Synergy in combining findings from mammography and ultrasonography in detecting malignancy in women with higher density breasts and lesions over 2 cm in Albania

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Aim of the study: To provide evidence of the synergy of combining findings from mammography (MM) and ultrasonography (US) in detecting malignancy in women with high-density breasts.

Material and methods: A total of 245 women were screened for breast cancer using both mammography and ultrasonography at the American Hospital in Tirana during 2013–2014. The data was used to identify possible benefits in detecting malignancy, by combining the findings of MM and US and confirming them with those of the biopsy. Data on age, breast density, BI-RADS classification, and biopsy confirmations were collected and analysed.

Results: Out of the 245 women, 36 biopsies were taken (17 for women classified BI-RADS 4 and 5; 19 for women with BI-RADS 3 that had grown in size from the previous examination). The accuracy in detecting malignancy for low-density-breast women was 90% for MM, 70% for US, and 90% for combined. For high-density breasts, the accuracy was 65% for MM, 79% for US, and 82% for combined findings. Multivariate analysis indicates that high-density-breast women who have a malignant finding in at least one of the examinations (MM or US) are 24 times more likely (p = 0.039) to have a positive finding in biopsy for malignancy. The odds increased 32 times for lesions over 2 cm (p = 0.056).

Conclusions: Our study results indicate additional benefits of combining findings from MM and US for high-density-breast women. Further study is warranted in a larger population and for different kinds of cancer.

Key words: breast cancer, screening, mammography, and ultrasonography.

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Introduction

The evidence for breast screening benefits in achieving early detection and saving lives has already been published. Early detection has been shown to be associated with reduced breast cancer morbidity and mortality [1, 2]. The American Cancer Society (ACS) recommended in 2015 regular breast screening for women with average risk, starting at age 45 years, annually for ages up to 54 years, and biennially for ages 55 years and older. One study [3] concluded that breast cancer screening in women of average risk was associated with a reduction in breast cancer mortality of approximately 20%.

Breast cancer screening is beneficial in general not only for women with average risk for breast cancer but also for those who underwent transplants or who have other benign diseases of the breast [4]. Breast screening is routinely done using mammography that detects grouped micro-calcifications [5]. Different breast imaging tests have been evaluated as adjunct diagnostic methods to mammography [6], or as a first screening procedure [7] replacing mammography. It has been suggested that ultrasonography (US) is a useful complementary tool to mammography (MM) in assessing symptomatic breast diseases because it helps in the characterisation and localisation of the breast lesions seen on MM and is not limited by dense breasts [8].

The cancer detection rate with US has been reported to be comparable with mammography [9], while the MM was more accurate in detecting residual disease following bioptic lumpectomy [10]. Mammographic density has been proven as an independent risk factor for breast cancer. Women with dense breast tissue visible on a mammogram have a much higher cancer risk than women with low breast density [11]. However, it has also been reported that use of US as an adjunct to MM, in women with dense breasts and negative results on MM, brought only a limited increase in breast cancer detection rate [12].

Other authors have reported that the addition of automated US to screening MM in women with dense breasts increased the cancer detection yield of clinically important cancers, but it also increased the number of false-positive results [13]. Other diagnostic methods like MRI and tomosynthesis are now emerging as new screening tools for a selected group of breast cancer patients [14].

Ultrasonography, like MM, can define the parenchymal breast pattern accurately. Strong correlation exists between parenchymal breast pattern and demography, parity variables, and breast cancer risk factors [15]. One study

in the USA reported on plans to enact national legislation that would mandate that women are informed when they have mammographically dense breasts and are encouraged to discuss supplemental breast cancer screening with their health providers [16, 17].

But not all breast cancers are detectable with MM or US. A rare breast cancer was reported [18] to be palpable on clinical examination but did not show up on MM or US. For these cases and for women with high risk of breast cancer, authors have reported the need to use MRI in women with suspected breast cancer, especially in those with dense breast parenchyma, for which the sensitivity of both US and MM is low [19].

In addition to cancer detection, both MM and US have been used to diagnose conditions other than cancer [20] or evaluate response to chemotherapy for cancer cases [21]. Lesion size measurements using US have been reported to be more correct than MM, irrespective of breast density [22].

