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A projection of benefits due to fecal occult blood test for colorectal cancer

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ABSTRACT

Objectives: A prospective study to estimate benefits due to fecal occult blood tests for colorectal cancer are carried out for both males and females, under different screening frequencies. *Methods*: We apply the statistical method developed by Wu et al. (2007) [1] using the Minnesota colorectal cancer study group data, to make Bayesian inference for the lead time, the time of diagnosis advanced by screening for both male and female participants in a periodic screening program. The lead time is distributed as a mixture of a point mass at zero and a piecewise continuous distribution. The two parts of the mixture correspond to two aspects of the screening: the probability of no benefit, or the percentage of interval cases; and the probability distribution of the early diagnosis time. We present estimates of these two measures for males and females by simulation studies using the Minnesota study group data. We also provide the mean, mode, variance, and density curve of the program's lead time by gender. This may provide policy makers important information on the effectiveness of the FOBT screening in colorectal cancer early detection. *Results*: The mean lead time increases as the screening time interval decreases for both males and females. The standard error of the lead time also increases as the screening time interval decreases for both genders. Females seem get more benefit than males, in that females usually have a longer lead time than males if both take the test at the same time interval and the lead time mode for females is greater than that of males in the same screening time interval. *Conclusion*: According to the predictive estimation of the lead time distribution, to guarantee a 90% chance of early detection, it seems necessary for the males to take the fecal occult blood test every 9 months, while the females can take it annually.
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1. Introduction

Colorectal cancer (CRC) is the third most common form of cancer and the second leading cause of death for both genders among cancers in the United States. In 2008, the estimated new cases of CRC is 148,810 and the estimated CRC deaths is 49,960 [2]. CRC is most often found in people 50 years and older. The age-specific colorectal cancer risk rises continuously with advancing age [3].

Colorectal cancer can take many years to develop and early detection of colorectal cancer greatly improves the chances of a cure. Therefore, screening for the disease is recommended in individuals who are at increased risk. However, the acceptance of CRC Screening has been low in the United States [4]. In most areas of the United States, less than half of the population is in compliance with recommended colorectal cancer screening guidelines and the compliance rates may be even lower in other parts of the world [5]. Since tumors tend to bleed, blood in the stool can be a sign of colon cancer. That is where the fecal occult blood test (FOBT) comes in. It is a relatively simple, inexpensive method. Nearly 350,000 individuals [4] have participated in four FOBT randomized clinical trials. One was in Minnesota (USA) and the other three were in Europe (Nottingham, UK; Funen, Denmark; and Göteborg, Sweden).

Between 1976 and 1982 the Minnesota Colon Cancer Control Study (MCCCS) randomized approximately 46,000 subjects to receive either five annual FOBT screenings, or three biennial FOBT screenings or no screening. Each screening cycle consisted of six hemoccult slides (Hemoccult®, Beckman Coulter, Palo Alto, California), about 83% of slides were re-hydrated. If any of the slides was positive, then the screen was positive and a definitive work-up exam was done, including colonoscopy. Due to a lower than expected death rate among controls, the investigators resumed screening between 1986 and 1992. We restricted this analysis to the annual group and to the original five screenings.

We assume that the disease develops by progressing through three states, denoted by $S_0 \rightarrow S_p \rightarrow S_c$, corresponding, respectively,

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to the disease-free state; the preclinical disease state, in which an asymptomatic individual unknowingly has disease that the screening exam can detect; and the clinical state when the disease manifests itself in clinical symptoms. If a person enters the preclinical state (S_p) at age t_1, and his (or her) clinical symptoms present later at age t_2, then $(t_2 - t_1)$ is the sojourn time in the preclinical state. If he (or she) is offered a screening exam at time t within the interval (t_1, t_2), and cancer is diagnosed, then the length of the time $(t_2 - t)$ is the lead time.

The rationale behind screening is that early detection should lead to a better prognosis. For a particular case detected by screening, the lead time is unobservable. Wu et al. [1] derived the exact probability distribution for the lead time for the whole cohort who takes part in the screening, including both the screen-detected cases and the interval incident cases. The distribution is a mixture with a point mass at zero, and a piecewise continuous probability density function (PDF). Based on this research, the proportion of patients who do not benefit from the screening (whose lead time is zero) could be estimated, and the proportion who would benefit from the program could be estimated in a long run. We apply this method to the Minnesota Colorectal Cancer Control Study data and the result may help policy makers to determine how a screening program will contribute to human's health.

