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Estimating key parameters in periodic breast cancer screening—Application to the Canadian National Breast Screening Study data

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ABSTRACT

Problem statement: Breast cancer screening in women of younger age has been controversial. The screening sensitivities, transition probabilities and sojourn time distributions are estimated for females aged 40–49 years and 50–59 years separately, using the Canadian National Breast Screening Study (CNBSS) data. The purpose is to estimate the lead time distribution and the probability of not detecting the cancer early. *Approach*: Within the 40–49-year-old and 50–59-year-old cohorts separately, the age-independent statistical model was applied. Bayesian estimators along with 95% highest probability density (HPD) credible intervals (CI) were calculated. Bayesian hypothesis testing was used to compare the parameter estimates of the two cohorts. The lead time density was also estimated for both the 40–49 and 50–59-year-old cohorts. *Results*: The screening sensitivity, transition probability of the disease, and mean sojourn time were all found to increase with age. For the 40–49-year-old and 50–59-year-old cohorts, the posterior mean sensitivities were 0.70 (95% HPD-CI: 0.46, 0.93) and 0.77 (0.61, 0.93), respectively. The posterior mean transition probabilities were 0.0023 (0.0018, 0.0027) and 0.0031 (0.0024, 0.0038), while the posterior mean sojourn times were 2.55 (1.56, 4.26) years and 3.15 (2.12, 4.96) years. Bayes factors for the ratio of posterior probabilities that the respective parameter was larger vs. smaller in the 50–59-year-old cohort were estimated to be 2.09, 40.8 and 3.0 for the sensitivity, transition probability, and mean sojourn time, respectively. All three Bayes factors were larger than two, indicating greater than 2:1 odds in favor of the hypothesis that each of these parameters was greater in the 50–59-year-old cohort. The estimated mean lead times were 0.83 years and 0.96 years if the two cohorts were screened annually. *Conclusions*: The increase in sensitivity corresponds to an increase in the mean sojourn time. Breast cancer in younger women is more difficult to detect by screening tests and is more aggressive than breast cancer in older women. Women aged 50–59 tend to benefit more from screening compared with women aged 40–49.

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1. Introduction

One in eight women will eventually develop breast cancer over their lifetime [1], making it the most common form of cancer in American women and the second leading cause of death after lung cancer. The America Cancer Society [1] states that the same statistic was 1 in 14 in 1960. According to the National Cancer Institute, in 2009 [2] the expected number of new cases of breast cancer in women is 192,370, and the expected number of breast cancer deaths in women is 40,170.

As a chronic disease, breast cancer can take many years to develop without any clinical symptoms. Early detection of the disease with screening exams can greatly improve the chances of survival. Since age is one of the greatest risk factors of breast cancer besides gender, it is reasonable to start routine screening exams after a certain age. However, there is little reference and evidence to answer questions like what age to start regular screening exams and how often they should be. Early age screening exams remain controversial. As in November of 2009 the U.S. Preventive Services Task Force (USPSTF) announced new recommendations for mammography screening, women should start to get mammograms at age 50, rather than age 40, and that women between the ages of 50–74 should take screening mammography every other year, instead of every year. The necessity of a screening exam depends on a variety of factors, such as the sensitivity of the screening exam and the incidence of the disease. These factors change as age increases, and quantifying these parameters for different ages provides necessary information for policy making regarding the timing and frequency of screening exams.

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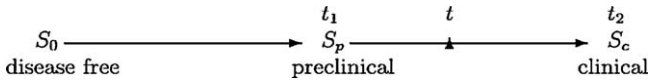

Fig. 1. Illustration of disease progression model.

Many clinical trials have been conducted to help address the above questions [3–9]. The CNBSS recruited 50,430 women between the ages of 40 and 49 years and 39,405 women between the ages of 50 and 59 years from 1980 to 1985 [3,4]. The volunteers selected were not pregnant, had not been diagnosed with breast cancer previously, and had not had a mammography in the preceding 12 months. The 40–49-year cohort was followed for a mean of 8.5 years, and the 50–59-year cohort was followed for a mean of 8.3 years. Participants were randomly assigned to two groups: the treatment group and the control group. The treatment group received both mammography and breast physical examination annually. The control group received the usual community care with annual follow-up. Our researches focus on the treatment group data.

