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Personalized Mammography Screening and Screening Adherence—A Simulation and Economic Evaluation

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ABSTRACT

Objective: Personalized breast cancer screening has so far been economically evaluated under the assumption of full screening adherence. This is the first study to evaluate the effects of non-adherence on the evaluation and selection of personalized screening strategies. **Methods:** Different adherence scenarios were established on the basis of findings from the literature. A Markov microsimulation model was adapted to evaluate the effects of these adherence scenarios on three different personalized strategies. **Results:** First, three adherence scenarios describing the relationship between risk and adherence were identified: 1) a positive association between risk and screening adherence, 2) a negative association, or 3) a curvilinear relationship. Second, these three adherence scenarios were evaluated in three personalized strategies. Our results show that it is more the absolute adherence rate than the nature of the risk-adherence relationship that is important to determine which strategy is the most cost-effective. Furthermore, probabilistic sensitivity analyses showed that there are risk-stratified screening strategies that are more cost-effective than routine screening if the willingness-to-pay threshold for screening is below US $60,000. **Conclusions:** Our results show that "nonadherence" affects the relative performance of screening strategies. Thus, it is necessary to include the true adherence level to evaluate personalized screening strategies and to select the best strategy.

Keywords: adherence, breast cancer screening, decision analysis, economic evaluation, mammography, Markov model, personalized medicine.

Introduction

Many countries worldwide have introduced systematic population-based mammography screening programs. However, it remains controversial whether the benefit of screening, in terms of reduced mortality, outweighs the harm caused by overdiagnosis, referring to cancers detected at screening that would not have been detected during the woman's lifetime, as well as unnecessary diagnostic procedures involving radiation [1–4]. The Cochrane Review concluded that for every 2000 women invited for screening over a period of 10 years, 1 will be saved from cancer-related death but 10 will be treated unnecessarily, and more than 200 will suffer distress from false-positive findings [1]. The Swiss Medical Board's report 2014 concluded that "no new systematic mammography screening programs be introduced and that a time limit be placed on existing programs" [5]. With increasing knowledge about the development of breast cancer and its potential drivers, the identification of high-risk women has become more and more feasible and allows risk-based screening recommendations. It has been shown that better understanding about the individual risk of breast cancer strengthens informed choices and may thus motivate those with a higher risk to use screening opportunities [6] while reducing false-positive findings in individuals at a lower risk. A risk-based approach would therefore allocate expensive screening resources to those who would benefit the most.

Participation in breast cancer screening programs is low, especially in European countries (average 53.5%) [7]. These levels therefore do not reach the European Union benchmark of acceptable participation (>70%) for effectiveness in the reduction of mortality [8]. There is scientific evidence that screening adherence is influenced by a woman's perceived risk [9–11]. All this raises the imperative to rethink current, one-size-fits-all mammographic screening programs. It has been suggested to guide screening decisions by patients' individual risk profiles and preference [12].

Decision analytical modeling is a very useful tool to balance the benefits and harms of personalized screening under various circumstances [13–17]. However, these simulation models have not so far incorporated adherence into the decision analysis. We decided to base our simulations on a validated Markov state transition model [13], which allows the integration of

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nonadherence. This is the first study to incorporate screening adherence into the economic evaluation of personalized mammography screening, using three different risk-adherence associations.

Methods

Model Structure and Adaptation

We use a Markov state transition model of individual women, as described by Schousboe et al. [13]. The original model is validated [13] and provides an elaborate technical report, allowing for reconstruction. The Markov model assumes that healthy women may develop invasive breast cancer, ductal carcinoma in situ, or die from other causes. For women who develop breast cancer, the time spent in a healthy state before death from breast cancer or from other causes is determined depending on the cancer stage at diagnosis (local, regional, or distant). Women diagnosed with ductal carcinoma in situ can progress to invasive cancer. Figure 1 shows the state transition paths via the health states. Additional descriptions are given in Supplemental Materials found at https://doi.org/10.1016/j.jval.2017.12.022.

We use a microsimulation approach to simulate individual women with combinations of three independent risk factors—history of biopsy (28.2% of women), history of breast cancer in first-degree relative (16.1% of women), and breast density (at 50 years, 39.2% of women have heterogeneously dense and 6.4% have extremely dense tissue)—and compare three different scenario-dependent adherence behaviors (positive, negative, and curvilinear). A sample size of 3,000,000 women was found to produce robust results at relatively little variability in results within strategies compared with variability across strategies [18]. Simulations run from a start age of 50 years until the end of their life or 100 years.

