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Estimation of screening sensitivity and sojourn time from an organized screening program

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ABSTRACT

Regular screening with mammography is widely recommended to reduce breast cancer mortality. However, whether breast screening does more harm than good has long been debated. Since a full evaluation of the effect on mortality could take 10–15 years in order to provide a reliable estimate of the eventual benefits and harms, it is unrealistic to expect each new modification of a screening technique to be evaluated in this way. Therefore, one needs to rapidly estimate suitable measures of the screening effect. In this paper, two measures of interest, the length of the pre-clinical state and the screening false negative rate, are discussed. A procedure is proposed to model the pre-clinical disease state duration, the false negative rate of the screening exam, and the underlying incidence rate in the screened population. We applied the model to data from the Ontario Breast Screening Program in Canada. Our results suggest that the mean preclinical duration is longer than 2 years. We also find only small marginal gains by screening every two instead of three years. The most important objective of a screening program should be to encourage first-time screening attendance.

1. Introduction

Breast cancer was the most frequently diagnosed cancer in Ontario women in 2012, and among cancers, breast cancer mortality is second only to lung cancer in women [1]. Regular mammographic screening and clinical breast examinations are widely recommended for reducing breast cancer mortality. However, whether breast screening does more harm than good has long been debated. For population screening programs, the debate has focused on the reduction in mortality attributable to screening, the numbers of women overdiagnosed, and the accuracy of the screening exams [2–6]. Some studies showed that the benefits of screening outweigh harms, while others found no evidence supporting it. In 2009 and 2016, the US Preventive Services Task Force updated their recommendations on breast screening in the general population. They recommended that women younger than 50 years need not be screened routinely and that women between the ages of 50 and 74 years should have biennial screening mammograms [5,7]. The Canadian Taskforce on Preventative Health Care updated their guidelines in 2011 and found that the mortality reduction associated with screening mammography is small for women at average risk of breast cancer [8]. Reviews on mammography screening concluded that it was likely to reduce breast cancer mortality, but at the expense of 30% overdiagnosis and overtreatment [9,10]. The Independent UK Panel on Breast Cancer Screening suggested that breast screening extended lives and concluded that the UK breast screening program, where women aged 50–70 years are invited for screening every 3 years, conferred significant benefit and should continue [11].

The purpose of a screening program is to advance the time of diagnosis into the “pre-clinical phase” so that prognosis might be improved by earlier intervention. To evaluate the efficacy of a screening program, there are two important parameters involved: the false negative rate and the sojourn time. The sojourn time measures how much earlier the disease might be detected by the screening procedure. Lead time, as a part of sojourn time, is the interval by which diagnosis is actually brought forward; the longer the sojourn time the greater is the potential for detecting disease in an early phase. The sensitivity (equivalent to one minus

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the false negative rate) is the probability that a screening examination detects disease in the pre-clinical phase. A screen-detected case might have initiated since the last examination, or it may represent a false-negative result on a previous screening examination. The sensitivity being modelled here is inferred from a cohort being followed for up to 6 years, which is slightly different from the Ontario Breast Screening program reported sensitivities where one to two years of follow up is examined. Knowledge of these two parameters facilitates the development of optimal breast cancer screening strategies. However, neither sojourn time nor the false negative rate is directly observable since a woman's "real" cancer status is unknown unless she has presented clinically with symptoms. As a consequence, various investigators have modelled the screening process to estimate those quantities; see e.g. [12–18].

Evidence has shown that the sensitivity of screening exams is higher among women aged 50 years and older compared to those under age 50 [19–22], possibly because the breast tissue of older women is less dense than in younger women [20,23]. The age at detection has also been found to be related to the length of the pre-clinical phase. Younger women tend to have shorter sojourn times, due to rapid tumor growth and relatively dense breasts [24,25,18]. For example, Shen & Zelen [26] estimated the mean sojourn time as 1.9 years for the 40–49 age group versus 3.1 years for the 50–59 age group using data from the Canadian National Breast Screening Studies (CNBSS). They concluded that the interval between screenings should be shorter for younger women. The differences in screening sensitivity and sojourn time between different age groups raise a challenge for the design of population screening programs. If the screening interval is too long, some of the potentially detectable cancers might progress into the clinical phase and thus be missed by screening. However, too short an interval might result in an unnecessary burden on the health care system, because of the relatively low yield of cases at each screen, and the extra resources involved. Therefore, while it is of great interest to estimate the sojourn time and screening sensitivity by age, little has been done to model such relationships based on data from organized screening services.