To analyze the data from the CNBSS study, we follow the disease progression model that was initially developed by Zelen and Feinleib [5]. This model assumes that the disease develops through three states, the disease-free state (S_0), the preclinical state (S_p), and the clinical state (S_c), as shown in Fig. 1. The preclinical state represents the stage in which an asymptomatic individual unknowingly has the disease that could be detected by a screening exam, marked to start at time t_1. The clinical state means that the disease has manifested itself by the symptoms, marked to start at time t_2. The time period $t_2 - t_1$ is defined as the sojourn time. The lead time is the length of time between detection of the disease by the screening exam and the onset of clinical symptoms ($t_2 - t$) if left untreated. Thus lead time is the time gained for early treatment prior to the onset of clinical symptoms. The transition probability is the probability a woman will move from the disease free to the preclinical state in a small time interval (t, $t + dt$).

2. Materials and methods

The CNBSS data is summarized in Table 1. There were five annual screening exams in the study. Let n_i denote the number of individuals participating in the ith screening, s_i denote the number of cases diagnosed in the ith screening, and r_i denote the number of cases diagnosed in the clinical state S_c within the interval (t_{i-1}, t_i), also known as the interval cases.

After a screening examination, a participant is either detected by the test (and confirmed by subsequent biopsy), becomes an interval case, or is qualified to have the next screening test. As a multinomial event, the likelihood function for the model is [6]:

$$L(\beta, a_1, a_2, w|\text{data}) = \prod_{i=1}^{5} D_i^{s_i} I_i^{r_i} (1 - D_i - I_i)^{n_i - s_i - r_i},$$

where D_i is the probability of a confirmed diagnosis at the ith screening exam; and I_i is the probability of an interval case between ith and $(i + 1)$th screening exam. The formula for D_i and I_i are derived by Wu et al. [6] as follows.

$$D_i = \beta\left\{\sum_{j=0}^{i-2}(1-\beta)^{i-j-1}\int_{t_{j-1}}^{t_j} w(s)Q(t_{i-1}-s)ds + \int_{t_{i-2}}^{t_{i-1}} w(s)Q(t_{i-1}-s)ds\right\},$$

$$I_i = \sum_{j=0}^{i-1}(1-\beta)^{i-j}\int_{t_{j-1}}^{t_j} w(s)[Q(t_{i-1}-s) - Q(t_i-s)]ds + \int_{t_{i-1}}^{t_i} w(s)[1 - Q(t_i-s)]ds.$$

Here β is the sensitivity of the screening exam, and $w(t)dt$ is the transition probability from S_0 to S_p during $(t, t + dt)$. In addition, $q(t)$ is the probability density function of the sojourn time in the preclinical state S_p before progressing into the clinical state S_c. Therefore, $Q(t) = \Pr(T > t) = \int_t^\infty q(t)dt$ is the survival function of the sojourn time in S_p.

The two sets of data for the different age groups allow us to consider β and $w(t)$ as constants in the 40–49-year age group and 50–59-year age group, respectively. The age-independent model is applied here, since we do not have an age specified data set.

We adopted the gamma distribution to model the sojourn time in the preclinical state,

$$q(t) = \text{gamma}(a_1, a_2) = t^{a_1-1}\frac{e^{-t/a_2}}{a_2^{a_1}\Gamma(a_1)} \quad \text{for } t > 0, \text{ and } a_1, a_2 > 0,$$

where t is the sojourn time, a_1 is the shape, and a_2 is the scale (inverse of the rate).

Bayesian estimates were obtained, using MCMC to sample from the posterior distributions for each parameter. Two chains with different starting points were run to guarantee convergence of the MCMC sampling. For each chain, the total number of iterations was 10,000, with the first 1000 samples used as burn in. Every 10th value of the chain was sampled to ensure independence, resulting in 1800 pooled posterior samples for each parameter. The means of the MCMC samples were used to estimate and compare the parameters.

