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THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: COMMENTARY

Commentary ACOG Practice Bulletin July 2017: Breast Cancer Risk Assessment and Screening in Average-Risk Women

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ABSTRACT

Screening mammography reduces breast cancer mortality in average-risk women. However, adverse consequences include false-positive findings possibly leading to benign breast biopsies and patient anxiety. There is also potential for overdiagnosis and overtreatment. Differences in how to balance benefits and harms have led to varying recommendations by the U.S. Preventive Services Task Force, the American Cancer Society, the National Comprehensive Cancer Network and the American College of Radiology/Society of Breast Imaging. These recommendations differ with respect to what age to start, what age to stop, and frequency of screening in average-risk women. Most recently, the American College of Obstetricians and Gynecologists have issued updated clinical management guidelines for breast cancer risk assessment and screening in average-risk women that aim to maximize the benefits of screening while keeping in mind the potential harms of false-positive results. This commentary summarizes the clinical management guidelines of the American College of Obstetricians and Gynecologists Practice Bulletin July 2017 for breast cancer risk assessment and screening in average-risk women. We review evidence of the benefits and adverse consequences of screening mammography and briefly discuss new advances in breast cancer screening with recent technologies such as digital breast tomosynthesis and risk-adapted screening.

SUMMARY OF CLINICAL MANAGEMENT GUIDELINES

Currently, breast cancer screening recommendation guidelines vary between groups, creating confusion for patients and healthcare providers. In July 2017, the American College of Obstetricians and Gynecologists (ACOG) issued clinical management guidelines for breast cancer risk assessment and screening in average risk women.¹ The recurring theme throughout these recommendations is shared decision making, a process in which patients and physicians share information, express preferences, and agree on a plan. These recommendations were made with the goal of assisting women in balancing their own values regarding potential benefits and harms of screening and making personalized choices within a range of reasonable

options. While ACOG acknowledges the overall benefits of screening mammography such as decreased breast cancer mortality and potential reduced need for advanced cancer treatment, they also consider potential adverse consequences such as false-positive test results (leading to callbacks and biopsies), anxiety/distress, risk of not attend following screening round, discomfort, overdiagnosis, overtreatment and radiation exposure. They acknowledge that the assessment of harms can be subjective and may be valued differently between individuals and groups, proposing that the latter is a likely contributor to the varying recommendations between major groups.

In summary, ACOG guidelines state that average-risk women should be offered screening mammography at age

40, and not before. Due to improved benefit-to-harm ratio with age, if women decide not to screen in their 40s, it is recommended they begin no later than 50 years of age and continue until at least 75 years of age. The recommended age at which to begin and stop screening mammography and the interval to be screened (every 1 or 2 years) should be agreed upon by the patient and her physician through a shared decision making process. The decision of when to stop screening should be informed by the woman's general health and estimated life expectancy. If the life expectancy is less than 10 years, the woman is unlikely to have appreciable mortality reduction from mammographic detection of an early breast cancer.

ACOG notes that there is no standardized approach to office-based breast cancer risk assessment in the USA. They recommend that breast cancer risk be periodically assessed by healthcare providers. The AGOG guidelines recommend that patients with potentially increased breast cancer risk undergo further risk assessment, counseling regarding breast cancer surveillance, risk reduction and potential genetic testing. Causes of increased breast cancer risk include family history of breast cancer, ovarian cancer or other hereditary breast and ovarian associated cancer, known deleterious gene mutation, prior breast biopsy with specific pathology such as atypical hyperplasia and lobular carcinoma *in situ*, early menarche, late menopause, nulliparity, prolonged hormone therapy with estrogen and progesterone, not breast feeding, increasing age, certain ethnicities (Ashkenazi Jewish women), higher body mass index, alcohol consumption, smoking, dense breast on mammography, prior exposure to high-dose therapeutic chest irradiation in young women. Further risk assessment can be performed with a validated online assessment tool such as Gail, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, Tyrer-Cuzick or the Claus model. In addition questionnaires, assessment of breast density and using a panel of common low penetrance single nucleotide polymorphisms might be used to further stratify the screening population.

