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Commentary

Cancer Prevention Research

Towards Prevention of Breast Cancer: What Are the Clinical Challenges?

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Abstract

The dramatic increase in breast cancer incidence compels a paradigm shift in our preventive efforts. There are several barriers to overcome before prevention becomes an established part of breast cancer management. The objective of this review is to identify the clinical challenges for improved breast cancer prevention and discuss current knowledge on breast cancer risk assessment methods, risk communication, ethics, and interventional efforts with the aim of covering the aspects relevant for a breast cancer prevention trial. Herein, the following five areas are discussed: (i) Adequate tools for identification of women at high risk of breast cancer suggestively entitled Prevent! Online. (ii) Consensus on the definition of high risk, which is regarded as mandatory for all risk communication and potential prophylactic interventions. (iii) Risk perception and communication regarding risk information. (iv) Potential ethical concerns relevant for future breast cancer prevention programs. (v) Risk-reducing programs involving multileveled prevention depending on identified risk. Taken together, devoted efforts from both policy makers and health care providers are warranted to improve risk assessment and risk counseling in women at risk for breast cancer to optimize the prevention of breast cancer. *Cancer Prev Res; 11(5); 255–64. ©2018 AACR.*

Breast cancer is the most common cancer in women worldwide with a steady increase in incidence, particularly in the developing world (1–3). An expanding middle class and a more westernized lifestyle contribute to increasing breast cancer rates in less developed countries as well (4–7), while limited health care resources and insufficient infrastructure challenge the management of the rising number of breast cancer patients (8). The dramatic increase in breast cancer incidence compels a paradigm shift in our preventive efforts. Despite the increasing incidence, few preventive measures have been implemented apart from identification and surveillance of genetically identified high-risk women with BRCA1 and BRCA2 mutations (9). Early detection through mammography screening and treatment of newly diagnosed cancers represent current clinical standards. There are several barriers to overcome before prevention becomes an established part of breast cancer management (Table 1). Consequently, the success of prevention efforts relies strongly on an ambitious interdisciplinary approach dedicated to the potential high-yield gain of intercepting breast cancer development (10).

The initiative to this review originated while preparing a breast cancer prevention trial and identifying the gap of comprehensively bridging, not only risk assessment and intervention, but also communication of risk. Thus, the objective of this review is to identify the clinical challenges for improved breast cancer prevention and discuss current knowledge on breast cancer risk assessment methods, risk communication, ethics, and interventional efforts with the aim of covering aspects relevant for a prevention trial. Future comprehensive risk prediction models and effective communication hereof hopefully will allow for state-of-the-art identification of high-risk women among whom individualized surveillance and prevention through adequate intervention can reduce breast cancer incidence.

Breast Cancer Risk Prediction Models

Current breast cancer risk assessment tools and prediction models

The identification of women at increased risk for developing breast cancer improves the likelihood these women will benefit from intensified surveillance and/or preventive intervention. Risk assessment systems have been developed successfully for women with a strong family history of breast cancer to predict BRCA1 or BRCA2 mutation carriers; these carriers are invited to established programs involving more frequent surveillance and interventions, both surgical and medical. Thus, earlier risk assessment methods

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Table 1. Clinical challenges for breast cancer prevention

1. Risk assessment models
Adequate tools for identification of women at high risk of breast cancer are imperative for making primary prevention efficient. Indeed, comprehensive, easily accessible, risk assessment models are required in order to develop sound breast cancer preventive programs and interventional trials.
2. Definition of high risk
There is currently no consensus on the definition of high risk, which is regarded as mandatory for all risk communication and potential prophylactic interventions. Is a lifetime breast cancer risk above 20% considered high risk? Who owns the right to define high risk: society, health care providers, or women themselves? These questions warrant a discussion in which health-care providers, politicians/officials concerned with public policy, patients, and the healthy populations are all heard.
3. Risk communication and perception
Additional work on risk perception and the way risk information and estimates are communicated is necessary, both how women identified as having a certain breast cancer risk perceive the risk information provided, and how physicians interpret and communicate a given risk to the woman.
4. Ethical concerns
The concepts of breast cancer prevention represents a paradigm shift given that the majority of the population, including physicians, regard breast cancer as an unpreventable disease. Several ethical concerns arise when introducing risk assessment, communication, and intervention. Potential ethical concerns deserve a thorough debate to ensure that all parties are confident in future breast cancer prevention programs, similar to the acceptance of current preventive programs for other diseases, i.e., cardiovascular diseases.
5. Prevention trials and clinical programs
Women identified as being at increased risk for breast cancer should not be left without options for managing their risk, but be invited to programs involving multileveled prevention depending on their identified risk. Targets for possible interventions include both modifiable lifestyle risk factors and chemoprevention, and the challenge is to identify interventions that respect the balance between benefit in risk reduction and harm from potential adverse effects of medications. Notably, the optimal and adequate intervention to prevent a given breast tumor in a given woman is of utmost importance pointing toward the need for individualized prevention strategies.