Since β, the sensitivity, is a probability, we bounded its value between 0 and 1. Based on the previous literature [6], the boundary of w, the transition probability, was set up as (0, 0.06). The mean sojourn time was previously found to vary from a few months to 5 years [7], so the corresponding boundaries for a_1 and a_2 were set to (0, 10) for both. We picked non-informative uniform distributions over the support for each parameter as the prior distributions, since we did not assume any prior knowledge concerning the parameter values.

We calculated Bayes factors to test the hypotheses that the respective parameter in the 40–49-year-old cohort was larger vs. smaller than that for the 50–59-year-old cohort.

Letting θ_1 be the parameter of interest (sensitivity, transition probability, and sojourn time) in the 40–49-year-old cohort and θ_2 be the same parameter of interest in the 50–59-year-old cohort, we set the first hypothesis H_1 to be $\theta_1 \geq \theta_2$, and the second hypothesis H_2 to be $\theta_1 < \theta_2$. The Bayes factor is considered as the odds in favor of H_2 vs. H_1 that are given by the data, which is formulated as

Table 1
CNBSS dataset.

ith year	40–49 years age			50–59 years age		
	n_i	s_i	r_i	n_i	s_i	r_i
$i=1$	25,214	98	19	19,711	108	15
$i=2$	22,424	39	16	17,669	51	10
$i=3$	22,066	44	8	17,437	43	8
$i=4$	21,839	52	10	17,193	54	9
$i=5$	14,146	26	9	9876	28	5

Table 2
Posterior sample means and 95% HPD credible intervals.

Age		β	w	a_1	a_2	Sojourn time (years)
40–49 years	Posterior sample mean (95% HPD)	0.70 (0.46, 0.93)	0.0023 (0.0018, 0.0027)	1.77 (0.87, 3.63)	1.67 (0.58, 3.73)	2.55 (1.56, 4.26)
50–59 years	Posterior sample mean (95% HPD)	0.77 (0.61, 0.93)	0.0031 (0.0024, 0.0038)	1.57 (0.92, 3.11)	2.25 (0.84, 4.39)	3.15 (2.12, 4.96)

$B = (P_2/P_1)/(\pi_1/\pi_2)$, where P_2 and P_1 are the posterior probabilities of each hypothesis given the data, and π_1 and π_2 are the prior probabilities. If the Bayes factor is much larger than 1, it is strong evidence in favor of H_2. Since we do not have any prior preference for either hypothesis, we assigned each prior probability to be 0.5, so that $B = P_2/P_1$. To estimate P_1, P_2, and B, we randomly sampled 10,000 samples from the 1800 posterior samples for each age cohort, and calculated the proportion of the time that the sampled value was greater in the 50–59-year-old cohort compared to the 40–49-year-old cohort (to obtain an estimate for P_2).

For the lead time, the posterior predictive distribution can be estimated as follows [7]:

$$f(L) \approx \frac{1}{n}\sum_{i=1}^{n} f(L|\Theta_i), \tag{1}$$

where the set $\{\Theta_i\}$ are the posterior samples and $f(L|\Theta_i)$ is a mixture distribution of a point mass at zero $P(L = 0|D = 1)$ and a piecewise continuous density $f_L(z|D = 1)dz$:

$$P(L = 0|D = 1) = \frac{P(L = 0, D = 1)}{P(D = 1)}, \tag{2}$$

$$f_L(z|D = 1) = \frac{f_L(z, D = 1)}{P(D = 1)}. \tag{3}$$

The numerator in (2) is the probability of being an interval case. The joint density in (3) is

$$f_L(z, D = 1) = \sum_{i=1}^{j-1}\beta\left\{\sum_{r=0}^{i-1}(1-\beta)^{i-r} \times \int_{t_{r-1}}^{t_r} w \times q(t_i + z - x)dx + \int_{t_{i-1}}^{t_i} w \times q(t_i + z - x)dx\right\} + \beta_0 \int_0^{t_0} w \times q(t_0 + z - x)dx. \tag{4}$$

The common denominator is expressed as

$$P(D = 1) = \int_0^{t_0} w(x)[Q(t_0 - x) - Q(T - x)]dx + \int_{t_0}^{T} w(x)[1 - Q(T - x)dx], \tag{5}$$

where t_0 is the age of first screening exam and T is the age of last screening exam. The outcome $D = 1$ indicates that there is development of clinical disease before death.