For asymptomatic, average-risk women, the ACOG guidelines recommend offering screening clinical breast exams following informed shared decision-making, every 1–3 years for women 25–39 years of age and annually for women 40 years or older. Breast self-examination is not recommended for average-risk women due to the lack of evidence regarding benefits and known risk of harm/false-positive results. The guidelines also recommend average-risk women to be educated about “breast self-awareness,” *i.e.* a women's self-awareness of the normal appearance and feel of her breasts, and inform her physician if a change or potential problem is identified. They distinguish this from breast self-examination in which a woman examines her breasts in a systematic way on a routine basis.

Due to varying judgments of the benefits and harms of screening, the ACOG guidelines differ from the recommendations issued by the U.S. Preventive Services Task Force, the American Cancer Society, the National Comprehensive Cancer Network and the American College of Radiology/Society of Breast Imaging (Table 1).

BENEFITS AND ADVERSE CONSEQUENCES OF SCREENING MAMMOGRAPHY

Both the U.S. Preventive Services Task Force and the American Cancer Society published systematic reviews of the evidence for breast cancer screening in average-risk women derived from available randomized and observational studies.^{2,3} There is consensus that screening mammography reduces mortality, yet the magnitude of reduction varies across study types and duration of follow-up. The U.S. Preventive Services Task Force further analyzed results by age and found that the risk of advanced breast cancer ($\geq$ Stage IIB) is reduced with screening mammography in women $\geq$ 50 years. The American Cancer Society investigated the impact of screening mammography on life expectancy. Their systemic review states there is high-quality evidence that mammographic screening increases life expectancy by decreasing breast cancer mortality. It must be noted that screening mammography may also have adverse consequences. Both systematic reviews acknowledge the occurrence of false-positive results, patient anxiety and discomfort during imaging and overdiagnosis and overtreatment. Although the U.S. Preventive Services Task Force reported the results of a modeling study estimating that the number of deaths caused by mammography radiation-induced cancer was 2 per 100,000 among women aged 50–59 years screened biennially and 11 per 100,000 among women aged 40–49 years screened annually, a more recent study concluded that the benefits of annual screening mammography starting at age 40 years significantly outweigh the risk of dying from a mammography radiation-induced cancer.⁴ The NHS Breast Screening Programme UK (NHSBSP) reviewed the number of deaths due to radiation-induced cancers and the number of lives saved due to digital breast screening in England. The main findings are that the risk of a radiation-induced cancer for a woman attending two views full field digital mammography screening within the NHSBSPs is between 1 in 49,000 and 1 in 98,000 per visit. It is estimated that about 400 to 800 cancers are detected by the NHSBSP for every cancer induced and the mortality benefit of screening exceed the radiation-induced detriment by about 150:1 to 300:1. (gov.uk Radiation Risk with digital mammography in breast screening).

Due to the emphasis on different outcome aspects and analysis approaches of the available data, screening recommendations differ between issuing societies (Table 1). The updated ACOG recommendations aim to maximize benefits of screening in the setting of informed decision-making while keeping in mind the potential harms. In the UK, women at average risk of breast cancer aged 50–70 are invited mammography screening every 3 years. Women who are BRCA1/2 gene mutation carriers or not tested and with an equivalent risk, with TP53 Li Fraumeni syndrome, AT homozygote or supradiaphragmatic radiotherapy before the age 30 are offered annual mammography $\pm$ MRI. It was decided by an independent panel in 2012 that starting breast screening before the age of 50 cannot be routinely recommended and the advantages and disadvantages have to be further investigated.⁵ However in the UK Age trial at 17 years' follow-up, there was reduction in breast cancer mortality in women aged 40–49 years who underwent breast cancer screening with annual mammography without a significant increase in overdiagnosis.⁶ The same