Breast Cancer Incidence and Mortality

Breast cancer incidence, breast cancer mortality, and overall mortality are extracted from the original model by Schousboe et al. [13] and the Surveillance, Epidemiology, and End Results Program [19]. Schousboe et al. [13] used the Surveillance, Epidemiology, and End Results Program register data to calculate invasive and in situ breast cancer incidence rates, breast cancer mortality, and overall mortality. As the description in Schousboe et al. [13] does not provide the complete set of age-specific mortality rates, data were extracted directly from the Surveillance, Epidemiology, and End Results Program program using the updated relative survival rates from November 2014. The calculation follows the description in the original model [13].

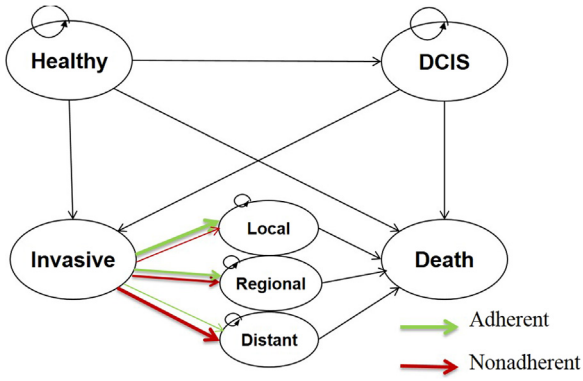

Fig. 1 – State transition model. DCIS, ductal carcinoma in situ.

Cancer incidence is stratified by the relative risk of each woman, using three risk factors: 1) breast biopsy yes/no, 2) history of breast cancer yes/no, and 3) breast density, classified by four categories 1 to 4 from the Breast Imaging Reporting and Data System [20]. Consistent with Schousboe et al. [13] and Tice et al. [21], the relative risk of invasive cancer is 1.454 or 0.938 in the presence or absence of a family history and 1.495 or 0.906 in the presence or absence of a previous biopsy. The relative risk of breast density lies between 0.388 and 1.675 depending on the Breast Imaging Reporting and Data System categorization of breast density levels and the age of the woman. We assumed that the relative risks are mutually independent and have a multiplicative effect. More details are given in Supplemental Materials.

Each woman in the simulation has a risk profile using a random combination of these three risk factors. The choice of risk factors follows the original model [13] and is derived from prevalence and relative risks from the Breast Cancer Surveillance Consortium [22]. Accordingly, 28% of all woman have a family history of breast cancer and 16% have experienced a previous biopsy. Schousboe et al. [13] assigned breast density categories independently of each other in intervals of 10 years. However, in this model, breast density is allowed to change with age, similar to Sprague et al. [16] and Trentham-Dietz et al. [15]. To reflect the natural decrease in breast density, especially at menopause, we allowed breast density to change every 10 years. With this approach, we can simulate a change in breast density and thus evaluate the complete screening strategy even when risk profile and recommendation change. We used the age-specific Breast Imaging Reporting and Data System distribution from Schousboe et al. [13] to calculate the probability of maintaining the same breast density or dropping one category every 10 years. Details can be found in the Relative risk and prevalence of breast density levels section in Supplemental Materials found https://doi.org/10.1016/j.jval.2017.12.022.

Screening Strategies

We assess mammography screening strategies for women aged between 50 and 74 years, for whom routine mammography screening is recommended. In our model, women have a combination of three risk factors reflecting a 10-year risk of breast cancer between 0.41% and 4.65%. Women with very high risk, such as the breast cancer (BRCA) susceptibility gene carriers, or high risk at younger ages have access to intensified screening including magnetic resonance imaging and are excluded from this study. Three different personalized strategies are identified from the literature with stratified screening intervals based on the combination of the three risk factors, as shown in Table 1: 1) Schousboe et al. [13], 2) Vilaprinyo et al. [14], and 3) Trentham-Dietz et al. [15]. We use the following annotation when referring to these strategies: SK, VF, and TDK.

Adherence Scenarios

From the literature, three alternative adherence scenarios were chosen. The first scenario is that women with higher perceived risk are more likely to adhere to screening. This scenario is supported by systematic reviews [23,24] and meta-analyses [9–11]. The Positive risk-dependent adherence section found in Supplemental Materials at https://doi.org/10.1016/j.jval.2017.12.022 describes the supporting evidence.

A second cluster of studies found the opposite association between perceived risk and adherence: high perceived risk may lead to psychological distress, and any form of psychological distress causes nonadherence to mammography screening. The supporting evidence consists mainly of observational