3. Results

Bayesian parameter estimates for β, w, a_1, and a_2 are given in Table 2, along with the 95% HPD credible intervals. The mean of the posterior samples for the sensitivity β increased from 0.71 for the 40–49-year age group to 0.78 for the 50–59-year age group. The probability of H_2: $\beta_1 < \beta_2$ (P_2) was estimated to be 0.676, P_1 to be 0.324, and the corresponding Bayes factor as 0.676/0.324 = 2.09. This indicates greater than 2:1 odds in favor of H_2, and thus strongly supports the hypothesis that the screening sensitivity is larger in the 50–59-year-old cohort. The posterior distribution density curves for β, w and $a_1 \cdot a_2$ are shown in Fig. 2a, b, and c, respectively, where $a_1 \cdot a_2$ represents the mean sojourn time. From the density plot of the MCMC simulation for the sensitivity we also conclude that the posterior sample for the 40–49-year age group is more heavy tailed than the sample for the 50–59-year age group, and the standard deviation is 0.13 for the 40–49-year age group and decreased to 0.08 for the 50–59-year age group.

For the transition probability, the mean of the posterior samples from the MCMC simulation increased by a factor of 1.37 from 0.00227 for the 40–49-year age group to 0.00311 for the 50–59-year age group. The Bayesian hypothesis testing gives a Bayes factor of 40.8 in favor of H_2 ($P_2 = 0.976$), and strongly suggests that the transition probability for the 40–49-year age group is lower than the one for 50–59-year age group.

The mean sojourn time is estimated by multiplying a_1 by a_2, since the density distribution of the sojourn time is defined as a gamma distribution. The mean sojourn time from the MCMC simulations is estimated by multiplying the mean of the posterior samples for a_1 by the mean of the posterior samples for a_2, which had 2.83 years for the 40–49-year age group and 3.42 years for the 50–59-year age group. The Bayesian hypothesis testing gives a Bayes factor of 3.0, indicating 3:1 odds in favor of H_2, and strongly favors accepting the hypothesis that the 50–59-year age group has a longer mean sojourn time compared to the 40–49-year age group.

To estimate the lead time, the posterior samples for the parameters (β, w, a_1, and a_2) from both age cohorts were used, with screening interval times of 6 months, 12 months and 24 months. For the 40–49-year-old cohort, we estimated the lead time for screening exams conducted between the ages of 40 and 50, using the parameters estimated from this cohort. For the 50–59-year-old group, we estimated the lead time for screening exams conducted between the ages of 50 and 60, again using the specific parameter estimates obtained from this group.

The density curves of the lead time for both age groups are illustrated in Fig. 3. The area underneath the density curve of the lead time is the probability to have early-detection from the screening exams. As seen in Table 3, the lead time estimates decrease as the interval time Δ between screens increases from 6 months to 24 months for both age groups. Given the same interval time between screens, the lead time estimated with posterior samples from the 40–49-year-old women data is shorter than the lead time estimated with posterior samples from the 50–59-year-old women data. The probabilities of having early detection from screening tests increases as the interval time Δ between screens decreases, and is also higher for the 50–59-year-old age group. For instance, if the screening exam is taken annually, the probability of early detection increases from 77.4% to 83.1% as the screening age period increases from 40–50 to 50–60, and the mean sojourn time also increases from 0.83 years to 0.96 years.

