Risk-stratified screening – status and vision

Dr. Paolo Giorgi ROSSI

We can speak of risk-stratified screening when different protocols of screening are scheduled for different groups of individuals of the same target population according to characteristics conditioning the individual risk.

A specific condition or combination of conditions (family history, a genetic predisposition, a specific biomarker, or behavior) should characterize such groups of individuals for having a different risk of disease (higher or lower than the general population) and may justify modification of the screening program by variable protocols. Stratification by age, sex, and symptoms is usually not considered a "risk-stratified" screening[(1)].

The hard outcomes of screening, in terms of desirable effects, i.e. reduction of mortality and severity, can be experienced only by those who have the disease. On the contrary, undesirable effects of screening, i.e. unnecessary invasive procedures for assessment in the false positive and direct effect of the test as the radiation dose, are relevant for those who do not have the disease.

Therefore, screening desirable effects are proportional to the risk of disease in the population, while undesirable effects are mostly independent from the risk of disease (that is by definition low in the healthy population).

This implies that screening a population with increased risk should have a more favorable balance between desirable and undesirable effects and that modulating the screening intensity according to the individual risk have the potential to optimize this balance.

This aim can be obtained at the individual level or at the population level, i.e. optimizing the balance for each individual independently from the allocation of resources or considering the available resources of the health service and optimizing the benefits that can obtain in the whole population.

Screening can be stratified by: 1) modifying the age at which we start or stop screening; 2) changing the screening interval (more frequent screening in people at higher risk); 3) identifying a group at so low risk that screening is not beneficial at any age; 4) identifying a group with a sufficiently high risk for which an intervention or test, that is too invasive for the general population, reaches a beneficial balance of benefits and harms [(1)].

For breast cancer, the most studied risk factor is mammographic breast density. This variable affects both the risk of cancer and the effectiveness of screening.

Risk-stratified screening – status and vision

Dr. Paolo Giorgi ROSSI

In fact, women with dense breasts have a higher risk of cancer [2], and mammography is less sensitive [3] and less specific in dense breasts [4]. Several studies tried to define tailored screening based on breast density proposing the use of shorter intervals [5], adding ultrasounds (US) [6], using tomosynthesis, magnetic resonance (MR) [7], or contrast enhancement mammography (CEM) [8].

To date, European recommendations only suggest the use of tomosynthesis in women with dense breasts; nevertheless, recommendations on the use of US and MRI are continuously updated to consider the emerging evidence [9]. In addition to breast density, information about family, reproductive, and screening history has been used to estimate the risk [10]. Nevertheless, the predictivity of the models based on these variables was never considered sufficient to justify and recommend a risk-stratified screening.

Artificial intelligence-guided radiomic showed a promising ability to stratify women according to the risk of developing cancer in the next 2-4 years [11,12]. Polygenic risk scores, based on hundreds of DNA polymorphisms, also showed the ability to accurately predict the risk of cancer [13,14]. Trials are ongoing to test whether risk-stratified breast cancer screening may improve the balance between desirable and undesirable effects [15,16]. The rationale and design of the MyPeBS trial will be illustrated [16].

References

1. Anttila A, Lipponen S, Singh D, Lönnberg S, Bingham C, Molina Barceló A, Giorgi Rossi P, Zappa M. Advances in the criteria for cancer screening. iPAAC Work Package 5, task 5.2. Cancer Screening: Background Paper. 2019. https://www.ipaac.eu/res/file/20191205-wp5-helsinki/20191205-helsinki-background-paper.pdf
2. Bodewes FTH, van Asselt AA, Dorrius MD, Greuter MJW, de Bock GH. Mammographic breast density and the risk of breast cancer: A systematic review and meta-analysis. Breast. 2022 Dec;66:62-68.
3. Nguyen TL, Li S, Dite GS, et al. Interval breast cancer risk associations with breast density, family history and breast tissue aging. Int J Cancer. 2020 Jul 15;147(2):375-382.
4. Weigel S, Heindel W, Hense HW, et al. Breast Density and Breast Cancer Screening with Digital Breast Tomosynthesis: A TOSYMA Trial Subanalysis. Radiology. 2023 Feb;306(2):e221006.
5. Paci E, Mantellini P, Giorgi Rossi P, Falini P, Puliti D; TBST Working Group. Tailored Breast Screening Trial (TBST) [Tailored Breast Screening Trial (TBST)]. Epidemiol Prev. 2013 Jul-Oct;37(4-5):317-27. Italian. PMID: 24293498.
6. Ohuchi N, Suzuki A, Sobue T, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial.Lancet. 2016 Jan 23;387(10016):341-8.
7. Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. N Engl J Med. 2019 Nov 28;381(22):2091-2102.
8. Sudhir R, Sannapareddy K, Potlapalli A, Krishnamurthy PB, Buddha S, Koppula V. Diagnostic accuracy of contrast-enhanced digital mammography in breast cancer detection in comparison to tomosynthesis, synthetic 2D mammography and tomosynthesis combined with ultrasound in women with dense breast. Br J Radiol. 2021 Feb 1;94(1118):20201046.
9. European Commission Initiative on Breast Cancer (ECIBC) Guidelines Developing Group. Women with high breast density. Available at: (last access 17/09/2022) https://healthcare-quality.jrc.ec.europa.eu/european-breast-cancer-guidelines/dense-breast
10. Vachon CM, van Gils CH, Sellers TA, et al. Mammographic density, breast cancer risk and risk prediction. Breast Cancer Res. 2007;9(6):217. doi: 10.1186/bcr1829. PMID: 18190724; PMCID: PMC2246184.
11. Yala A, Mikhael PG, Strand F, et al. J Clin Oncol. 2022 Jun 1;40(16):1732-1740. doi: 10.1200/JCO.21.01337. Epub 2021 Nov 12. PMID: 34767469; PMCID: PMC9148689.
12. Eriksson M, Czene K, Strand F, et al Identification of Women at High Risk of Breast Cancer Who Need Supplemental Screening. Radiology. 2020 Nov;297(2):327-333. doi: 10.1148/radiol.2020201620. Epub 2020 Sep 8. PMID: 32897160.
13. Mavaddat N, Michailidou K, Dennis J, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet. 2019 Jan 3;104(1):21-34. doi: 10.1016/j.ajhg.2018.11.002. Epub 2018 Dec 13. PMID: 30554720; PMCID: PMC6323553.
14. Pashayan N, Antoniou AC, Ivanus U, et al. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. Nat Rev Clin Oncol. 2020 Nov;17(11):687-705. doi: 10.1038/s41571-020-0388-9. Epub 2020 Jun 18. Erratum in: Nat Rev Clin Oncol. 2020 Jun 29;: PMID: 32555420; PMCID: PMC7567644.
15. Esserman LJ; WISDOM Study and Athena Investigators. The WISDOM Study: breaking the deadlock in the breast cancer screening debate. NPJ Breast Cancer. 2017 Sep 13;3:34. doi: 10.1038/s41523-017-0035-5. PMID: 28944288; PMCID: PMC5597574.
16. Roux A, Cholerton R, Sicsic J, et al. Study protocol comparing the ethical, psychological and socio-economic impact of personalised breast cancer screening to that of standard screening in the «My Personal Breast Screening» (MyPeBS) randomised clinical trial. BMC Cancer. 2022 May 6;22(1):507. doi: 10.1186/s12885-022-09484-6. PMI