Table 1. Recommendations for Breast Cancer Screening in Average Risk Women

	American College of Obstetrics and Gynecologists	U.S. Preventive Services Task Force	American Cancer Society	National Comprehensive Cancer Network	American College of Radiology/Society of Breast Imaging
Clinical breast examination	May be offered every 1–3 years for women 25–39 years and annually for women 40 years and older	Insufficient evidence to recommend for or against	Does not recommend	Recommend every 1–3 years for women 25–39 years and annually for women 40 years and older	–
Mammography initiation age	Offer starting at age 40 years. Initiate at ages 40–49 years after counseling, if patient desires. Recommend by no later than age 50 if patient has not already initiated	Recommend at age 50 years. Age 40–49 years: the decision to start screening mammography in women before age 50 years should be an individual one	Offer at ages 40–45 years. Recommend at age 45 years	Recommend at age 40	Recommend at age 40
Mammography screening interval	Annual or biennial	Biennial	Annual for women aged 40–54 years. Biennial with the option to continue annual screening for women 55 years or older	Annual	Annual
Mammography stop age	Continue until age 75 years. Beyond age 75 years, the decision to discontinue should be based on shared decision-making process that includes a discussion of the women's <i>health status and longevity</i>	The current evidence is insufficient to assess the balance of benefits and harms of screening mammography women 75 years and older	When life expectancy is less than 10 years	When severe comorbidities limit life expectancy to 10 years or less	When life expectancy is less than 5–7 years

trial also addresses the radiographic findings of women aged 40–48 years presenting with interval cancers. Interval cancers in this population were small, occurred in dense breasts and false-negative rates were similar to the older populations. The most common mammographic feature that was missed constituted granular microcalcification.⁷

There is currently the AgeX trial ongoing to reliably establish the risks and benefits of an additional screening mammography in both women aged 47–49 and women after age 70.

NEW AVENUES IN SCREENING MAMMOGRAPHY

Digital breast tomosynthesis

Breast density, or breast composition, indicates the amount of fibroglandular tissue in relation to fatty tissue within the breast. It has been recognized that the sensitivity of screening mammography for breast cancer detection decreases with increasing breast density due to a “masking effect,” *i.e.* the overlap with normal breast tissue thus obscuring breast lesions.⁸ To overcome this limitation of mammography, digital breast tomosynthesis (DBT), a technology providing three-dimensional images of the breast, has been implemented in breast imaging. A growing body of evidence indicates that in women with higher breast density, there is improved cancer detection and reduced recall rates when adding tomosynthesis to

mammography with an additional cancer detection rate between 1.8 and 2 depending on study.^{9–11} A recent meta-analysis which included data, both studies conducted in both in the USA and Europe demonstrated that DBT in combination with mammography has higher invasive cancer detection rates compared to mammography also and thus is able to increasing breast cancer screening effectiveness. DBT can reduce recall rates, programme costs and patient anxiety caused by a false-negative recall.¹²

Risk-adapted screening

Mammographic breast density has been identified as a strong and independent risk factor for the subsequent development of breast cancer conferring a 5-fold risk in pre-menopausal women and 2.5-fold in the post-menopausal population when compared with the lower breast density and falls to 60% of sensitivity of mammography.^{13,14} An analysis of 365,426 women from the American Breast Cancer Surveillance Consortium demonstrated that advanced stage interval cancers were highest in women with extremely dense breasts and a 5 year risk of 1.67% or more and in those with heterogeneously dense breasts and a 50 year risk of 2.5% or more.

In the context of shared decision-making as advocated by ACOG, another avenue of exploration in breast cancer screening

is the implementation of risk-adapted breast screening strategies incorporating breast density. This could further refine the risk assessment process in average-risk women, and based on risk stratification patients may then be offered risk-adapted screening with an individually adjusted starting age and different imaging modalities such as mammography/DBT-only, supplemental breast ultrasound¹¹ or functional imaging tests such as Contrast Enhancement Spectral Mammography and MRI annually, bi- or even triennial based on national recommendations.

In conclusion, according to the recent ACOG recommendations, average-risk women may start screening mammography at the age of 40, no later than age 50, and continue until at least 75 with the age to start and stop screening mammography and the

frequency determined through a shared decision-making process on an individual basis. It remains to be seen if such conversations can be routinely incorporated into busy clinical practices and how clinician values regarding benefits and harms of mammography will influence this discussion. The ACOG approach will likely lead to less women starting mammography screening at 40, as we recommend based on ACR/SBI guidelines. Although risk-assessment including familial and personal risk factors is part of this shared decision making, risk-adapted screening strategies that include a mammographic breast assessment or the use of other available imaging modalities such as DBT, supplemental ultrasound or MRI are not yet part of the recommendations and should be considered in the future.

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