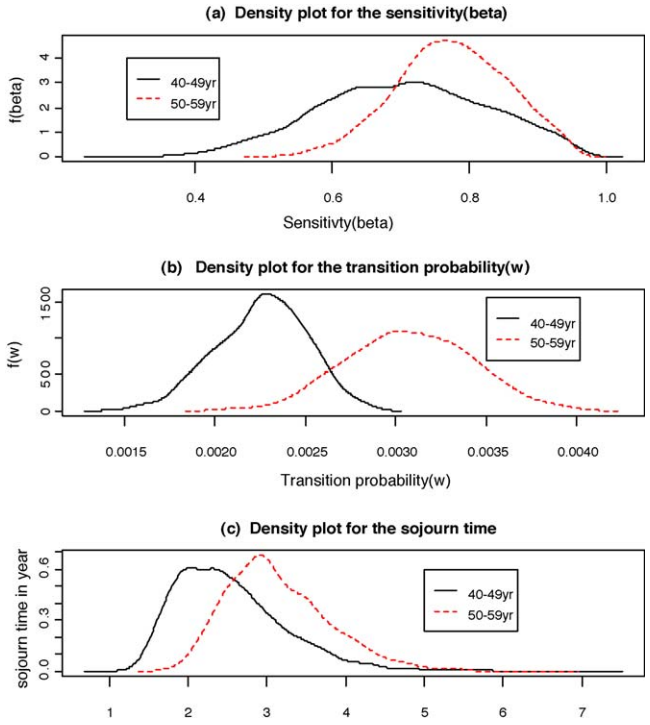

Fig. 2. Density plots for the sensitivity, the transition probability and the sojourn time. Sojourn time is in years.

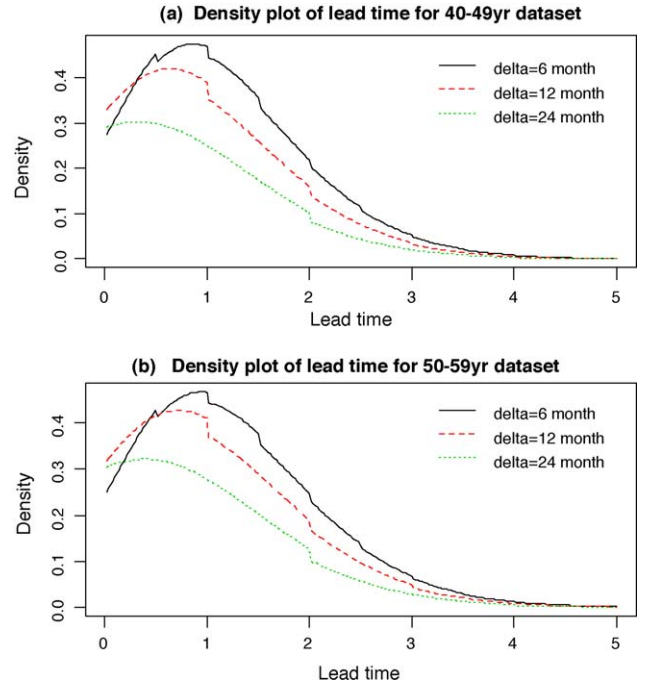

Fig. 3. Density plot for lead time. The "delta" in the plot is the time interval between 2 consecutive screens. Lead time is in years.

4. Discussion

There were other large breast cancer cohort studies done in Europe as well. The Swedish Two-County Study suggested that, in the age groups 40–49 years, 50–59 years and 60–69 years, the mean sojourn time increased from 1.7 to 3.3 and to 3.8 years respectively, and it dropped to 2.6 years in the age group 70–79 years [9]. The shorter mean sojourn time in the younger cohort was explained as faster progression of tumors in that age group. According to the Norwegian Breast Cancer Screening Program (NBCSP) [10], the mean sojourn time was estimated to be 2.9 years for women aged 50–59 and 5.0 years for those aged 60–69 years. The screening test sensitivity was also estimated to be 75% and 85%, respectively. Duffy et al. [11] estimated that the sensitivity of mammography screening for women aged 40–49 years ranged from 72% to 83% using the Swedish Two-County Trial data and from 69% to 85% using the Florence program data [11]. Maximum likelihood estimates of the mean sojourn time were done with a breast cancer screening program in The Netherlands, and it was 1 year for women aged 40–49 years and 3 years for women over the age of 54 [12]. Wu, Rosner and Broemeling analyzed data from the HIP study with an age-dependent model to estimate these parameters. However, with CNBSS data, we can only apply the age-independent model to estimate similar parameters, since the age-specific data is not available. It is reasonable to use the age-independent model applied to each dataset since the age range of each study is restricted.