aimed at predicting breast cancer risk with a strong emphasis on family history, as incorporated, for example, in the Gail model first developed in 1994 and The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) from 2004 (11, 12) and updated in 2014 (13).

An updated Gail model and other models have been developed to predict breast cancer risk beyond BRCA1/BRCA2, that is, the Tyrer-Cuzick model (14) and the Rosner-Colditz model (15, 16). However, in a recent systematic review identifying 17 different breast cancer risk prediction models, no model was found to discriminate and accurately identify women likely to develop breast cancer (17). This inability highlights the need to develop more refined risk prediction models to adequately inform women undergoing risk evaluation and to offer appropriate interventions. Because available models were composed, additional breast cancer risk markers have been identified and established, that is, mammographic density (18) and single-nucleotide peptides (SNP; ref. 19), which may add information to future risk assessment models (20, 21).

Risk prediction models are considered most relevant for predicting the common estrogen receptor (ER)-positive breast cancer; however, the ability to identify younger women and women at increased risk for fatal breast cancer subtypes, for example, ER-negative breast cancer, are considered high-priority research areas in order to reduce mortality rates through primary prevention (3, 22). Similar to prediction of breast cancer recurrence risk, prediction of primary breast cancer risk needs to consider the heterogeneity of breast cancer; however, these efforts are hindered by the paucity of risk factors identified for more aggressive breast cancer (23, 24). Consequently, there is a need to combine achievements gained in both basic science and epidemiology into trans-disciplinary approaches as discussed by Colditz and colleagues (25), and exemplified by a recent meeting in molecular pathologic epidemiology (26).

The website www.cancer.gov/bcrisktool (27) offers validated breast cancer risk models. The National Cancer Institute (NCI) lists the available breast cancer risk prediction models, although stressing that they are intended to be used primarily for research (28). The list is separated into models associated with and without associated websites. Evidently, the challenges are (i) validation of risk prediction models for clinical usage, (ii) gaining easy access to relevant websites, and (iii) making variables of the models easily accessible, that is, having mammographic density measured in an automated fashion.

Novel approaches and challenges for future risk prediction models

Mammographic breast density is regarded as an established marker for breast cancer risk (29–31). Mammographic density has received substantial attention as a promising risk marker to be integrated into existing breast cancer risk prediction models (32–34), and may provide added predictive value (33, 35–38). This added value may, however, depend substantially on the density measurement method used (39). The clinically widely used Breast Imaging Reporting and Data System (BI-RADS) classification is based on subjective two-dimensional estimates of breast density using four categories: (i) representing fatty tissue, (ii) scattered density, (iii) heterogeneous density, and (iv) extreme density. The weaknesses of the BI-RADS system are that it is crude, time consuming, and reader dependent. Not being finely quantified makes the BI-RADS system less adequate for research use. The Cumulus software is a semi-automated method for measuring

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mammographic density that is currently considered the gold standard (36). However, Cumulus suffers from the same shortcomings as BI-RADS. Use of mammographic density in future risk prediction models will benefit from fully automated programs for measurement of mammographic density, such as the Volpara program (40, 41). Compared with BI-RADS, advantages of automated systems include objectivity in measures and a continuous scale from which the entire spectrum of density values can provide information. These automated systems should be evaluated for their added value in future risk prediction models.

