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Adaptive decision-making of breast cancer mammography screening: A heuristic-based regression model[☆]

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ABSTRACT

The American Cancer Society (ACS) updated their breast cancer screening guidelines in late 2015 and recommends that all women have the choice to start annual mammography screenings beginning at age 40. For women ages 45–54, the ACS explicitly recommends annual mammograms. However, due to the potential harms associated with screening mammography, such as overdiagnosis and unnecessary work-ups, the best strategy to design an appropriate breast cancer mammography screening schedule remains controversial. Instead of recommending a one-size-fits-all screening schedule, this study identifies a personalized mammography screening strategy adaptive to each woman's age-specific breast cancer risk. We present a two-stage decision framework: (1) age-specific breast cancer risk estimation and (2) annual mammography screening decision-making based on estimated risk. The results suggest that the optimal combinations of independent variables used in risk estimation are not the same across age groups. Our optimal decision models outperform the existing mammography screening guidelines in terms of the average loss of life expectancy. While most earlier studies improved the breast cancer screening decisions by offering lifetime screening schedules, our proposed model provides an adaptive screening decision aid by age. Since whether or not a woman should receive a mammogram is determined based on her breast cancer risk at her current age, our "on-line" screening policy adapts to a woman's latest health status, which reflects the current individual risk of each woman more accurately.

1. Introduction

Breast cancer is the most common non-skin cancer among U.S. women. According to the American Cancer Society (ACS), an estimated 246,660 women will be diagnosed with breast cancer, and an estimated 40,450 women will die from this disease in 2016 [1]. Routine screening mammography may reduce mortality from breast cancer by detecting the disease at early stages, before the cancer has spread. Several clinical trials and population-based evaluations suggest that mammography may reduce breast cancer mortality significantly [2,3].

Nevertheless, there are potential harms associated with screening mammography, such as overdiagnosis, exposure to radiation, and work-up of positive findings. A cohort study by Hubbard et al. [4] reported that after ten years of annual screenings, over half of participating women will receive at least one false-positive result. The high false-positive rate of screening mammography (i.e., the mammogram is interpreted as positive but no cancer is present) often results in unnecessary follow-up imaging and biopsy exams, which rule in or out the presence of breast cancer after a positive test result. As an invasive procedure, a biopsy may place a woman at risk of morbidity and, in rare cases, mortality [5]. The proportion of women with abnormal mammography findings that are diagnosed with breast cancer is less than 10% [6].

Due to the significant benefits and harms associated with screening mammography, designing the most efficient breast cancer screening guideline that maximizes the benefit and minimizes the harms remains controversial in the public health community [7,8]. The ACS updated their breast cancer screening guidelines in late 2015 and now recommends that women begin annual breast cancer screenings at age 45. The guidelines also recommend that a woman when reaching age 55 should either switch to biennial screenings or continue annual mammography. In addition, the American College of Radiology (ACR) recommends all women begin annual mammography at the age of 40, while the U.S. Preventive Services Task Force (USPSTF) and the American College of Physicians (ACP) advocate beginning screening mammography at age 50 and doing so on a biennial basis [7]. In addition, the age at which to cease mammography screening is also debated. Although

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the ACS and ACR do not specify the age to stop routine screening mammography, the USPSTF and ACP recommend against routine screening for women 75 years or older. Furthermore, there are ongoing discussions on screening frequency and whether it is necessary to perform annual or biennial screenings.