The result shows that the sensitivity (β) of the screening exam increases as age increases, which is reasonable and suggested by other literature [13]. The medical explanation is that younger women tend to have denser and more fibrous breast tissue compared to older women, whose breast tissue is relatively softer and fattier.

The transition probability is higher in the older age group compared to the younger one, which also agrees with other research [6]. The prevalence of breast cancer increases with age. The MCMC posterior sample means suggest that the transition probability increases by 36.3% from 0.00227 in the 40–49-year-old cohort to 0.00311 in the 50–59-year-old cohort.

Females in the 50–59-year-old cohort had longer sojourn times compared to the 40–49-year-old cohort (3.15 years vs. 2.55 years, MCMC posterior sample mean). Longer sojourn times mean that the screening test has a better chance to detect the disease prior to clinical manifestation. For a fixed screening interval, both the mode and mean of the lead time distribution and the probability of early-detection from screening for the 40–49-year-old model are shorter than that for the 50–59-year-old model. For both age cohorts, the mode and mean of the lead time distribution and the probability of early-detection from screenings decrease when the interval time between screenings is increased.

While a lot of previous work on the lead time focused on screen-detected cases only, our lead time estimation is a model-based approach. The distribution of the lead time is a mixture of a point mass at zero and a piecewise continuous density function. A lead time of zero is defined as no early-detection from the screening exams. The lead time results are comparable with the previous study by Wu et al. [8] with the HIP dataset and an age dependant model.

Table 3
Lead time estimation using parameters from 40 to 49-year-old age women and 50 to 59-year-old age women with CNBSS data. Where P is the probability of having early-detection from the screening tests, and $(1-P)$ is the probability of having no early-detection from the screening tests.

Δ	Number of screens	40–49-year-old age					50–59-year-old age				
		$1-P$(%)	P(%)	Mode	Mean	S.E.	$1-P$(%)	P(%)	Mode	Mean	S.E.
6 months	20	7.7	92.3	0.86	1.1	0.85	5.14	94.86	0.94	1.21	0.88
12 months	10	34.21	65.79	0.64	0.83	0.83	27.57	72.43	0.72	0.96	0.88
24 months	5	44.68	55.32	0.32	0.54	0.76	37.92	62.08	0.4	0.65	0.82

The result that the lead time is longer for 50–59-year-old women compared to 40–49-year-old women is compatible with the result that the screening test has a higher sensitivity when applied to the older age group of women. Higher sensitivity also indicates that it is easier to catch the disease, thus, the probability of early-detection is higher in the older age group women according to the lead time analysis. Therefore, the lead time result and the MCMC result are comparable to each other.

Shen and Zelen [7] performed MLE with the CNBSS dataset. The difference is that the exponential distribution was used as the distribution of the sojourn time in their model, while we used the gamma distribution. Also, for the 40–49-year age group, they only used data from the first three screening intervals instead of the whole dataset, because they considered the fourth screening examination to be an irregular trend. Our MCMC posterior means are comparable with their results except for the sensitivity of the 40–49 age group because of the different datasets used.

The results suggest that the benefit from breast cancer screening increases as age increases. The sensitivity of the screening test increases, the transition probability of breast cancer increases, and the mean sojourn time of the disease increases. The lead time increases as well. All of the above suggest that there will be an increased chance of detecting the disease in the preclinical status at higher ages. This is consistent with the study by Tabar et al. [9], who estimated that the mean sojourn time and the sensitivity increased from the 40–49 age group to the 50–59 age group. However, in our analysis, we did not assess the potential drawbacks from screening exams, including the cost to follow-up false-positive results. This will be an important consideration in future models.

However, with the model we also get that although breast cancer in younger women is rarer (lower transition probability) and harder to be detected by a screening test (lower sensitivity of the screening test), the cancer is more aggressive (shorter sojourn time). It would be reasonable to have a woman with a lot of risk factors such as a family history, late age of first birth, or late age of menarche [14], start the screening test at a younger age with more frequent screening exams.

Conflict of interest statement

None.

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