Another marker to consider in risk prediction models is the level of endogenous hormone, at least among postmenopausal women (42). Tworoger and colleagues evaluated the added value of endogenous hormone levels to the Gail and the Rosner-Colditz risk scores, and showed them to improve risk prediction, especially for estrone sulfate, with individual hormones improving the area under curve (AUC) by 1.3 to 5.2 units relative to the Gail score, and 0.3 to 2.9 for the Rosner-Colditz score (42). The clinical utility of including endogenous hormones, as stated by the authors, is hindered by the ability to detect low levels in postmenopausal women as well as assay costs (42). Similar to the challenges stated for advanced mammography systems, accessibility is a barrier to the use of endogenous hormones in risk prediction models on a global level, and, importantly, adding endogenous hormone levels may not enrich breast cancer risk prediction for younger premenopausal women.

In addition to currently used parameters for estimating risk (e.g., family history of breast cancer, reproductive history, menopausal status, and previous breast biopsies), other lifestyle factors may predict future breast cancer. For example, physical activity is emerging as a modifiable risk factor for breast cancer (43–45), especially for premenopausal breast cancer (46, 47). The biological rationale for the inverse association between physical activity and breast cancer incidence may be mediated partly through reduced absolute mammographic dense volume among physically active women (48). The challenge of incorporating physical activity into risk models include recording of physical activity, which is often self-reported and prone to recall bias resulting in risk of misclassification (e.g., overreporting amount of physical activity). Improvement of reported physical activity, at least for prospective studies, may benefit from use of mobile health apps, although lacking are sufficient data that available physical activity apps are clinically useful (49).

On the other hand, anthropometric factors as objectively measureable data are less challenging to record accurately. Weight and height are included in the Tyrer-Cuzick model, whereas anthropometric measures do not appear in other commonly used prediction models. There are indications that body composition earlier in life, that is, during childhood and adolescence (50, 51), and potential changes in body measurements (52, 53) hold important information for risk prediction. Barriers to use of anthropometric measures include the need to retrospectively collect and obtain repeated measures. This highlights the need for a comprehensive infrastructure in the health care system that allows health care providers access to essential patient data longitudinally collected.

Taken together, available risk prediction models can probably be improved by a variety of biomarkers in addition to lifestyle factors. Overall, risk predictions markers likely to improve novel risk prediction models would be categorized into five main categories: (i) Imaging related biomarkers (i.e., density, calcifications, and masses), (ii) genetic signatures, (iii) circulating markers, (iv) pathologic breast tissue signatures (i.e., lobular cancer *in situ*, atypical hyperplasia), (v) lifestyle factors.

For the prediction of breast cancer recurrence risk, clinicians often use the web-based tool Adjuvant! Online (54) to estimate prognosis based on simple patient data and widely available core disease characteristics. No similar clinically validated tool exists for prediction of primary breast cancer risk. It would be desirable to reach consensus on a similar predictive tool for primary breast cancer risk prediction, suggestively entitled Prevent! Online, where defined breast cancer risk variables are entered and the estimated risk calculating score can serve as basis for risk communication, level of surveillance and potential intervention. Ultimately, the major challenge remains developing a program that can calculate a woman's individual risk score accurately, precisely and comprehensively. One approach is to estimate the absolute risk of breast cancer for a woman with a particular risk profile as a function of an individual's relative risk, the age-specific incidence of breast cancer, and the age-specific competing mortality due to other causes. This ability, to predict absolute outcomes in individual women, is not yet possible. However, incorporation of genetic markers into future models may pave the way to discriminate more accurately which women are likely to develop breast cancer.

Definition of High Risk of Breast Cancer

A definition of "high risk" is important especially if assessing and providing risk feedback is associated with potential harm. For example, interventions that involve risk-reducing medications with potentially significant side effects, or prophylactic mastectomies, require a careful consideration of the estimated benefit relative to potential harm. The decision to adopt such interventions would occur when there exists clearer benefit than harm. However, the threshold of when this benefit to harm ratio occurs depends on a clear definition of "high risk." Therefore, the definition of high risk will be related to the harmfulness of the suggested intervention.

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The term high risk is often defined in relation to a person's risk of breast cancer compared with the background population; it is infrequently defined by a specific threshold or cutoff. For clinical implementation, a cutoff is often required to enroll women into risk-reducing programs. Contrary to well-established and clinically implemented risk-reducing programs for BCRA 1 and 2 mutation carriers (55), similar programs for other high-risk women remain a challenge to implement, partly due to less accurate estimates of risk. While agreement exists for the requirement of a threshold value for high risk, how does one reach consensus and decide upon who defines such a threshold? Stakeholders include the healthy general population, breast cancer patients, oncologists, primary health caregivers, and politicians as each has unique insights pertaining to how high risk should be defined.

