (control group), and to investigate the effect of time frame and/or prandial status on the blood inflammatory and tumor markers studied.

Data availability

The data are available for researchers (for research purposes only) on request by directly contacting the corresponding author.

Statistical analysis

The Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation [SD], median, frequency, ratio, minimum, and maximum) were used. The normality of data distribution was tested by the Shapiro-Wilk test. Mann-Whitney U test was used to compare two groups of quantitative data that did not show normal distribution. One-way ANOVA test was used for comparisons of three or more groups with normal distribution and Bonferroni test was used for binary comparisons. Kruskal Wallis test was used for comparisons of three or more groups that did not show normal distribution, and Bonferroni-Dunn test was used for binary comparisons. Comparisons in the groups of data without normal distribution were performed using Wilcoxon sign test. Pearson's χ^2 -test was used to compare qualitative data. A p value of <0.05 was considered statistically significant.

Results

The mean \pm standard deviation (SD) age of the participants was 53.36 ± 11.90 (min-max [median]: 31-84 [53]) years. There was no significant difference in the mean and/or median age values among the 3 study groups ($p > 0.05$). There was no significant difference in the menstrual status (pre- and/or postmenopausal status) among the 3 groups ($p > 0.05$) either, as shown in Table 1.

Regarding the studied blood parameters of CRP, CEA, and CA15-3, the 1st and 2nd CRP measurements in group 3 participants were higher compared to those recorded in group 1 and 2 participants ($p = 0.048$ and $p = 0.038$, respectively). Difference between the two CRP measurements was significant only in group 1 participants ($p = 0.029$). The 1st CEA measurement in group 1 participants was higher compared to those recorded in group 2 and 3 participants ($p = 0.022$).

Table 1. Age and menopausal status of study groups

		Group 1 (n=48)	Group 2 (n=17)	Group 3 (n=23)	p
Age (years)	Min-Max (Median)	31-84 (48)	41-74 (58)	38-70 (56)	^a 0.123
	Mean ± SD	51.06±12.75	57.18±9.87	55.35±10.71	
Menopausal status, n (%)	Pre-menopausal	26 (54.2)	7 (41.2)	9 (39.1)	^b 0.404
	Post-menopausal	22 (45.8)	10 (58.8)	14 (60.9)	

SD = standard deviation; ^aone-way ANOVA test; ^bPearson's χ^2 -test

Table 2. Comparison of the 1st and 2nd measurements of CRP, CEA, and CA 15-3 blood levels

		Group 1 (n=48)	Group 2 (n=17)	Group 3 (n=23)	^c p	^d p ₍₁₋₂₎	^d p ₍₁₋₃₎	^d p ₍₂₋₃₎
CRP (mg/dL) 1 st measurement	Min-Max (Median)	0-23 (3)	0-20 (4)	0.1-52 (5)	0.048*	1.000	0.049*	0.398
	Mean±SD	4.62±5.28	4.88±5.04	9.70±11.68				
CRP (mg/dL) 2 nd measurement	Min-Max (Median)	0-21 (3)	1-19 (4)	0-55 (5.6)	0.038*	1.000	0.032*	0.557
	Mean±SD	4.38±4.91	4.88±4.66	9.63±11.89				
		^c p	0.029*	0.957	1.000			
CRP (mg/dL) (2 nd -1 st measurement)	Min-Max (Median)	-2-5 (0)	-1-2 (0)	-5-3 (0)	0.451	1,000	0,669	1,000
	Mean±SD	-0.24±1.17	0±1.00	-0.07±1.35				
CEA (ng/mL) 1 st measurement	Min-Max (Median)	0.5-161 (2)	0.6-3.4 (1.5)	0.4-3.7 (1.4)	0.022*	0.033*	0.021*	0.955
	Mean±SD	7.59±23.88	1.60±0.76	1.69±0.98				
CEA (ng/mL) 2 nd measurement	Min-Max (Median)	0.3-163.3 (1.8)	0.7-3.4 (1.4)	0.5-3.6 (1.4)	0.432	1.000	0.751	1.000
	Mean±SD	7.05±24.13	1.63±0.76	1.68±0.94				
		^c p	0.001**	0.485	0.796			
CEA (ng/mL) (2 nd -1 st measurement)	Min-Max (Median)	-8.7-2.3 (-0.2)	-0.2-0.4 (0)	-0.5-0.5 (0)	0.001**	0.003**	0.010*	1.000
	Mean±SD	-0.54±1.47	0.04±0.15	-0.01±0.24				
CA 15-3 (U/mL) 1 st measurement	Min-Max (Median)	1.7-223.7 (13.9)	4.2-21.4 (11.4)	4.5-39.4 (10.4)	0.067	0.650	0.074	1.000
	Mean±SD	20.89±32.51	12.26±5.24	11.73±7.56				
CA 15-3 (U/mL) 2 nd measurement	Min-Max (Median)	1.8-225 (12.7)	4.2-19.3 (11.1)	4.3-36.6 (11.5)	0.062	0.252	0.098	1.000
	Mean±SD	20.50±32.57	11.12±4.95	11.34±6.74				
		^c p	0.022*	0.059	0.758			
CA 15-3 (U/mL) (2 nd -1 st measurement)	Min-Max (median)	-7.5-9.8 (-0.5)	-8.9-1.7 (-0.7)	-8.6-2.9 (-0.3)	0.407	1.000	0.773	0.675
	Mean±SD	-0.39±3.05	-1.15±2.51	-0.38±2.15				

