SCREENING FOR BREAST CANCER: WHAT DOES THE FUTURE BRING?

Jelmer Raaijmakers[1]

[1] Master Student Biomedical Sciences, Radboud university medical center, Nijmegen, the Netherlands.

Abstract

Practice Innovations

BACKGROUND: Breast cancer has become an enormous burden on society due to the daunting consequences on physical- and emotional health, as well as the effects on healthcare expenditures. Since breast cancer incidence is at the top of cancer incidences in females, a screening program is crucial to detect early cases of breast cancer and subsequently improve breast cancer prognosis. Although the benefits caused by the current mammography screening program outweighs the harms, the high numbers of screened individuals necessitate the development of alternative techniques to reduce the total burden caused by misdiagnosis and over-treatment.
OBJECTIVE: In this review, new approaches are discussed which show high potential for future screening programs. The first approach that is discussed is molecular imaging, followed by breath- and urine analysis.
CURRENT RESEARCH AND FUTURE DIAGNOSTICS: Current research focuses on the molecular mechanisms of disease, as well as biomarkers. These approaches (molecular imaging, breath- and urine analysis) show high sensitivity and specificity with regards to breast cancer detection. Although the initial results are very promising, further research must be performed in order to prove their clinical relevance for the application in a screening program for breast cancer screening.
CONCLUSION: Several approaches are currently researched and are tweaked in order to gain a higher sensitivity and specificity for the application as a breast cancer screening program.

Introduction

Consequences of breast cancer cast an enormous burden on human health, healthcare costs and emotional suffering at a population-wide level [1]. From data between 2005 and 2009, a one in eight probability of developing breast cancer during a lifetime has been estimated [2]. Breast cancer incidence in the Netherlands is estimated to be a devastating 18,000 new cases in 2017 and the incidence is increasing every year [2]. These numbers make breast cancer the most common form of newly detected cancer in females with a frightening 30% of all female cancer incidences [1]. Furthermore, with a 14% mortality rate, breast cancer is the second leading cause of female death due to cancer [1]. Since female breast cancer is considered a major health concern, screening programs are implemented for the reason that early diagnosis improves breast cancer prognosis, resulting in an estimated 20% reduction of breast cancer mortality [3]. This review first sets out the limitations of current practice as a population-based screening program. Then, it will introduce the ideal characteristics of future diagnostics and lastly, it will introduce promising techniques that are currently under development to inform you what the future of breast cancer screening might bring.

Current practice

Currently, screening programs mainly utilise X-ray mammogram technology in order to detect breast cancer at an early stage [3]. However, alongside the harms caused by mammography (e.g. exposing women to low doses of radiation, which may cause cancer), a screening program has a serious impact on screened persons such as increased anxiety, discomfort and more serious: over-diagnosis [3, 4]. Over-diagnosis is the detection of cancers due to screening which would otherwise not have gained clinical relevance, which is estimated at approximately three percent in the Netherlands [3, 5]. Furthermore, mammography has limitations when it comes to breast cancer screening, such as the detection of breast cancer in females who have high density breast tissue (due to the lack of X-ray contrast in these tissues). However, these women are individuals with a markedly higher risk of developing breast cancer [6]. Also, breast cancer can remain undetected due to overlapping breast tissue, which obscures the tumor, and leads to misinterpretation of mammograms [7, 8]. Including the aforementioned limitations of mammography, other limitations resulting in false-positive and -negative results contribute to the four billion overspent dollars (in the United States) due to under- and overdiagnosis [9]. Although these benefits are considered to outweigh the harms, other methods are necessary in order to diminish harms and increase the benefits of breast cancer screening.

Future diagnostics

When mammography was implemented as a screening method, an alternative was the well-known and appreciated MRI-technique. Utilising MRI in screening programs mainly increases the diagnostic value in hard to evaluate, dense breast tissue, as well as occult breast cancer with metastasis at other cancer sites [10]. Unfortunately, the main reason why utilisation of MRI is not as feasible as a breast cancer screening program is the drawback of high costs that come with the use of MRI [10]. Therefore, in order to improve the current breast cancer screening program, future diagnostic techniques should minimise harms, increase benefits (such as MRI) and suppress healthcare expenditure. In the next sections, the following three promising diagnostic tests, which are currently under development are briefly summarised: molecular imaging, breath- and urine biomarker analysis [4, 11].