Our study is the first of its kind in Albania and provides evidence from the breast screening data of Albanian women who underwent both MM and US examinations at the American Hospital in Tirana (Albania) from June 2013 to December 2014, in an attempt to explore not only the sensitivity, specificity, and accuracy of MM and US in Albanian settings but also to explore the additional benefits of combining the findings of MM and US in detecting breast malignancies prior to biopsies. The study was approved and received the certificate of approval by the American Hospital Tirana 1 – Ethics Committee for project 2011/11/BCS-AHT, dated 5 Dec 2011.

Material and methods

This study uses data from the breast screening examinations (using MM and US) of Albanian women who requested such a service at the American Hospital in Tirana, between June 2013 and December 2014. Records of over 2200 women who underwent US examination and those of over 1100 women who underwent MM examination, stored into two separate registers, were examined. Patient numeric ID codes were used to match the records of women who had undergone the two examinations during the reported time. Information on age, BI-RADS classification, benign or malign findings on either MM or US, and breast parenchyma type was analysed. Imaging examinations were performed using US (GE Logiq 6, linear transducer 10-15 Mhz) and MM (GE Digital Senograph 2000D Mamography) equipment.

BI-RADS classification was determined using the guidelines published by the American Radiology College in 2013 [23]: (0 – Incomplete, Need Additional Imaging Evaluation and/or Prior Mammograms for Comparison; 1 – Negative; 2 – Benign; 3 – Probably Benign; 4 – Suspicious; 5 – Highly Suggestive of Malignancy; 6 – Known Biopsy-Proven Malignancy). All the cases classified as BI-RADS 4 or 5, as well as BI-RADS 3 that had grown in size from a previous examination, were sent for biopsy. Biopsy confirmations of malignancy as well as lesion size (in cm) were also analysed.

Information on the parenchyma type of the breast was initially coded using the guidelines of the ACR into four groups: type A – the breasts are almost entirely fatty; type B – there are scattered areas of fibroglandular density; type C – the breasts are heterogeneously dense, which may obscure small masses; and type D – the breasts are extremely dense, which lowers the sensitivity of mammography. For the purposes of our study, the breasts were divided into two groups: lower density (type A and B) and higher density (groups C and D).

Statistical methods

MM and/or US (benign or malign) findings were coded as binary variables for each of the individual findings (lesions, nodules, calcifications). New binary variables were coded for a benign or malignant finding in either MM, US, or their combination if any of the individual findings (lesions, nodules, or calcifications) were positive. A binary variable was coded for the parenchyma type of the breast (less dense vs. more dense). BI-RADS classification was coded in the same way as ARC recommendations. Biopsy findings were coded into a binary variable (negative vs. positive finding for malignancy). The age of the patient and size of lesion were originally continuous numerical variables, subsequently coded into categorical variables (five-year age-groups and cutoff point at 2 cm).

Two- and three-way tables were created to analyse/summarise the characteristics of the study population as well as benign and malign findings by method. Sensitivity, specificity, and accuracy were calculated for each of the methods – MM and US (and their combined findings) for suspected malignancies by having the biopsy confirmations as the gold standard. Multivariate analysis (logistic regression) explored the likelihood of having a positive response in biopsy for malignancy and the suspect malignancies in MM, US, and their combination. Additional independent variables were entered into the models related to parenchyma type and lesion size (cutoff point at 2 cm).

Results

The benign and malign findings (percentage) from the MM and US examinations from 245 women by their age group and parenchyma density are shown in Table 1. The results are displayed as the percentage of positive findings by method (MM or US) for any benign (lesions, lymph nodules, or calcifications, fibro-adenomas, or other benign conditions) or malign findings (lesions, lymph nodules, or calcifications). An overall benign or malignant finding was considered positive if any of the above was positive. MM detected suspicions of malignancy in 4.1% while US detected in 5.7% of the cases. If any suspicion of malignancy was detected either in MM or US, the number increased to 7.8% of cases.