In this paper, we revisit and extend the Markov-type model developed by Day & Walter [13] and apply it to a cohort of women in the Ontario Breast Screening Program. We show how the sojourn time and screening sensitivity can be estimated from cohort data on the observed prevalence of breast cancer at successive screens and on the incidence of disease during intervals between screens. We further investigate the variation of screening sensitivity and the mean sojourn time for different age groups. Lastly, we apply the methods to data from two clinical trials.

2. Methods

2.1. The cohort

A cohort of women aged 50–69 years who were first screened through the Ontario Breast Screening program (OBSP) between Jan 1, 2003 and Dec 31, 2004, was identified from information routinely collected by an integrated client management system on all OBSP participants, and who had been followed up until Dec 31, 2009. The OBSP participation rate is approximately 29% for women aged 50–74 during the period from 2003 to 2004 [1]. Women who participate in the OBSP must be residents of Ontario, have no history of breast cancer or augmentation mammoplasty, and have no acute breast symptoms. Screen-detected breast cancer includes ductal carcinoma in situ (DCIS) or invasive cases diagnosed within a year of an abnormal OBSP screening mammogram result after completion of diagnostic assessment.

We used the data from the first six years of follow-up after the start of screening and considered the idealized situation where the population is screened at regular intervals.

2.2. Statistical method

As represented in Fig. 1, it may be supposed that breast cancer is initiated by a change in a single cell and then may develop characteristics that make it potentially detectable by screening (at time T_0). If a woman is not screened, her disease may progress to the phase where it becomes symptomatic and clinically detectable (at time T_1). If a woman is screened between T_0 and T_1, the disease will possibly be detected in the prevalent phase, but alternatively there may be a false negative result. The interval between T_0 and T_1 is called sojourn time and it constitutes the detectable pre-clinical phase of the disease.

We assume that sojourn times are exponentially distributed, primarily for pragmatic reasons given the convenient mathematical properties of the exponential distribution, but also for consistency with previous work in this area. Day and Walter [13] proposed a method for estimating test sensitivity and the sojourn-time distribution jointly, and concluded that the sojourn time distribution for breast cancer was better approximated by an exponential distribution than either a log-normal distribution or a piecewise-constant distribution function. Using clinical trial data, Zelen and Feinleib [12] proved that a necessary and sufficient condition for the sojourn time to have an exponential distribution was that the mean ages of diagnosis for the first exam in a control group is equal to the mean age at diagnosis in the study group. With data from a randomized trial for breast cancer by the Health Insurance Plan of Greater New York, they showed that the

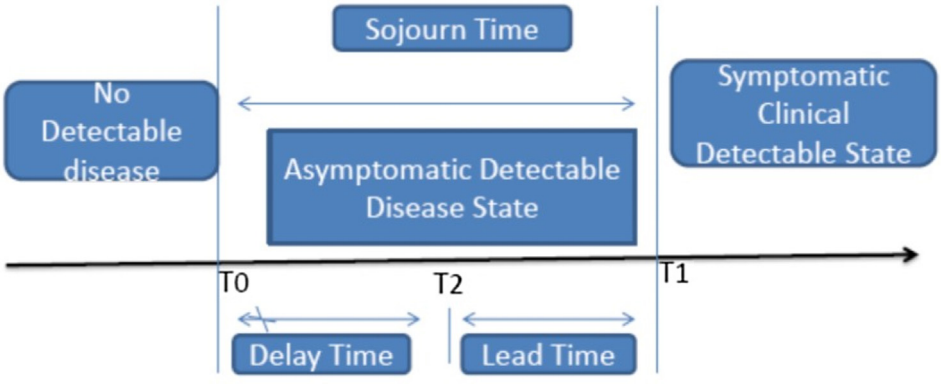

Fig. 1. Stages of disease progression in the presence of a screening test.