The debate surrounding screening mammography guidelines motivates researchers to pursue a decision policy that finds the optimal trade-offs between the negative effects of screening and patients' long-term benefits of early diagnosis of breast cancer. Kirch and Klein [9] designed a mathematical model to determine the frequency of mammography screening that minimizes the detection delay for the general population. Their model assumed perfect mammography screening sensitivity and specificity, but in fact, the actual false positive rate of mammography is high. Some additional studies, such as Ozekici and Pliska [10] and Zelen [11], considered false positives and false negatives of screening mammography exams in their mathematical models. However, the parameters used in these models were not age-specific, making their solutions less practical since breast cancer risk increases with age. According to Gail and Rimer [12], an appropriate screening recommendation should reflect each woman's individual risk. Since each woman has different levels of breast cancer risk based on her personal risk factors, breast cancer screening schedules should not be uniform across women. Several more recent studies addressed this issue by including age- and patient-specific input parameters and generated some effective optimization models for mammography screening policies [13–16]. Maillart et al. [13] employed a partially observable Markov process model considering women's age and menopausal status to evaluate different screening mammography policies. Their model used different stages of breast cancer as core states and generated a set of efficient policies in terms of life-time breast cancer mortality and the expected total number of screening mammograms. Chhatwal et al. [14] focused on how to make biopsy referral decisions after positive screening mammograms to maximize patients total expected quality-adjusted life years (QALYs). They developed a finite-horizon discrete-time Markov decision process (MDP) model to offer optimal biopsy referral policies for patients with different breast cancer risk scores (i.e., a woman's current probability of cancer based on her risk factors and mammographic features). Ayvaci et al. [15] applied an MDP model to optimize biopsy referral decisions for different breast cancer risk scores under budgetary restrictions. The model by Ayer et al. [16] is the first screening decision study that directly personalizes mammography screening. They developed a partially observable Markov decision process (POMDP) model that offers optimal screening mammography schedules based on five personal risk factors: age, race, age at menarche, age at first birth and prior screening history. Moreover, similar modeling approaches have also been applied to the screening decisions of some other cancers, such as prostate cancer. Zhang et al. [17] developed a POMDP to determine optimal biopsy referral decisions for prostate cancer screening based on prostate-specific antigen tests. Erenay et al. [18]'s POMDP model optimized colonoscopy screening policies for colorectal cancer. Besides age, Erenay et al.'s personalized model incorporated both static (i.e., gender) and dynamic factors (i.e., history of colorectal cancer and polyp). In particular, Alagoz et al. [19] provided an overall review regarding the applications of various operations research models in cancer screening.

Most of these previous studies utilized Markov modeling approaches, which are inefficient in solving problems with high computational complexity. Since incorporating additional breast cancer risk factors into the model leads to a higher dimensionality of the decision-making framework, a Markov model will inevitably suffer from the so-called curse of dimensionality [20], which refers to the computational complexity that grows exponentially with the dimensionality. Incorporating too many risk factors could cause a Markov model to be computationally intractable. In addition, since all states and transition probabilities between states in Markov models must be precisely pre-specified, it is difficult for these models to process some dynamic risk factors, such as a woman's body mass index (BMI), which are fluctuating over time and thus unpredictable. Hence, these prior studies mainly focused on optimal static lifetime screening policies such that optimal decisions cannot be updated dynamically or adjusted with unpredictable new information.

Our study aims to circumvent the limitations of traditional Markov modeling approaches on this topic by proposing a two-stage individualized mammography screening decision framework that is adaptive to changes in risk factors. We first perform a heuristic-based regression analysis with model selection to evaluate a woman's probability of breast cancer at her current age based on a range of personal risk factors. Then we determine whether this woman should undergo a screening mammogram based on her estimated breast cancer risk at her current age.

Advances in health informatics and analytics in recent years have improved health prediction and management for chronic diseases [21–23]. In this study, we not only take advantage of logistic regression to eschew the curse of dimensionality of Markov models, but also discuss the dimensionality reduction of regression models in the context of medical decision-making. We design a novel model selection method for logistic regression from the perspective of making optimal screening decisions. The optimality of a decision is defined in terms of minimal misclassification cost (i.e., the cost of false positives and false negatives), which is a critical concern in medical practice.

The remainder of the paper proceeds as follows: in Section 2, we describe the decision-making framework. We then present the numerical results by implementing the model in Section 3. In Section 4, we discuss the results and their significance to the decision-making of breast cancer mammography screening as well as other disease prevention and treatment problems.

2. Methods

In this study, the decision-making process consists of two sub-models: breast cancer risk estimation and decision-making of mammography screening utilization based on the estimated risk. The risk estimation model is a regression model used to predict a woman's probability of developing breast cancer at her current age based on a number of breast cancer risk factors. The risk estimation model is built based on the predictors from the widely accepted Barlow model [24]. We improve their model by conducting a model selection with the aim of increasing life expectancy, which is impacted by the false-positive and false-negative prediction errors. According to the estimated probability of developing breast cancer, the next sub-model determines whether this woman should be referred for a screening mammogram or if she should skip the mammogram in the current year and return for screening the following year. In this sub-model, a pre-specified optimal cut-off point of cancer probabilities, which is expected to minimize the woman's loss of life expectancy, serves as a threshold of recommending a screening mammogram. Therefore, the decision-making framework works in an adaptive manner such that it allows women to input their current risk factor levels, and then the framework generates corresponding optimal decisions regarding mammography screening.

2.1. Breast cancer risk estimation model

The probabilities of breast cancer for women with various risk factors are estimated using a logistic regression model. We formulate the regression model based on the results from