Table 2 shows the BI-RADS classification of women examined, as well as the biopsy findings for all those classified BI-RADS 4 and 5 and those classified BI-RADS 3 that had grown in size from a previous examination. The average size of lesion detected using US is also reported by type of finding in biopsy. The women classified as BI-RADS

Table 1. Benign and malignant findings (as percentages) in mammography and ultrasonography, by age-group and parenchyma density

		Mammography								Ultrasonography					Malignancy suspect		
		Patient		Benign (%)			Malign (%)			Benign (%)			Malign (%)		MM %	US %	MM/US %
		Number	Lesions	Nodules	Calcif.	Lesions	Nodules	Calcif.	Cysts	FA	Other	Nodules	Lesions	Nodules	Any	Any	Any
Age-groups	≤ 40	31	48.4	12.9	19.4	3.2	0.0	6.5	54.8	22.6	45.2	58.1	9.7	3.2	6.5	9.7	12.9
	41–45	84	64.3	16.7	25.0	1.2	0.0	0.0	59.5	21.4	32.1	63.1	0.0	1.2	1.2	1.2	2.4
	46–50	43	51.2	18.6	30.2	2.3	2.3	2.3	60.5	32.6	41.9	62.8	7.0	2.3	4.7	7.0	11.6
	51–55	41	61.0	9.8	43.9	0.0	0.0	0.0	51.2	17.1	26.8	58.5	2.4	2.4	0.0	4.9	4.9
	> 55	46	45.7	21.7	45.7	8.7	2.2	6.5	30.4	10.9	32.6	54.3	10.9	6.5	10.9	10.9	13.0
	Total	245	55.9	16.3	32.2	2.9	0.8	2.4	52.2	20.8	34.7	60	4.9	2.9	4.1	5.7	7.8
Paren.	Less dense	90	51.1	17.8	32.2	4.4	1.1	3.3	47.8	17.8	32.2	57.8	6.7	2.2	4.4	6.7	8.9
	Denser	153	58.8	15.7	32.0	2.0	0.7	2.0	54.9	22.2	36.6	60.8	3.9	3.3	3.9	5.2	7.2
	Total	243	56.0	16.5	32.1	2.9	0.8	2.5	52.3	20.6	35.0	59.7	4.9	2.9	4.1	5.8	7.8

Table 2. BI-RADS classification, biopsy findings (as percentages), and average size of lesion (in cm), by age-group and parenchyma density

		BI-RADS (%)							Biopsy (%)				Ave. size (cm)		
		No.	1	2	3	4	5	Total	No.	Ben	Mal	Total	Ben	Mal	Total
Age-group	≤ 40	31	3.2	38.7	45.2	9.7	3.2	100.0	7	71.4	28.6	100.0	0.9	1.5	1.1
	41–45	84	2.4	75.0	20.2	2.4	0.0	100.0	9	55.6	44.4	100.0	1.2	2.3	1.7
	46–50	43	4.7	65.1	18.6	11.6	0.0	100.0	8	50.0	50.0	100.0	0.7	3.0	1.5
	51–55	41	4.9	63.4	26.8	4.9	0.0	100.0	2	50.0	50.0	100.0		1.4	1.4
	> 55	46	2.2	67.4	17.4	4.4	8.7	100.0	10	40.0	60.0	100.0		3.0	3.0
	Total	245	3.3	65.3	23.7	5.7	2.0	100.0	36	52.8	47.2	100.0	0.9	2.5	1.8
								$p = 0.009$				$p = 0.792$			
Paren.	Less	90	3.3	63.3	24.4	6.7	2.2	100.0	15	66.7	33.3	100.0	1.1	4.4	2.2
	Denser	153	3.3	66.7	22.9	5.2	2.0	100.0	21	42.9	57.1	100.0	0.7	1.9	1.6
	Total	243	3.3	65.4	23.5	5.8	2.1	100.0	36	52.8	47.2	100.0	0.9	2.5	1.8
								$p = 0.984$				$p = 0.158$			

4 or 5 amount to 7.7% of the total. 47.2% of the 36 cases for biopsy came back as positive for malignancy, with an average lesion size of 2.5 cm. On average, the lesion size was reported to be 2–3 times bigger in women with a malignant finding in the biopsy.

