Editorial Commentary

Breast cancer screening: in the era of personalized medicine, age is just a number

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"*The great end of life is not knowledge but action*."—Thomas Henry Huxley.

While breast cancer screening has a long and established history dating back to the 1960s, screening programs still allow for little to none personalization, both when considering the choice of the imaging technique and the age boundaries, save for specific groups of high-risk women (1). This almost "one-size-fits-all" paradigm currently characterizes most European and North American screening strategies (1-4), with only few exceptions (5,6).

A study by Mukama *et al.* (7) recently published in *JAMA Oncology* under the title "Risk-Adapted Starting Age of Screening for Relatives of Patients With Breast Cancer", aimed to improve and refine the age-related side of screening strategies for women outside the restricted high-risk category. By analyzing data from more than 5 million women born from 1932 onwards and included in the Swedish breast cancer screening registry from 1958 to 2015, the authors stratified women in 15 categories according to the number of their first- and second-degree relatives with a proved diagnosis of breast cancer, then they calculated how much each woman should bring forward or delay the beginning of her screening examinations to match the average 10-year cumulative breast cancer risk at which screening is currently recommended to begin in the general population (7,8). Of note, increasingly earlier risk-adapted starting ages are already suggested by this study when a woman has only one second-degree relative with breast cancer (7).

When compared with guidelines that recommend a screening mammography starting age of 50 years—such as the ones from the US Preventive Services Task Force (3) and the International Agency for Research on Cancer (2), widely adopted also in European countries—starting ages calculated by Mukama *et al.* (7) would call for a 5-year-earlier start (i.e., 45 years of age) in women with no more than one second-degree relative with breast cancer and as much as a 24-year-earlier start (i.e., 26 years of age) in a woman that has at least a first-degree relative and a second-degree relative diagnosed with breast cancer before age 40. These differences are of course curtailed when a 45 years screening starting age is considered, as suggested for example by the American Cancer Society guidelines (4) or, albeit with a conditional recommendation, by the European Commission Initiative on Breast Cancer (1): if a woman has no more than a second-degree relative with breast cancer, a 3-year-earlier start would be recommended, while a 20-year-earlier start would be recommended for a woman that has at least a

first-degree relative and a second-degree relative diagnosed with breast cancer before age 40.

Two main points need to be clarified. First, all aforementioned thresholds are unvaryingly based on data obtained from the general population. Second, when Mukama *et al.* (7) compared their 15 risk-adapted starting ages to equally risk-tiered guidelines, such as the ones issued by the American College of Radiology (5,6), with recommended screening starting ages varying from 25 years (women with one first-degree relative and one or more second-degree relatives with breast cancer) to 40 years (women with no family history or women with no first-degree relatives with breast cancer), they found that an earlier start was to be recommended only in 5 out of 15 categories, with only one category being assigned a >5 years anticipation, i.e. women with 2 or more first-degree relatives with a diagnosis of breast cancer before age 40, with a 7-year anticipation. Compared to the risk-tiered American College of Radiology guidelines (5,6), Mukama *et al.* (7) calculations would result in a postponement of the screening starting age in 10 out of 15 categories, with a deferral as high as 6 years for women with no second-degree relatives with breast cancer and no more than a first-degree relative with a diagnosis of breast cancer after age 49. Notably, the authors also recommend short deferrals in the screening starting age for the largest category of women, those without family history, with a 1-year postponement when compared to guidelines that recommend to begin screening at 40 or 45 years of age, and a 2-year postponement compared to guidelines that recommend a 50 years screening starting age. These and other adjustments proposed by members of the same research group in two recently published papers (9,10) represent a contribution to evidence-based decision making. However, it should be noted that these adjustments are still driven by just a couple of variables, i.e., family history (7,10) or reproductive profile (9), therefore remaining far from a multifactorial tailoring of screening strategies (11,12). Even if they are backed by a population-based analysis, these adjustments would need to be validated in large prospective trials before being introduced in routine screening practice. To date, they seem more useful to orientate a research agenda rather than to shape immediately applicable policies. A potentially more viable application of these findings would see them guide the referral of selected subsets of a population to genetic counselling and, when appropriate, to genetic testing (13). As already envisaged by other authors (8), the best contribution of these findings could come from an integration of family history into currently more comprehensive prediction models such as the last version of Tyrer-Cuzick model [also including breast density (14)], the Gail model, or the Breast Cancer Surveillance Consortium model (15,16), which could convey to such a large scale counselling a better chance of being practically feasible. Importantly, the use of a multivariate model instead of an exclusive reliance on family history would also allow to overcome the effect of ongoing demographic and socio-economic transformations that, especially in European and North American countries, see the ubiquitous rise of smaller families with fewer and fewer first- and second-degree relatives, making the use of family history as a risk factor very challenging.

