Routine MRI to Screen for Breast Cancer?

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Up to 15 years ago, to join the concepts "screening" and "MRI" was a mission impossible. Even though during the Nineties of the last century contrast-enhanced MRI had been demonstrated to be a very sensitive method for diagnosing invasive breast cancers, a lot of doubts remained about: 1) the so-called low specificity of MRI; and 2) the lower sensitivity of non-invasive cancers (ductal carcinoma in situ, DCIS). Thus, on one side there was a big fear of a deluge of MRI false positives, on the other side there were the possibility to miss many DCIS, so well-depicted by x-ray mammography through the detection of microcalcifications. In this context it was very difficult to propose MRI as a population-based screening method.

This scenario changed when researchers applied MRI as a screening tool to women with an increased risk of breast cancer (equal to or greater than 15% lifetime) and, especially, to high-risk populations (equal to or greater than 20% lifetime). This option had a logical basis in the higher prevalence and incidence of the disease in high-risk subjects, such as carriers of BRCA1 and BRCA2 deleterious mutations and women with relevant family history of breast/ovarian cancer (even when genetic test is negative/inconclusive or in the absence of genetic testing). In the last twelve years, a number of original studies [1-9], meta-analyses (10-14], an cost-effective analyses [15-17] clarified that breast MRI largely outperforms any other method (clinical breast examination, mammography, and ultrasound) in terms of sensitivity for asymptomatic invasive and non-invasive breast cancer when it is used as a screening tool in women at high-risk of breast cancer. Overall, specificity and, most important in this setting, positive predictive value of MRI resulted absolutely acceptable and well comparable to that of mammography or ultrasound. Thus, we had no deluge of false positives from breast MRI while a learning curve in terms of DCIS detection was reported [18]. We have now initial evidence on the impact of the MRI screening in high-risk women on patient outcome, when we look at free-disease and overall survival of the women enrolled in some of these studies [19,20]. However, the ethical impossibility to perform randomized controlled trials prevents to obtain a "pure" demonstration that the diagnostic anticipation permitted by MRI implies longer survival.

One relevant result of some the most recent studies on MRI screening of high-risk women is the lack of added diagnostic power when mammography and/or ultrasound are performed in addition to MRI [8,9], also when ultrasound is performed every six months [8]. In other words, when screening high-risk women, if MRI is negative, no other diagnostic modality is needed, inverting the old logic of MRI "as an adjunct to mammography" as said by the American Cancer Society in the 2007 statement on high-risk screening [21]. This new approach ("MRI alone") may be a relevant point for future programs using MRI for screening breast cancer in the general population, in terms of reduced cost and simple organization. However, to counteract this hypothesis, we should consider that two studies [22,23], both of them dedicated to a special group of high-risk women (those who underwent mantle thoracic radiation therapy for lymphomas in the young age). These women have a risk level similar to BRCA1/2 mutation carriers, with a higher incidence of DCIS. In that special population, mammography should be used "as an adjunct to MRI", not to miss DCIS.

As a matter of fact, studies on "high-risk" women partly included also women with an intermediate risk (equal to or greater than 15% but lower than 20% lifetime) and, above all, precise methods for calculating the individual risk are not yet available, even though advanced models can be freely available from the Internet [24]. Thus, the very good idea to modulate, to "personalize" the screening program taking in consideration the individual risk level is a challenge first of all for the difficulty in risk calculation. The discussion on breast density as a real risk biomarker [25] is an example. On the other side, while MRI has been demonstrated to have a higher sensitivity than mammography also for DCIS (obviously, when a positive mammography is not the entry criterion), in particular for high-grade DCIS [26], in the world of breast cancer screening cannot ignore the big discussion on overdiagnosis happened in the last years. In other words, even though screening mammography is still burdened by a too high incidence of interval cancers, also ignoring economic issues, screening MRI cannot be proposed as an alternative to screening mammography on the only basis of a higher sensitivity and an acceptable positive predictive value.

To move towards "routine MRI to screen for breast cancer" we need not only studies confirming the higher sensitivity in intermediate risk groups (such as those with a previous history of breast cancer [27] or of lobular neoplasia) [28]. We need randomized controlled trials on intermediate-risk populations which started in the Netherlands and in Italy. On the other side, the research on contrast-enhanced breast MRI "fast" protocols [29] could be an important aid in the development of future programs for "routine MRI to screen for breast cancer".

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