Overall, women in the Western world have a life-time breast cancer risk of around 10% to 12%—the current incidence rates in the United States being 12.4% (56); similarly, the cumulative risk for Swedish women to develop breast cancer before the age of 75 years is 10.4% (28). The latest ASCO guidelines on pharmacologic interventions for breast cancer risk reduction (57), define women to be at higher risk if their 5-year projected absolute risk is 1.66% or above as calculated from the National Cancer Institute Breast Cancer Risk Assessment Tool (BCRAT) or equivalent measures. At this risk level or above, health care providers are encouraged to discuss chemoprevention for breast cancer. Although never intended to be the absolute definition, this cutoff was used for the first NSABP prevention trial, and is now part of the BCRAT to identify women eligible for tamoxifen in the prevention trial, and therefore clinically based on those data. Even for genetics, recent data by Rebbeck and colleagues (58) speak to mutation-specific risk in BRCA1/2 carriers, where the hope is to refine risk assessment to adequately limit use of surgeries. Notwithstanding, the newly identified risk-associated genes present new challenges because their penetrances are not yet well characterized (59).

To decide on the threshold for "high risk," competing risks need to be considered regarding the actual risk estimate used to invite women to an intervention program and the estimated disadvantages from intervention. The absolute risk estimate is viewed as the most useful information to determine risk-reducing interventions all the while taking competing risks into account (60, 61). In such models, the competing causes of mortality prior to a diagnosis of breast cancer are accounted against the "pure" cumulative breast cancer risk, which do not consider risks of competing fatal events and thus provide higher-risk estimates (60). Based on the absolute risk and a given intervention, one can obtain the benefit:harm ratio and thus obtain estimates of anticipated side effects, that is, thromboembolic events and endometrial cancer from tamoxifen (62). The critical question is whether receipt of intervention should be based only on absolute risk estimate of benefit exceeding the risk of other life-threatening events caused by that intervention. A search for efficient interventions with limited adverse effects is thus a high priority, as current available drugs for breast cancer prevention and the current standard doses are associated with side effects considered less acceptable for healthy women (57, 63).

Communication and Perception of Breast Cancer Risk

Risk communication

An accurate understanding of risk among all parties involved in preventing breast cancer is fundamental to motivate risk-reducing efforts, such as behavioral changes (e.g., exercising) and adherence to medical interventions. Of import, a comprehensive understanding of breast cancer risk includes not only understanding the estimated probability of occurrence (e.g., 5-year numerical estimate), but also understanding one's risk factors, consequences of disease/treatment (e.g., social, physical, psychological, and economic consequences of being afflicted with the disease), and what can be done to prevent the disease, with limited adverse effects, and consequently diminish associated consequences (64). Far too often, providers' communication of breast cancer risk captures only a few of these critical dimensions. Ultimately, the form of the risk communication exchange should be guided by the goals set forth between the provider and the patient; this will likely encompass dimensions of what it means to understand a risk. For example, is the goal to gain an appreciation of the magnitude of the absolute risk and/or relative risk? Does the goal emphasize changes in the risk magnitudes over time with and without intervention? In each case, various strategies exist, some of which are discussed below.

A substantial amount of attention has been focused on delivery format of the breast cancer risk absolute/relative risk estimates and how these estimates influence subjective perceptions of risk (65, 66). To a substantial degree, risk estimates are provided numerically, using for example frequencies or probabilities (67, 68). The advantages of presenting numerical risk estimates include creating the impression of precision, being derived from the use of scientifically-based algorithms enhancing the view of credibility and accuracy, their ease of conversion from one metric to another based on patient preferences (e.g., going from 1/10 to 10%), and that numerical outcomes can be empirically verified (69). The disadvantages are that the meaning of numbers can be very context dependent (e.g., 10% may be viewed as high or low depending on the situation) and that a substantial proportion of the populous are innumerate; that is, they have difficulties understanding and applying numerical information (69). As such, while providing a numerical estimate of breast cancer

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can align women's numerical perceptions of risk with their "objective" estimate, a match does not signify understanding—but rather reflecting back what they were told. Providers are discouraged from using a match as a metric of understanding. Rather, providers are encouraged to ask patients interpretation of the meaning of the risk estimate, that is, get at the gist (70).

