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Tailored screening for breast cancer in premenopausal women: not just looking at sensitivity, but aiming to reduce burden

“The scope of individualized risk-based screening is to offer more sensitive and intensive screening to women at higher risk. Little consideration has been given to the other side of the coin, namely the need for reducing the burden of screening in women who are assessed as being at lower risk.”

The recent revision of the mammography recommendations by the US Preventive Task Force raised contrasting comments in scientific and lay media [1]. The issue of screening mammography in younger women is a traditional topic of controversy, exemplified by the disagreement that happened in the USA at the NIH–NCI Consensus Conference in 1997 on screening in 40–49-year-old women [2]. In Europe, screening mammography has been discussed for 30 years, since the Forrest report in the UK proposed – and implemented – the launch of a nationally organized population-based screening program; this represents the origin of the successful screening program that is still ongoing. The European literature was, at that time [3], oriented to prudence concerning mammography screening in premenopausal women, highlighting the uncertain/insufficient evidence of efficacy for reducing breast cancer mortality in those younger than 50 years of age. In the 1990s, the need for an age-based trial emerged [4], with a design that could disentangle the uncertainty regarding efficacy in 40–50-year-old women. Of the planned studies, only the ‘Age’ trial – mammography in the under 50s – was funded and conducted [5]. It published the first results, confirming a significant (although smaller than that observed in those over 50 years of age) effect of mammography screening in younger women after 10 years (17%) [6]. In this study, for the first time, the effect was only due to screening of women who started screening in premenopause, being enrolled at 40–41 years of age. The characteristics of the tumors diagnosed in the trial, as screen-detected or interval cancers, have been investigated [7]. Breast density was a strong determinant of the probability of having an interval cancer (i.e., a factor strongly conditioning screening sensitivity).

A recent report on the implementation of the EU Council Recommendations on cancer screening [8] confirmed the initiation of starting service screening at 50 years of age and the diffusion of screening in Europe. However, in recent times, it has been considered that breast cancer screening programs in several countries could extend service screening to those under 50 years of age, with different age ranges and screening protocols. Screening younger women (i.e., those aged 40–49 years) was implemented in Sweden many years ago [9]; in the UK, the age range was recently reduced to 47 years [10]. Recently, in Italy, regional public screening programs started to screen at 45 years of age, in accordance with a document of the National Monitoring Centre [11].

An individualized approach

In an editorial published in *Annals of Internal Medicine*, Kerlikowske discussed the importance of individual risk in decision-making relating to prevention and asked for an ‘improvement of primary and secondary breast cancer prevention effectiveness by implementing risk assessment in primary care and mammography facilities and providing tailored recommendations for prevention based on individual risk’ [12]. However, she acknowledged that the evidence for cancer prevention using risk models had limitations and asked for further research to be conducted into these limitations. In 2008, Cuzick evaluated the state of the art of risk assessment, confirmed the relevance of mammography density as the single most important factor in terms of population attributable risk, and concluded that there was a need for more learning about how to combine different factors and counseling [13].

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Eugenio
Paci

Author for correspondence:
ASP Laziosanità, Via di S. Costanza,
53, 00198 Rome, Italy
Tel.: +39 068 306 0384
Fax +39 068 306 0469
paci@asplazio.it



Paolo
Giorgi Rossi

ASP Laziosanità, Via di S. Costanza,
53, 00198 Rome, Italy

consideration has been given to the other side of the coin, namely the need for reducing the burden of screening in women who are assessed as being at lower risk by, for example, reducing screening frequency. Longer intervals and greater attention paid to a lower recall rate in women with low density of the breast will offer an advantage for the individual woman (reduced potential harms) and lower costs for the screening program.

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In the US Preventive Task Force recent recommendations, the issue of the harms related to screening in younger women was discussed in depth, but the conclusion of the report – suggesting a 2-year interval and averaged screening – in our opinion, is unlikely to be accepted by women and professionals, particularly in countries where opportunistic screening is already so widespread in young women.

Critical & open issues for tailored screening

The usual method to fight the lower sensitivity of screening in younger women is shortening interscreening interval. In women aged between 40 and 50 years, interscreening intervals of 12 (or 18) months have been suggested. The implication is a lower cost–effectiveness, mainly owing to the very low detection rate at the incidence rounds (i.e., the rounds following the first one, called the ‘prevalence round’) and its effect on positive predictive value (i.e., strong decrease in comparison with older women). A tailored screening will increase the round sensitivity for women at raised risk (we do not consider here the genetically susceptible women who are BRCA1- and BRCA2-positive). In lower risk women, an interval of 2–3 years might be considered safe and effective. Globally, the more intensive screening should determine a greater mortality reduction for women at raised risk, without impact on the efficacy for lower risk women. On the other hand, intensive screening will increase the screening burden only for women at raised risk, but should be balanced by a decreasing burden for lower risk women.

Many critical issues are still open to discussion, including a homogeneous classification of breast density, and the relevance of other risk factors as assessed by risk models. Breast density is much more comparable and objective in the new era of digital mammography. Algorithms for the quantitative or semi-quantitative measure of the density are in use, but still much work needs to be done to harmonize common procedures and agree measurements. The use of breast density as a predictor seems to be affected by the same problem. Building better models, including the possible use of predictive biomarkers, is still a research objective, but it could be the object of translational research if a tailored screening program were to be implemented as a trial. To increase screening sensitivity in a dense breast it has been suggested that ultrasound should be added to the program and the concern today is regarding sustainability of this practice in mass screening.

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Further investigation is needed concerning the modification of the breast cancer risk in relationship with a change in density of the breast. The risk models, including the Gail model and variants, have been shown to predict the expected number of cases, but are weak in the discrimination power (i.e., the ability to identify who will have a cancer in a given period).

Conclusion

The proposal of tailored screening protocols for women according to the breast density and risk assessment should be evaluated not only with the aim to increase sensitivity for women at raised risk, but to maximize the harm:benefit ratio for the whole population and the sustainability of programs (i.e., including a strategy for decreasing the burden [recall rates and overdiagnosis] for women at lower risk). Breast cancer screening tailored according to the level of risk should be evaluated in prospective trials in order to assess not only the possible contribution of this practice to improve surrogate indicators (such as severity of the disease, stage at diagnosis, detection at screening and interval cancer rates) for women at raised risk of cancer, but also to estimate the impact in terms of possible harms and costs related to the more intensive approach.

In the evaluation of tailored screening program and in the assessment of the harm:benefit ratio, a noninferiority approach is suggested, considering that the tailored screening policy should at least achieve similar, if not better, sensitivity than the standard annual screening. The other side of the identification of a raised risk group is the possibility of suggesting a less aggressive protocol for women at lower risk. It is extremely important to have the opportunity of reducing the tests performed, decreasing the number of mammograms, false-positive results, overdiagnosis and the related harms owing to screening.

Recommendations in Europe and the USA regarding mammography screening in premenopausal women highlighted the need for

research in this field, acknowledging the difficulties in achieving important benefits and the risk of harms in these women. In the assessment of risk and possible selective screening we see the opportunity for both increasing efficacy on mortality and reducing the human and economic cost of screening and prevention.

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