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Characteristics of breast cancer detected by supplementary screening ultrasonography

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PERSPECTIVE

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Introduction

Dense breast tissue increases the risk of breast cancer [1,2] and can mask breast cancer, thereby resulting in false-negative mammography examinations [3]. Recently, legislation has been passed in many states of the United States that requires direct notification to women of their breast density on screening mammography, and information on supplementary screening tools such as ultrasononography (US) or magnetic resonance imaging (MRI) for women with dense breasts [4]. Thus, after the enactment of this law, the number of supplementary screening US evaluations performed in women with mammographically dense breasts in the United States has increased [5–7]. This review presents the cancer yield and the clinico-pathological characteristics of cancer detected by screening US only, including those found through supplementary hand-held screening US and automated breast ultrasonography (ABUS) in various countries.

Cancer Yield of Hand-Held US in Western Women at High Risk of Breast Cancer

In asymptomatic women, supplementary hand-held US performed by radiologists detected 1.9–6.8 additional cancers per 1,000 women [8–13]. In studies that included women at high risk of breast cancer, supplementary hand-held US identified 1.9 to 4.2 additional cancers per 1,000 women, and 83% to 100% of the US-detected cancers were invasive [8,10–12]. The median or mean tumor size of the invasive cancers was 10 mm [8,12], and 73% of the 15 invasive cancers were less than 10 mm in size [10]. About 89% to 97.3% of the invasive cancers were node-negative [8,12]. In a study that had screening mammography and US performed in a randomized order and that included women with dense breasts and with at least one high risk factor for breast cancer, supplementary US identified 12 additional cancers (4.2 additional cancers per 1,000 women) [8]. Only one of these 12 cancers (8.3%) was Breast Imaging Reporting and Data System (BI-RADS) category 5 on the supplementary US; 11 (91.6%) were invasive, and 89% (8 of 9 with staging) were node-negative [8]. In a large series study by Girardi et al. [12], 22,313 women with negative mammography were included and 9.8% of these women had a personal history of breast cancer. Forty-one cancers were identified on the supplementary US; thus, supplementary US identified 1.9 cancers per 1,000 women [12]. Of these 41 cancers, 37 (90%) were invasive cancer and 36 (97.3%) were node-negative [12].

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In women with a personal history of breast cancer, more cancers were found: 5.5 cancers per 1,000 women compared with 1.5 cancers in women without a personal history of breast cancer [12]. In a study by De Felice et al. [11], women without suspicious lesions (categories 4 and 5) on mammography underwent supplementary US. Supplementary US detected 6.8 cancers per 1,000 women, higher than in the other studies because of the different study population [11].

Cancer Yield of Hand-Held US in Asian Women at Average Risk of Breast Cancer

In women at average risk of breast cancer, supplementary screening US can also identify breast cancer [9,13]. In two studies that included Asian women at average risk of breast cancer and negative or benign mammography results and that excluded women with a familial or personal history of breast or ovarian cancer, with chest irradiation, and with a *BRCA* mutation, supplementary hand-held screening US by radiologists identified 2 to 3.3 additional cancers per 1,000 women [9,13]. In a study by Moon et al. [13], four cancers in 2,005 women were found and were assessed as BI-RADS category 4 or 3 on the supplementary US. Additional 1.8 cancers per 1,000 women were found in women with dense breasts who also underwent supplementary screening US more frequently, whereas 2.9 cancers were found in women with fatty breasts [13]. In a study by Chang et al. [9], all five cancers were found in women with heterogeneously or extremely dense breasts. Of the supplementary US-detected cancers in Asian women at average risk of breast cancer, only 50% to 60% of cancers were invasive cancer [9,13], which was lower than the invasive cancer frequency of 83.3% to 91.7% found in studies performed in Western countries, which included women at high risk of breast cancer [8,12]. This difference may be attributed to the inclusion of women at average risk of breast cancer rather than to any difference in ethnicity [9,13].

Prevalence Versus Incidence Screening

Prevalence screening is defined as the first round of screening using a screening tool, and incidence screening is defined as the subsequent round of screening. Prevalence screening with US can detect more cases of breast cancer and more advanced breast cancer cases than incidence screening [7]. One point of interest is whether or not even incidence screening with US can detect small invasive node-negative cancer. To define the detection benefit of supplementary screening US on incidence screening, the clinical and pathological characteristics between the cancers detected on prevalence and incidence screening US should be compared in the same study population. Berg et al. [14] reported the results of three rounds of screening US in the same study population. In the second and third rounds, 20 cancers were found on the supplementary US; thus, 3.7 additional cancers per 1,000 women per year were identified [14]. In each subsequent round, the detection rate of 3.7 cancers per 1,000 women was lower than 4.2 cancers per 1,000 women detected on prevalence screening [8,14]. Of the 20 cancers on the supplementary US, 19 (95%) were invasive cancer. Thus, upon incidence screening, US could identify additional cancers, particularly invasive cancer, although the cancer yield decreased.