2. Methods

We will briefly review the probability distribution of the lead time that Wu et al. [1] developed under the progressive disease model.

Consider a cohort of initially asymptomatic individuals who enroll in a screening program. Assume there are K ordered screenings that, for a specific individual, occur at ages $t_0 < t_1 < \cdots < t_{K-1}$. The lead time distribution is a conditional distribution given that someone will develop clinical disease before death. We define D as a Bernoulli random variable, with $D = 1$ indicating the development of clinical disease and $D = 0$ indicating the absence of the clinical disease before death. We use L to denote the lead time. We consider the lead time to be zero for individuals whose disease is not detected by the screening exam but who develop clinical symptoms. The distribution of the lead time is a mixture of the conditional probability $P(L = 0|D = 1)$ and the conditional probability density function $f_L(z|D = 1)$, for any $0 < z \le T - t_0$. Here, T represents the span of the human life, which is a fixed upper bound, and t_0 is the individual's age at his/her initial screening exam.

Let $\beta(t)$ be the screening sensitivity; that is, the probability that the screening is positive conditional on the individual being in the preclinical state, where t is the individual's age at the screening exam. Define $w(t)\,dt$ as the probability of a transition from S_0 to S_p during $(t, t + dt)$. Let $q(x)$ be the probability density function of the sojourn time in S_p, and let $Q(z) = \int_z^\infty q(x)\,dx$, be the survivor function of the sojourn time in the preclinical state S_p. Throughout this article, the time variable t represents the participant's age.

The distribution for the lead time was derived as [1]:

$$P(L = 0|D = 1) = \frac{P(L = 0, D = 1)}{P(D = 1)} \quad \text{and} \quad f_L(z|D = 1) = \frac{f_L(z, D = 1)}{P(D = 1)}. \tag{1}$$

where $P(D = 1) = \int_{t_0}^{T} \int_0^t w(x)q(t - x)\,dx dt$, is the probability of developing colorectal cancer in one's life time after age t_0.

The lead time is zero if and only if the individual is an interval case, therefore the joint probability $P(L = 0,\ D = 1) = I_{K,1} + I_{K,2} + \cdots + I_{K,K}$, where $I_{K,j}$ is the probability of an interval case within the interval (t_{j-1}, t_j), and it was derived as:

$$I_{K,j} = \sum_{i=0}^{j-1}(1 - \beta_i)\cdots(1 - \beta_{j-1}) \int_{t_{i-1}}^{t_i} w(x)[Q(t_{j-1} - x) - Q(t_j - x)]\,dx + \int_{t_{j-1}}^{t_j} w(x)[1 - Q(t_j - x)]\,dx$$

for all $j = 1, 2, \ldots, K$, with $\beta_i = \beta(t_i)$ is the sensitivity at age t_i.

The joint PDF $f_L(z, D = 1)$ in Eq. (1) was derived as:

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

where $z \in (T - t_j,\ T - t_{j-1})$, $j = 2, \cdots, K$. And when $j = 1$, it is simplified as:

$$f_L(z, D = 1) = \beta_0 \int_0^{t_0} w(x)q(t_0 + z - x)\,dx, \quad \text{if } z \in (T - t_1, T - t_0).$$

3. Results

We applied our method to the Minnesota colorectal data. Wu et al. [6] estimated the age-dependent sensitivity $\beta(t)$, the age-dependent transition probability $w(t)$ and the sojourn time distribution $q(x)$ from the MCCCS study group from a Bayesian approach [7]. The parametric models for $\beta(t), w(t)$ and $q(x)$ has six unknown parameters, that is, $\theta = (b_0, b_1, \mu, \sigma^2, \kappa, \rho)$. We used the same non-informative prior for both sexes, fitting them separately [6]. We summarized the Bayesian posterior estimates for the age-dependent sensitivity and transition probability for both genders in Table 1, for 40, 50, 60, ..., 90 years old, and we also draw the estimated sojourn time distribution in Fig. 1. The posterior median sojourn time was estimated as 1.66 and 1.88 years for males and females, respectively; however, the estimated posterior mean sojourn time was very different for both genders, it was 4.07 years for males and 2.41 years for females. It seemed that the estimated sojourn time distribution for males was more spread out than that of females. We will use the posterior samples θ_i^* to project the lead time distribution for the male and female participants.