The sensitivity (SN), specificity (SP) and accuracy (AC) of MM, US, and their combination (MM|US) are shown in Table 3. The gold standard used was the biopsy. The SN of MM is higher than US for breasts with lower density (80% vs. 60%) but lower than the combined MM|US (100%). The SN of MM decreased with increase in breast density, while for US it remained the same. Overall SN increased from MM alone and US alone when MM|US findings were combined (53% and 59% vs. 85%). Accuracy for MM was higher in less dense breasts and higher for US in denser breasts. The accuracy in detecting malignancy for low-density-breast women was 90% for MM, 70% for US, and 90% for combined. For high density breasts, the accuracy was 65% for MM, 79% for US, and 82% for combined findings. Interestingly, the accuracy of both MM alone and US alone was similar for lesions independently of their size, but the combined findings were 10% higher for breasts with higher density.

We analysed four different models exploring the likelihood of having a malignant biopsy by using the following as predictors: MM malignant findings and parenchyma type, US malignant findings and parenchyma type, MM|US malignant findings and parenchyma type, and finally MM|US malignant findings, parenchyma type, and size of lesion (cut-off at 2 cm) (Table 4).

The findings suggest that a malignant finding in MM alone or US alone increases the chances of having a malignant finding in the biopsy – as compared to a lack of malignant finding in MM or US alone – by several fold (MM: OR = 25.96, $p = 0.007$; US: OR = 15.89, $p = 0.005$). The likelihood of a malignant finding in biopsy is also higher for breasts with higher density (OR increases gradually from MM alone to US alone to their combination, from 4 to 7 times). The combined model (malignant finding in either MM or US) indicates that the likelihood of a malignant finding in biopsy

Table 3. Sensitivity, specificity, and accuracy (in percentage) by method, parenchyma density, and size of lesion

	Parenchyma	Sensitivity (%)			Specificity (%)			Accuracy (%)		
		Value	95% CI		Value	95% CI		Value	95% CI	
MM	Less dense	80.0	28.4	99.5	100.0	69.2	100.0	90.0	70.0	100.0
	Denser	41.7	15.2	72.3	88.9	51.8	99.7	65.0	47.0	83.0
	Total	52.9	27.8	77.0	94.7	74.0	99.9	74.0	61.0	87.0
US	Less dense	60.0	14.7	94.7	80.0	44.4	97.5	70.0	43.0	97.0
	Denser	58.3	27.7	84.8	100.0	66.4	100.0	79.0	65.0	94.0
	Total	58.8	32.9	81.6	89.5	66.9	98.7	74.0	60.0	88.0
MM/ US	Less dense	100.0	47.8	100.0	80.0	44.4	97.5	90.0	77.0	100.0
	Denser	75.0	42.8	94.5	88.9	51.8	99.7	82.0	65.0	99.0
	Total	82.4	56.6	96.2	84.2	60.4	96.6	83.0	71.0	96.0
	Size of Lesion	**Sensitivity (%)**			**Specificity (%)**			**Accuracy (%)**		
		Value	**95% CI**		**Value**	**95% CI**		**Value**	**95% CI**	
MM	< 2 cm	57.1	18.4	90.1	87.5	47.3	99.7	72.0	49.0	96.0
	≥ 2 cm	50.0	11.8	88.3	100.0	2.5	100.0	75.0	–	100.0
	Total	52.9	27.8	77.0	94.7	74.0	99.9	74.0	61.0	87.0
US	< 2 cm	71.4	29.0	96.3	75.0	34.9	96.8	73.0	49.0	97.0
	≥ 2 cm	50.0	11.8	99.6	100.0	2.5	100.0	75.0	–	100.0
	Total	58.8	32.9	81.6	89.5	66.9	98.7	74.0	60.0	88.0
MM/ US	< 2 cm	85.7	42.1	99.6	62.5	24.5	91.5	74.0	51.0	97.0
	≥ 2 cm	66.7	22.3	95.7	100.0	2.5	100.0	83.0	–	100.0
	Total	82.4	56.6	96.2	84.2	60.4	96.6	83.0	71.0	96.0

Table 4. Comparison of statistical models (odds ratios) of likelihoods of finding malignancy in biopsy by examination, parenchyma density, and size of lesion

Variable	MM	US	MM|US	MM|US size 20
MM malignancy	25.964759**			
Denser parenchyma	3.9721556	4.1103288	7,136943	24.089513*
US malignancy		15.890074**		
MM|US malignancy			44.549796**	24.089513*
Lesion size > 20 cm				32.416067
_cons	0.18244225*	0.16235036*	0.04464697**	0.01484249*

** p < 0.05; ** p < 0.01; *** p < 0.001*

increases to 44 times (OR = 44.55, $p = 0.001$). If size of lesion is included in the model the likelihood for malignant biopsy is as follows: OR = 24.1, $p = 0.039$ and for a lesion size over 2 cm: OR = 32.4, $p = 0.056$.