Supplementary Screening US in the State of Connecticut in the United States

Connecticut was the first state to pass legislation requiring direct notification to women of their breast density and supplementary screening tests, and the first state to require insurance companies to cover supplementary screening US [4–7]. Thus, Connecticut is the ideal place to assess the potential of supplementary screening US to detect mammographically occult breast cancer in women with dense breasts [6]. After the legislation was passed, Hooley et al. [4] retrospectively investigated the cancer yield and the characteristics of supplementary US-detected cancers in women with dense breasts for 1 year. Supplementary US examinations were performed by technologists. Three cases of cancer were identified by supplementary US, and the overall cancer yield was 3.2 cancers per 1,000 women. Two of the three cancers (66.7%) were invasive cancers, which were 9 mm and 5 mm in size. All invasive cancers were node-negative. After the new law was passed, supplementary screening US performed by technologists could identify additional cancers in women with dense breasts. These results from technologists were comparable with the cancer detection rates by radiologists [8,9,11–15].

To ascertain whether the implementation of a formal screening program in Connecticut affected the cancer yield of supplementary screening breast US, data after and prior to the passage of the law were compared [5]. Supplementary US examinations were performed by technologists. After the new legislation was introduced, women with older age, menopause, and dense breasts, and those without a family history of breast cancer underwent supplementary screening US more frequently [5]. In the pre-law group, supplementary screening US did not detect any malignancy [5]. In the post-law group, 10 cancers were found on supplementary screening US; thus, 1.8 cancers per 1,000 women were identified [5]. All 10 cancers were invasive cancers with a mean size of 9.7 mm, and 77.8% (7 of 9 with staging) were node-negative [5].

To ascertain the detection benefit of continuing annual US

screening after a formal screening program, the cancer detection rates of the first and the second year after the enactment of the new law were investigated using multicenter data [6,7]. In the first year, 28 cancers among 8,647 women were found on supplementary US; thus, supplementary US identified 3.2 cancers per 1,000 women [6]. In the second year, 24 cancers among 10,282 women were found; thus, 2.3 cancers per 1,000 women were found on supplementary US [7]. Although more women underwent supplementary screening US in the second year, the cancer detection rates were comparable [6,7]. Thus, in practice, supplementary screening US performed in both the first and the second year after the enactment of the new law was able to detect additional cancers.

Automated Breast US

Supplementary hand-held US examinations are performed by radiologists or technologists, are labor-intensive and operator-dependent, and are not standardized for acquisition and recording images. The number of supplementary screening US examinations performed continuously increased after the Connecticut legislation was passed [5–7]. ABUS can standardize imaging acquisition and recording and can separate the performance and interpretation of US examinations [16]. Kelly et al. [17] evaluated the cancer detection rate of ABUS (SonoCine, Reno, NV, USA). Among 6,425 examinations of mammography and ABUS, 23 cancers were found on supplementary ABUS only; thus, 3.6 cancers per 1,000 examinations were identified [17]. Of the 23 cancers, 17 (73.9%) were invasive cancer and 15 (88.2%) were less than 20 mm in size. In another study using three-dimensional ABUS (Somo V, U-Systems, Sunnyvale, CA, USA), 15318 asymptomatic women 25 years old or older with heterogeneously or extremely dense breasts were included [18]. Thirty cancers were detected on supplementary ABUS; thus, supplementary ABUS identified two cancers per 1,000 women [18]. Twenty-eight of 30 cancers (93.3%) were invasive, and the mean lesion size was 12.9 mm [18]. Of the 27 invasive cancers with staging, 25 (92.6%) were node-negative [18]. Supplementary ABUS can detect small invasive node-negative cancers. The cancer yield, the detected cancer size, the frequency of invasive tumors, and the node status of supplementary ABUS are similar to those of supplementary hand-held US.

Mortality Reduction

The efficacy and effectiveness of supplementary screening US have been proven through many studies [4–10,12,13,17–19]. About 50% to 100% of breast cancers identified by supplementary hand-held US or ABUS were small invasive node-negative cancers [4–10,12,13,17–19]. Thus, we assume that supplementary screening US can reduce mortality. However, a majority of women undergoing supplementary screening US are at average risk and no methodologically sound evidence for mortality reduction is available justifying the routine use of US as an adjunct screening tool in such a population [20]. The efficiency of supplementary screening US, that is, whether it is worth performing in daily practice, has not yet been proven. Problems related to high false-positive rates such as high short-term follow-up rates and high benign biopsy rates need to be solved along with issues of mortality reduction in order to achieve maximum efficiency.

Conclusion

No medical organization recommends supplementary screening US on the basis of breast density alone. The American College of Radiology and the Society of Breast Imaging recommends supplementary screening US only for women with a greater than 20% lifetime risk of developing breast cancer who cannot undergo MRI examinations. Currently, only legislation recommends supplementary screening US for every woman with dense breasts irrespective of the risk of breast cancer. In Korea, supplementary screening US examinations have been performed frequently in women with dense breasts. Clinicians and women need to first discuss breast density and individual risks of developing breast cancer, and then these women can decide whether or not to undergo supplementary screening US. A randomized controlled trial, although difficult, is needed.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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