The recent findings from Mukama *et al.* (7,10) could be usefully viewed as elements of the larger picture represented by the personalization of breast cancer screening (8,11,12). In addition, we should consider that the outcome efficacy of screening strategies is probably not the same for women with different breast cancer risk profiles, due to at least three reasons: (I) the still unascertained assumption that individual risk for each breast cancer subtype proportionally increases with age (17,18); (II) the variability of breast cancer prognosis according to age and other comorbidities (19-21); (III) the large difference in accuracy exhibited by different screening tools (1,22,23).

This last point is indeed the most complex hurdle in the path towards personalized breast cancer screening, as demonstrated for example by the design of the "My Personalized Breast Screening (MyPeBS)" study (24), including more than 85,000 women across Italy, France, Israel, Belgium, and the United Kingdom. Its key primary objective is to assess the non-inferiority of a risk-stratified screening strategy by evaluating the incidence of stage II or higher breast cancer, while the key secondary objective is to ascertain the superiority of the risk-based screening strategy compared to standard strategy in reducing the incidence of stage II or higher breast cancer. In the experimental arm, family history, genotyping with polygenic risk score, mammographic breast density, previous history of benign breast biopsy, and personal hormonal and reproductive history are not only used to propose a tailored schedule (25) but also to regulate the adoption of different imaging tools. Indeed, this tiered use of different imaging modalities and techniques is guided by the evidence on screening with tomosynthesis (26-29), hand-held (30-32) or automated breast ultrasound (33-36), and contrast-enhanced breast magnetic resonance imaging (CE-MRI) (37-40) alongside digital mammography (41). The introduction of these

modalities and of their refinements—e.g., non-contrast-enhanced MRI with diffusion weighted imaging (42-44), abbreviated CE-MRI (45-47), and contrast-enhanced mammography (CEM) (48-50)—represents indeed a composite answer to the historical diagnostic shortcomings of purely morphological imaging such as screen film and digital mammography, tomosynthesis and ultrasound. These shortcomings, particularly the reduced sensitivity of digital mammography in dense breasts (41), are indeed the most conspicuous hindrance to a direct implementation of risk-adapted strategies such as the ones proposed by Mukama *et al.* (7,9,10). Of note, annual organized screening with a combination of digital mammography/tomosynthesis and hand-held/automated breast ultrasound in young women may lead, as already demonstrated in small scale studies, to a high number of false positive findings and unnecessary biopsies (51,52). Moreover, in the case of women with familiar history of breast cancer, a progressively earlier beginning of annual screening mammography could also be at odds with precautions against the risk of radiation induced breast cancer (53), which may indeed concern not only the restricted population of proven *BRCA* mutation carriers but also women with an increasingly prominent familiar history of breast cancer.

Considering the still limited availability of CE-MRI screening (37)—even in its abbreviated form (47)—and intrinsic concern on gadolinium retention after multiple administrations (54), a compromise to ensure that advancements in the epidemiological tailoring of breast cancer screening are supported by a corresponding increase in the diagnostic performance of imaging tools could be represented by CEM, which retains the ability to provide morphofunctional information at much lower costs than CE-MRI (55), with comparable performance (56) and higher patient preference (57). Higher CEM tolerability would also favor its acceptance by women, potentially overcoming the only 59% uptake of CE-MRI screening reported by the DENSE Trial (40). In the meanwhile, new solutions are coming from the integration of artificial intelligence in established screening strategies such as digital mammography (58), while dual-energy mammographic techniques may also grant breast tissue characterization without contrast injection (59).

Future breast cancer screening will surely be different from that of the last decades. The mainstream approach should be a woman-centered multifactorial one, open to innovation coming from advances in biological knowledge and technological developments, supported by a multidisciplinary contribution of epidemiologists, radiologists, and oncologists, potentially also including women advocacy groups.

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