Discussion

Breast cancer screening is linked to decreased mortality and improved outcome after early detection. As breast screening methods, both MM and the US have great importance in early detection of breast cancer – as outlined in the ACR recommendations [1].

A recent paper [24] has confirmed an association between breast densities and reduced mammographic SN and SP, while another study has demonstrated the link between increased MM SN and low density in obese women whose breasts are fattier [25]. The inverse relationship between MM SN and breast density, and the increased risk for cancer of denser breasts, caused legislation [26] to be enacted that mandates informing women with high-density breasts of the increased risk for cancer and for the need of additional screening procedures [27].

While MM detects the majority of malignant findings, especially in low-density breast tissue [28], other studies state that very often US is used as an additional screening method because it is not limited by breast density, it does not use ionising radiation, and does not have the need for breast compression [29].

Our study, the first of its kind in Albania, confirmed the higher accuracy of MM in detecting malignancy in low density breast, while US had the higher accuracy in detecting malignancy in higher-density breasts.

Several studies have reported that US is a useful complementary tool to MM in assessing symptomatic breast diseases [30], by increasing the SN [31] and detection rate

of early cancers [32]. One study reported 4.6 additional cancers among 1000 reported by adding US to MM examination [33]. It has also been reported [34] that the population of patients undergoing screening US can be expected to differ from the average screening mammography population in that they will have higher breast density, they will be younger, and they may also have higher breast cancer risk than the population undergoing screening mammography. Higher risk for cancer [35] has been reported also by a study that used US in addition to MM to originally detect pathologic nipple discharge.

Only one study cautioned about using US in addition to MM for women with higher-density breasts, on the argument that despite the increased costs, the benefits produced were relatively small [36]. Another study produced evidence on US reducing the false negative rate of MM (usually 15%) among patients with palpable breast masses [37].

Our study provided evidence and confirmed the synergy and additional benefits of combining the findings of MM and US in increasing the likelihood of predicting malignancy in breasts in hospital settings in the Albanian capitol, Tirana.

While only 245 women who sought diagnostic services at the American Hospital in Tirana from June 2013 to December 2014 had undergone both MM and US breast screening examinations (out of 1100 MM and 2200 US), we were able to confirm that if a woman had either an MM or a US malignancy finding, the likelihood of having a malignancy confirmed by biopsy increased 44 times compared to those who did not have such findings in MM or US. The likelihood increased from 4 to 7 times for women with higher-density breasts. If the size of the lesion was entered into the models, the likelihood for malignant biopsy increased to 32 times for lesions over 2 cm.

The implication for the healthcare providers and the patients involved is that, for all high-density-breast women who have suspicion of malignancy in either MM or US, the chances are higher that their biopsy is positive for malignancy. While procedures like biopsy and surgery involve increased costs, time off work, and emotional distress, the ability to catch breast cancer early would increase the chances for survival [3].

Previous studies have suggested that US was as good as MRI in detecting lesion size, including measurements in post-chemotherapy situations [38], and slightly better than those of MM [39]. In our study, the average size of lesion detected was 2.5 cm. For any lesion over 2 cm detected in US, the chances increased that the biopsy would confirm malignancy in higher-density-breast women. Other diagnostic procedures, like tomosynthesis, could be used in the future to reduce recall rates [40], benign biopsy rate, or short-term follow-up [41].

Our study provided evidence from studying a subset of Albanian women during the period 2013–2014. It is unclear how the women that sought services at the American Hospital differ from other Albanian women – this would warrant another nation-wide survey. The sample size did not allow for detailed study of the type of cancers detected. Nonetheless, this study recommends that both MM and US are suggested to women who seek breast screening examinations, especially for higher-density breasts.

The authors declare no conflict of interest.

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