Verbal descriptors of a statistical probability have been used to standardize numerical probability estimates to ease interpretation of the absolute risks. For example, European guidelines use descriptors of risk expression ranging from very rare (up to 0.01%) through rare, uncommon, common, and to very common (more than 10%). Based on this approach, individuals informed that a treatment side effect is "very common" should translate the descriptor to at least a 10% numerical probability. However, little evidence exists to support that the populous translate verbal descriptors to the intended guideline numerical probability estimates (71). Hence, if the goal is to convey "precision" in breast cancer risk estimates, providing verbal probability descriptors is not optimal. However, verbal descriptors can serve well the goal of signaling the "direction" of risk (e.g., higher or lower) (72). For example, such terms as unlikely, improbable, small chance all signify that a person believes an event is less probably than the converse statements likely, probable and large chance, respectively. Overall, verbal probability statements are useful to denote general direction of risk.

Graphic displays (e.g., pie chart, bar and line graphs, and icon displays) can be useful adjuncts to verbal and numerical communication of risk (68, 69, 73), and may be especially helpful for individuals who are low in numeracy (74). For example, use of bar and line graphs as well as icon displays (e.g., symbols of women highlighted with different colors in a 10×10 matrix) are useful for displaying absolute and relative risk (75, 76). Changes in risk over time are served well by line graphs (69). However, degree of accuracy, and the perceived risk vary by type of graph and its preference. As demonstrated by Schapira and Nattinger (77), the authors evaluated the influence graphic formats on breast cancer risk communication among 254 female primary care patients. These patients were presented lifetime breast cancer risk estimates via a series of graphics. The pictorial display format was illustrated through highlighted female symbols of occurrences among the background population. Women preferred the pictorial display to bar graphs, but notably, risk was perceived to be higher with the pictorial presentation.

Relatedly, Dorval and colleagues highlighted the need for consensus regarding breast cancer risk communication tools given the plethora of breast cancer risk prediction models that provide not easily interpretable probability estimates (78). In their study, participants were shown six different illustrative risk formats, of which they indicated their appreciation of each format. Appreciation was based on merging of likeability, clarity, perceived risk understanding, and emotional impact. Participants preferred formats that integrated quantitative, qualitative, and visual approaches (78). In general, women at higher risk of breast cancer may view their perceived risk as higher than estimates from cancer risk prediction models; for these women, graphic illustrations may enhance the degree of match (79). Again, the caveat here is that such matching may not necessarily lead to a subjective interpretation of risk as intended. For example, even if a bar chart shows a 5-year absolute risk of 1.67% (FDA-approved risk level for medical intervention) as sufficiently high to consider intervention, many women may continue to perceive such a personally conveyed estimate as low. Therefore, counseling women as to how risk levels are determined and how estimates apply to them, are key considerations to inform the meaning of the estimates.

Importantly, framing of a communicated statistical risk can influence the perception substantially and what further actions to take as exemplified by a negative (i.e., loss) framing (1/100 risk of disease or side effects) as opposed to positive (i.e., gain) framing (99/100 chance of no disease or no side effects) (80, 81). In general, negative framing is associated with risk seeking, that is, willing to engage in a behavior to avoid a loss. Conversely, positive framing produces risk aversion, that is, avoiding to take action to maintain a benefit (80).

Counselors and medical staff often perceive risk differently than patients. Providers who counsel women about their breast cancer risk should be sensitive to several beliefs that may affect their interpretation of risk estimates, such as lay illness beliefs about breast cancer (82), degree of trust and source of information (83) and fatalistic beliefs (84). Perhaps more importantly is that these and other factors may shape emotional reactions to the risk information and discussions of intervention. These emotional reactions may be the strongest predictors of what women ultimately decide to do (85, 86). As such, providers should be trained and encouraged to probe for how providing risk estimates from risk prediction models shape beliefs and emotional reactions to risk estimates and any treatment decisions.

Conclusively, communicating results of risk assessment and present risk-reducing efforts requires abilities which many physicians have little if any training in; consequently, this communication may preferably be conducted within specific prevention units employing skilled risk counselors. To optimally transmit risk information there is an additional need for broader information at the general population level, that is, through advertising and educational measures.

Ethical Considerations

To estimate the risk of cancer is still debated. Risk assessments of other life-threatening diseases, such as stroke and myocardial infarction, are less controversial.