^cKruskal-Wallis test; ^dBonferroni-Dun test; ^eWilcoxon signed rank test; *p<0.05; **p<0.01; CRP = C-reactive protein; CEA = carcinoembryonic antigen; CA 15-3 = cancer antigen 15-3

Table 3. Relation between breast mass size and blood CRP, CEA and CA 15-3 levels

Small (n=17)		Mass size		^a p
		Large (n=48)		
CRP (mg/dL) 1 st measurement	Min-Max (Median)	0-10 (2)	0-23 (4)	0.039*
	Mean±SD	2.49±2.53	5.78±6.02	
CRP (mg/dL) 2 nd measurement	Min-Max (Median)	0-9 (1)	0-21 (4)	0.037*
	Mean±SD	2.29±2.34	5.52±5.58	
CEA (ng/mL) 1 st measurement	Min-Max (Median)	0.7-7.1 (1.8)	0.5-161 (2.3)	0.219
	Mean±SD	2.21±1.48	10.54±29.44	
CEA (ng/mL) 2 nd measurement	Min-Max (Median)	0.3-7 (1.6)	0.3-163.3 (1.9)	0.134
	Mean±SD	1.76±1.47	9.95±29.78	
CA 15-3 (U/mL) 1 st measurement	Min-Max (Median)	5.1-27.2 (14)	1.7-223.7 (13.7)	0.628
	Mean±SD	14.07±5.91	24.63±39.95	
CA 15-3 (U/mL) 2 nd measurement	Min-Max (Median)	4.6-21.9 (12.5)	1.8-225 (12.9)	0.779
	Mean±SD	13.55±5.12	24.30±40.08	

^aMann-Whitney U test; *p<0.05; SD = standard deviation; CRP = C-reactive protein; CEA = carcinoembryonic antigen; CA 15-3 = cancer antigen 15-3

The 2nd CEA measurements were similar in all groups (p>0.05). Difference between the two CEA measurements was significant only in group 1 participants (p=0.001). Although the 1st and 2nd CA 15-3 measurements in group 1 participants were higher compared to those in group 2 and 3 participants, they did not reach statistical significance (p>0.05 all). Difference between the two CA 15-3 measurements was significant only in group 1 participants (p=0.022). The CRP, CEA and CA 15-3 levels in all study groups are shown in Table 2.

The mean size of breast masses estimated by ultrasound in groups 1 and 2 was 31.08±15.14 mm (min-max: 07.00-60.00). Only the 1st and 2nd CRP measurements had a positive correlation with breast mass size (p=0.039 and p=0.037, respectively). The 1st and 2nd CEA and CA 15-3 measurements had no correlation with breast mass size (p>0.05 all) (Table 3).

Discussion

Mammography is the gold standard technique for screening and diagnosis of BC^{1,11}. Even the widely used noninvasive ultrasonographic examination usually is not the first-line investigation technique in this disease^{2,11}. In daily practice, when suspicion of malignancy is detected on a mammographic imaging study, the managing physician will order further

investigative studies such as imaging and/or blood tests^{1-3,12}. One of the important requisites of a successful mammographic study procedure is an appropriate breast compression process^{2,3}. Usually, patients (and their managing physicians as well) are so fussy and try to finalize every necessary measure as quickly as possible. In our system, other imaging tests (such as ultrasonography) and necessary blood tests usually are performed on the same day of mammographic examination. To our knowledge, blood sampling for most of the blood tumor markers and/or CRP does not necessitate fasting and/or a special diurnal time. A non-menstrual cycle period is advised only for CA 15-3 measurements⁵. In this pilot study, we attempted to see the acute effect of breast compression during mammography on the commonly ordered blood tests such as CRP, CEA, and CA 15-3. Post-mammography blood sampling yielded a significant increase in serum CRP levels, and a significant decrease in serum CEA and CA 15-3 levels in group 1 participants with a breast mass size of >20.0 mm in comparison with the same day pre-mammography blood sampling levels. Another important point to mention is that the pre-mammography serum CEA levels were significantly higher in group 1 participants compared to those in group 2 and 3 participants, but this significant difference became nonsignificant at post-mammography measurements (see p values

in Table 2). No significant change was found in the above-mentioned study parameters in group 3 between the two measurements in different time frames. This suggests that the significant change in the same parameters in group 1 was caused by the effect of the mammography procedure rather than the time frame and/or prandial causes. Thus, we could conclude with some certainty that breast compression procedure(s) such as mammography performed before blood sampling in patients with a breast mass will lead to serum CRP, CEA, and CA 15-3 measurements that differ from the actual values in the subject. Whether the late effect of this compression on the above-mentioned blood parameters is similar to the acute early effect needs to be studied. This acute effect of breast compression on the study blood parameters needs to be taken into consideration in preparation of future guidelines. Otherwise, it will mislead health care providers because we know that CRP is an important marker of inflammation or infection, while CEA and/or CA 15-3 are important biomarkers of metastasis, recurrence, and response to therapy in BC^{6,13}.