Researchers are currently exploring molecular imaging as an approach to perform breast cancer screening. Despite the almost ancient theory (year 1929) [12], this technique only recently cleared the road for a more patient acceptable diagnostic technique, in contrast to mammography, by oral administration of a pill. This pill contains a label that can be detected using near-infrared (NIR) fluorescence (light with a wavelength between 650-900 nm) [4]. The fluorescent label (fluorophore) is coupled with a targeting ligand, the part of the agent that can specifically bind the diseased site [4]. After ingestion of the pill and absorption by the intestines, the targeting ligands move toward the highly expressed integrin $\alpha v\beta 3$ receptors of tumor cells and can be identified using both spatial (3D imaging) and molecular information due to the coupled NIR fluorophores (Figure 1) [4]. Even though this method of cancer screening is expected to be theoretically superior to current practice, since it results in a feasible, safe and cost-effective screening approach, several obstacles have to be overcome in order for this method to be applicable in a clinical setting [4]. First, the pharmacokinetic (movement of the drug through the body) properties of the labels need to be optimised for human application with regards to human variability. Individuals that only absorb a low amount of the drug have a lower contrast between tumor specific fluorescence

and non-specific fluorescence coming in the body, which complicates interpretation for clinicians [4]. Furthermore, one single biomarker is not able to differentiate all tumors of the breast or metastasised tumors. Therefore, additional biomarkers with a different targeting ligand, which is detected at different wavelengths, should be combined in order to establish a more specific screening method [4]. Although this 'easy' applicable method looks promising, aforementioned barriers need to be overcome. After overcoming the barriers, clinical trials need to be performed in order to determine efficacy and safety in humans before its application as a population-based screening method [4].

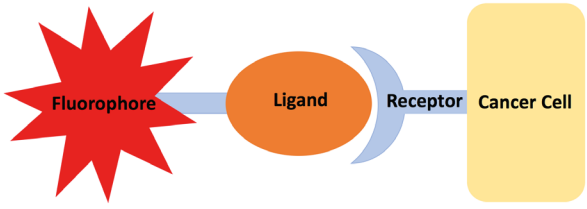

Figure 1: Principle of molecular targeting.
A fluorophore is bound to a targeting ligand that specifically binds avβ3 receptors of cancer.

In extension to the molecular imaging technique, this section elucidates on breath analysis as a breast cancer detection technique. Breast cancer is usually accompanied by oxidative stress alongside the induction of specific hepatic enzymes (polymorphic mixed oxidase Cytochrome P450 enzymes) [13]. Both the aforementioned processes affect the amount of outgassed volatile organic compounds (VOCs), which are hydrocarbons that originate from within the body. These outgassed VOCs mainly consist of (methyl-) alkanes, which are produced during lipid degradation of cell membranes [13, 14]. This origin nominates them as suitable biomarkers for breast cancer detection [13]. Exhaled VOCs are measured using a two-minute breath test and are subsequently quantified by means of gas chromatography [11, 14]. Data from the measured gasses of each individual patient are put into a predictive model for breast cancer, which has shown superior sensitivity and specificity in comparison with the current practice, but larger studies need to be performed to validate these findings [14].

Alongside breath exhaled-biomarkers, a similar technique utilises the measurement and evaluation of microRNAs (miRNAs) in urine samples as breast cancer biomarkers [11, 15]. MiRNAs are small non-coding RNAs which exhibit important post-transcriptional regulating properties, such as the modulation of tumor suppressor genes and oncogenes [15]. Aberrant miRNAs are involved in cancer progression as a consequence of (1) epigenetic mechanisms, (2) genetic alterations, (3) defects in the miRNA biogenesis pathways and (4) transcriptional repression [16, 17]. Analysis of miRNAs in urine samples enables tumor detection, estimation of tumor progression and tumor drug resistance [18, 19].

The approach of utilising biomarkers (VOCs and miRNAs) to detect breast cancer might allow us to specifically detect breast cancer with a high sensitivity and specificity. Furthermore, this approach would be a very rapid diagnostic test and cost-effective.

Conclusion

To summarise, multiple promising screening methods for breast cancer detection are currently under development that might overcome the limitations that come with mammography. Molecular imaging has gained high expectations with regards to feasibility, safety and cost-effectiveness, but several barriers have to be overcome such as the pharmacokinetics and technical interpretation before clinical application is possible. Regarding biomarker approaches utilising breath- and urine analysis, breast cancer biomarkers may contribute to early detection of breast cancer and might enhance prediction of tumor progression and identification, although more research is necessary in order to evaluate its value for clinical application with regards to a population-wide specificity, sensitivity and economical cost-effectiveness. All three methods are still far from implementation, but they have reached high expectations this far and might be what the future will bring us.

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