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Blood pressure and plasma cholesterol are normally measured without much information on implications of results. For a breast cancer risk-reducing program, the key ethical challenge is to first ask women if they want their individual risk assessed and then, pending the findings, invite them to consider intervention. Unlike screening, which aims to find malignancies early, the goal of breast cancer risk assessment is to depict a woman's risk of developing breast cancer within a defined time period. Assessment should guide decision making regarding future screening modalities, screening frequency, and need of risk-reducing efforts. Several ethical considerations arise when a healthy woman is categorized as high risk—admittedly, ethical challenges arise earlier, when a decision to undertake a risk evaluation is made. Several questions need to be addressed by policy makers and health care providers.

How may risk assessment advantage or disadvantage healthy women?

The thought of getting breast cancer produces anxiety for many women. Providing a risk estimate may induce emotional distress, itself based on cultural beliefs, history of breast cancer among relatives, different coping strategies, and so on (87). Conversely, individual breast cancer risk assessment offers benefits, including knowing one's risk estimate, potential benefits related to breast cancer prevention or early detection of a latent breast cancer diagnosis. The potential harms of "labeling" a healthy woman as high risk of breast cancer should be compared with the benefits of not having to cope with the uncertainty for wanting to know of their risk. Noteworthy, a number of women may overestimate their risk of developing breast cancer, as exemplified, in the Study of Tamoxifen and Raloxifene (STAR trial), only half of the women who presented for risk assessment to determine eligibility for the clinical trial were deemed to be at increased risk (88). Thus, half of the women believed they were at increased risk but actually were not. This also demonstrates that the performance of quantitative risk assessment can reduce anxiety about future risk and give a realistic assessment of the quantitative estimate of the risk that will be more accurate than many women's perception of their risk.

Which efforts can minimize the potential harm of risk information?

The challenge associated with the potential violation of the personal integrity by providing a risk estimate for breast cancer to a woman who has not actively desired the information needs to be recognized and addressed. To circumvent this challenge each and every woman must consent to risk stratification. In countries inviting women for mammography screening, the information regarding breast cancer risk assessment can accompany the mailed invitation for biennial mammography. Upon acceptance, the risk estimate along with carefully crafted risk feedback and interpretation may then be provided in a written format. Individuals at higher risk should be invited to a high-risk program for risk counseling and invitation to risk-reducing interventional strategies.

How are the anticipated benefits and harms by intervention balanced?

Another ethical consideration is the intervention strategies offered to high-risk women. For these women, currently proposed risk-reducing efforts include lifestyle changes (diet, weight-loss, physical activity, reduction of alcohol intake) and medical endocrine interventions. So far, no studies have reported on harmful effects of moderate lifestyle changes; rather, such intervention is beneficial for breast cancer prevention (89) and for other diseases including cardiovascular disorders. The benefit to harm ratio of medical intervention to healthy women should be compared with the wider benefits of a healthier life style.

Clinical Interventional Options

Current intervention agents and trial designs in prevention of breast cancer

Chemoprevention for high-risk women has been encouraged in recent guidelines from the United States Preventive Services Task Forces (USPSTF; ref. 90). The increasing use of medical intervention for prevention of ER-positive breast cancer is supported by the latest results from the IBIS-I (91) and IBIS-II trials (92), demonstrating long-term breast cancer preventive effects of tamoxifen and aromatase inhibitors (93). The benefit of raloxifene as a chemopreventive agent is acknowledged for the less challenging side effects (62, 94). The FDA approves of both agents in the preventive setting. Approval of tamoxifen was based on the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial, which included 13,388 women ages 35 and older with Gail scores of >1.66% (95). Similar criteria were applied in the STAR trial, which paved the way for raloxifene as a breast cancer prevention drug for postmenopausal women (88). The FDA approval of tamoxifen and raloxifene for primary breast cancer prevention is, however, not followed by their European counterpart, the European Medicines Agency (EMA).

Lasofoxifene is another promising agent for prevention of ER-positive disease in terms of supposedly fewer side effects based on the PEARL trial data (96). Lasofoxifene is a third-generation selective estrogen receptor modulator (SERM), which has received EMA approval for prevention of postmenopausal osteoporosis, although it has not yet been approved for breast cancer prevention.