Given the Minnesota study group data, the posterior predictive distribution of the lead time z can be estimated by the Monte Carlo

Table 1
Estimation of screening sensitivity, transition probability and sojourn time for males and females using MCCCS data.

Age	Males			Females		
	Median	Mean	S.E.	Median	Mean	S.E.
Sensitivity						
40	0.292	0.412	0.358	0.166	0.309	0.323
50	0.646	0.616	0.274	0.616	0.585	0.268
60	0.910	0.829	0.194	0.940	0.874	0.152
70	0.961	0.877	0.186	0.989	0.943	0.103
80	0.990	0.876	0.201	0.998	0.961	0.092
90	0.997	0.859	0.242	1.000	0.964	0.108
Transition probability density[a]						
40	0.248	0.353	0.312	0.032	0.069	0.114
50	0.795	0.828	0.311	0.298	0.338	0.206
60	1.389	1.394	0.301	0.987	1.008	0.226
70	1.674	1.698	0.450	1.773	1.788	0.385
80	1.611	1.597	0.431	2.021	2.055	0.467
90	1.294	1.259	0.289	1.753	1.732	0.290

[a] The unit is 10^{-3}.

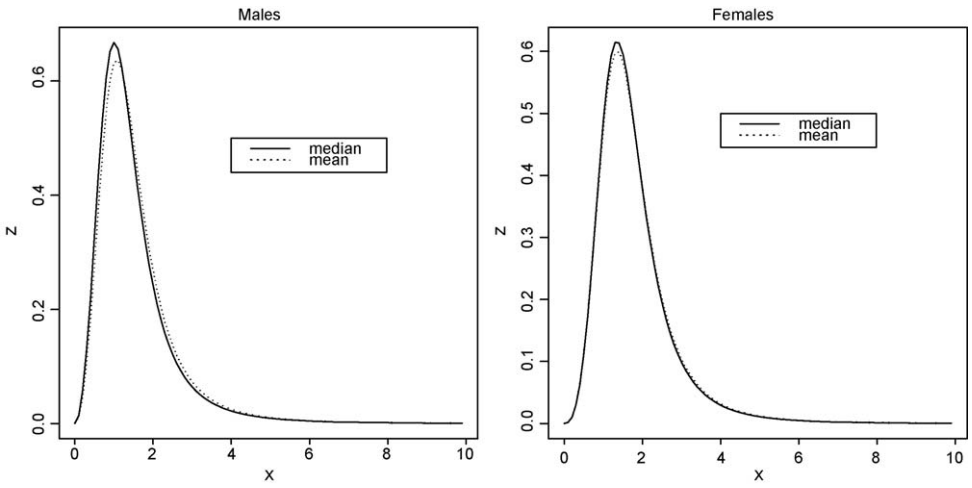

Fig. 1. The estimated sojourn time distribution for both genders using the posterior mean and median of parameters (κ, ρ).

simulation as follows [8].

$$f(z|Data) = \int f(z,\theta|Data)\,d\theta = \int f(z|\theta,Data)\,f(\theta|Data)\,d\theta \approx \frac{1}{n}\sum_i f(z|\theta_i^*). \quad (2)$$

where $f(z|\theta_i^*)$ represents the mixture distribution in Eq. (1).

We applied our method to make predictive inference in the case of a program consisting of periodic fecal occult blood tests for males and females aged 50–80 years. We estimated what the results would be if people were screened at different screening intervals. The results are summarized in Table 2. The time interval Δ between screens was 6, 9, 12, 18 and 24 months, within ages 50 (t_0) and 80 years (T). The density curves for the lead time are shown in Figs. 2 and 3 for different screening intervals for both males and females. From these results, we see that if a man begins annual screening (i.e. $\Delta = 12$ months) when he is 50 years old and continues until he reaches 80, then there is a 18.87% chance that he will not benefit from early detection by the screening program if he develops colorectal cancer during those 30 years. His chance of no benefit from the screening program decreases to 6.45% if the exams are 6 months apart. While for the females, the chance of no early detection is 9.48% for annual test and 2.39% for 6 months test.