The mechanism of compression-induced increase of serum CRP levels may be attributed to compression-induced increase of inflammation in participants with breast mass (group 1). On the other hand, compression-related decrease in CEA and CA 15-3 in the same group could not be explained by the same mechanism. In a study by Ricca *et al*¹⁴, brief transient compression applied to single malignant breast cells in laminin-rich extracellular matrix led them to form an acinar-like structure known as 'mechanical reversion'. This transient compression also restored coherent rotation in these malignant cells. The nitric oxide (NO) pathway had a role in this mechanical reversion. Some studies showed that increased NO synthase expression may have a cytostatic and/or cytotoxic effect on tumor cells, and *vice versa*¹⁵. Whether this was the cause or one of the causes of compression-related decrease in serum CEA and CA 15-3 levels in group 1 participants, needs to be further studied. After further detailed confirmatory studies in this field, mammography procedures such as transient breast compression may be used in the management of this patient group.

One of the important limitations of this study was that the late effects (in days) of breast compression on CRP, CEA and CA 15-3 levels were not studied. Every marker has a different half-life and some of

them are measured in days¹⁶. The main reason for not planning such a serial measurement was that we had no previous preliminary data on the best time frame of blood sampling, as this was a pilot study. So, from the beginning, we decided to make one measurement after the mammography procedure. The most important point of not adding other measurements to the proceeding days was to avoid any delay in the groups of participants with high suspicion of malignant mass in whom biopsy and management should be performed as soon as possible. We did not evaluate the effect of breast compression on other routine blood tests such as erythrocyte sedimentation rate, complete blood counts, pro-calcitonin, etc. These also need to be studied. Taking these pilot study results and the above-mentioned ethical issues into consideration, further detailed studies may be planned and conducted. We think that the results of the study will guide health authorities dealing with this patient population.

In conclusion, our pilot study results showed that the optimal time of blood sampling for CRP, CEA, and CA 15-3 testing in suspected BC patients on the day of mammographic imaging study is before mammographic imaging procedure rather than after it. Nevertheless, further detailed studies are needed to identify the long time effect of this imaging procedure on the levels of the above-mentioned blood tests.

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Sažetak

UČINAK MAMOGRAFSKOG POSTUPKA NA SERUMSKE RAZINE UPALNIH I/ILI TUMORSKIH BILJEGA

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Mamografija je jedan od 'zlatnih' standardnih testova probira za rak dojke. Učinci mamografskog postupka na krvne parametre nisu poznati. Cilj ovog istraživanja bio je ispitati djeluje li kompresija dojke povezana s ovim postupkom na često i istodobno izvođena mjerenja C-reaktivnog proteina (CRP), karcinoembrijskog antigena (CEA) i karcinom antigen (CA) 15-3 u krvi. Ispitanice su podijeljene u 3 skupine prema rezultatima ultrazvučnog pregleda dojki: 1. skupina (ispitanice s masom u dojci $\geq 20,0$ mm, n=48); 2. skupina (ispitanice s masom u dojci $< 20,0$ mm, n=17); 3. skupina (ispitanice bez mase u dojci, n=23). U 1. i 2. skupini serumske razine CRP, CEA i CA 15-3 mjerene su prije i nakon mamografskog postupka. Kod ispitanica 3. skupine krvni parametri mjereni su bez mamografije i/ili bilo kakve kompresije dojke. Mjerenja provedena nakon mamografije pokazala su značajan porast serumskih razina CRP i značajan pad serumskih razina CEA i CA-15-3 u 1. skupini u usporedbi s razinama tih parametara zabilježenim istoga dana prije mamografije ($p < 0,05$ sve). Iako su razine CEA u serumu prije mamografije bile značajno više u 1. skupini u usporedbi s 2. i 3. skupinom, značajnost tog porasta izgubila se kod mjerenja nakon mamografije ($p < 0,05$ odnosno $p > 0,05$). Dakle, u danu kad je zakazana mamografija optimalno vrijeme za uzorkovanje krvi za mjerenje razina CRP, CEA i CA 15-3 kod osoba s masom u dojci je prije, a ne poslije mamografskog postupka. Ovo pitanje zahtijeva daljnje detaljne studije.

Ključne riječi: *Rak dojke; Krvne pretrage; Kompresija dojke; Mamografija; C-reaktivni protein; Tumorski biljezi*