The far more aggressive and life-threatening ER-negative breast cancer, which constitutes about 15% of all breast

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cancers, lacks specific risk-reduction alternatives. Two major challenges are responsible for this gap. There are no risk prediction models that predict risk of specifically ER-negative breast cancer (97), and there are no preventive trials or even preventive agents for ER-negative breast cancer (3, 39).

Prevention trials should include biomarker-based endpoints to pave the way for deeper mechanistic understanding of preventive actions. Biomarkers should include both local and systemic biomarkers, such as image- or tissue-based breast markers and circulating substances. Unique for preventive trials, interventions may prevent several diseases; thus, trial designs can include multiple disease endpoints. Intensified preventive medical interventions require careful ethical considerations in light of expected efficiency and tolerability. Thus, design of large-scaled phase III trials in breast cancer prevention should be based on translationally edged early phase trials allowing for adequate selection of trial participants and a targeted intervention strategy.

Reducing the risk of development of breast cancer may be achieved via adaptive lifestyle factors, including low alcohol intake, eating healthy, following physical activity guidelines, and weight optimization (25, 39, 98). Breast cancer prevention through changes in modifiable lifestyle factors is not established in most countries. Of note, lifestyle interventions may generate nonintended experiences of unsuccessfulness among women who develop a breast cancer despite their efforts to live healthy. This again highlights the need to employ well-trained risk counselors when communicating breast cancer risk and potential interventions in order to establish realistic expectations among the women participating in such programs. Given the current ventures to identify women at high risk for breast cancer within risk programs, high-risk women can be invited to participate in intervention programs, preferably designed as a prospective trial. Risk, in addition to genetic counseling, should be offered whereby women will receive extensive information on their estimated risk along with recommended risk-reducing modifications. Risk-reducing intervention strategies should be multileveled and cover both lifestyle modifications and medical interventions. Participants could be assigned to both interventions, alternatively either/or depending on risk estimate, concurrent diseases/medications, and the choice of the woman.

Importantly, women identified at increased risk for breast cancer should not be left without options for managing their risk; they should be invited to programs involving multileveled prevention depending on their identified risk level. This represents the ethical notion that after having assessed and conveyed a healthy woman's risk of breast cancer, an intervention strategy should be provided to lower her risk. Tamoxifen and raloxifene are recommended as risk-reducing agents in some but not all countries, and these drugs are known to reduce the risk of some breast cancers, but not all, i.e., not estrogen receptor negative breast cancer. Importantly, in currently available doses both tamoxifen and raloxifene are associated with side effects, which may not be tolerated by all women. These encounter side effects such as weight gain, vaginal discharge, reduced sexual arousal, hot flushes, and hair loss among others. Symptoms that may be tolerated in a treatment setting, either adjuvant or metastatic, but are less likely to be tolerated by a healthy woman in the preventive setting (63). This may, in fact, be one of the largest barriers to risk-reduction interventions. In such case, women may be left with an identified high risk of breast cancer, which however may lack a feasible intervention.

To ensure the most accurate and personalized breast cancer prevention based on well-communicated risk assessment, dedicated breast cancer risk assessment clinics are preferable to convey these efforts as primary care physicians may not feel comfortable conducting complex risk assessment and having risk/benefit discussions.

Conclusions

Breast cancer incidence is rising worldwide, mostly in developed countries. Enhanced abilities to intervene very early on are required to achieve a paradigm shift in prevention. Approaching novel strategies for individualized breast cancer prevention will open new horizons for the obvious advantages of breast cancer prevention. It must be acknowledged that strengthened medical interventions necessitate careful consideration of expected efficiency and tolerability. A multidisciplinary scientific approach is essential to comprehend the interplay between host factors and cancer initiation, and in addition to classical epidemiologic approaches, functional laboratory experiments, and clinical trials are required. In alignment with recommendations of the U.S. Preventive Services Task Force, prevention efforts should follow the ABC paradigm: "**A**gents for prevention should be effective and nontoxic, **B**iomarkers of response are necessary, and **C**ohorts of high-risk individuals are needed to evaluate the interventions." Consequently, devoted efforts from both policy makers and health care providers are warranted to improve risk assessment and risk counseling in women at risk for breast cancer to optimize the prevention of breast cancer.

Disclosure of Potential Conflicts of Interest

S. Borgquist is a consultant/advisory board member for Novartis. No conflicts of interest were disclosed by the other authors.

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Towards Prevention of Breast Cancer: What Are the Clinical Challenges?

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