Table 2 shows that the mean lead time increases as the screening time interval decreases for both males and females. In other words, more screening exams will contribute to a longer lead time, which would translate to treatment of the disease at an earlier stage and, potentially improved prognosis. The increase in the mean lead time is partly due to the smaller point mass for zero lead time when screening exams are closer together. The standard error of the lead time decreases as the time between screening exams increases. Table 2 also reveals that the standard deviation for the program's lead time is larger than the mean lead time. In the table, the mode of the lead time, which is the value that is most likely taken by the lead time when it is positive, is 0.68 years (or 8 months), corresponding to screening exams every 6 months for males, and 0.96 years (or 11.5 months) for females. With annual exams, the mode value for the lead time is 0.6 years (6 months) for males and 0.78 years (9.4 months) for females.

4. Discussion

We applied the method of Wu et al. [1] to the Minnesota colorectal data and get some valuable information on the benefit of fecal occult blood test for colorectal cancer. Our model characterizes two aspects of a screening program's benefit. One aspect is the proportion of clinical (interval) cases among the program's participant; this is the same as the probability of no benefit. The second aspect is the length of time by which screening advances the age of diagnosis of cancer. This length of time will hopefully lead to treatment of disease in earlier stages of development and a better prognosis. The ultimate goal of a cancer screening program is to reduce cancer mortality. Reduction in cancer mortality is discussed in Mandel et al. [8]. Our model contributes to the study of a screening program in other ways. One can use our model to evaluate and compare the characteristics of different possible screening programs. For example, the model can provide answers to questions, such as what may be the outcomes of FOBT screening exams for an individual in his/her 50 s or 60 s? How do these outcomes change as the frequency of screening exams changes (e.g., screening every 6, 12, or 24 months)? What is the probability that one's cancer will be detected early if he/she has cancer? How does changing the screening program affect the lead time distribution? Our model showed that the mean lead time increases as the interval between screening exams became shorter.

There were other data sets to be used to estimate the FOBT screening sensitivity, mean sojourn time (MST). Launoy et al. [9]

Table 2
Lead time estimation for males and females using Minnesota data.

Δ	Number of screens	Males					Females				
		P_1	$1-P_1$	Mode	Mean	S.E.	P_1	$1-P_1$	Mode	Mean	S.E.
6 months	60	6.45	93.55	0.68	1.640	2.408	2.39	97.61	0.96	1.699	1.690
9 months	40	12.22	87.78	0.58	1.474	2.331	5.31	94.69	0.86	1.552	1.665
12 months	30	18.87	81.13	0.50	1.333	2.265	9.48	90.52	0.78	1.419	1.643
18 months	20	32.15	67.85	0.34	1.111	2.151	20.33	79.67	0.64	1.192	1.599
24 months	15	43.11	56.89	0.24	0.949	2.051	31.51	68.49	0.52	1.015	1.550

$\Delta = t_i - t_{i-1}$ is the time interval between screens.
$P_1 = P(L=0|D=1)$ is the probability of "no benefit." The columns of P_1 and $(1-P_1)$ are in percentages. All other columns are in years.

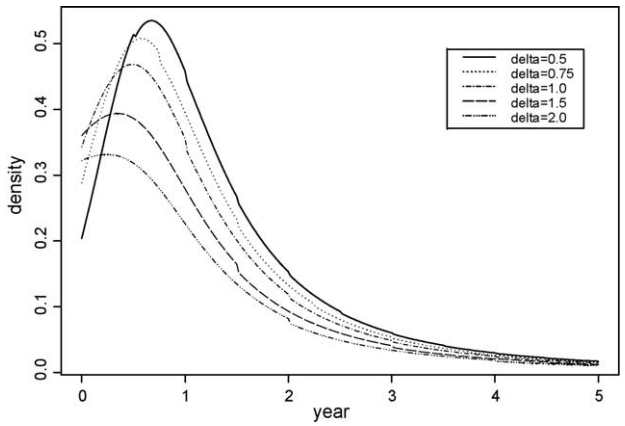

Fig. 2. The probability density curve of the lead time for male participants.

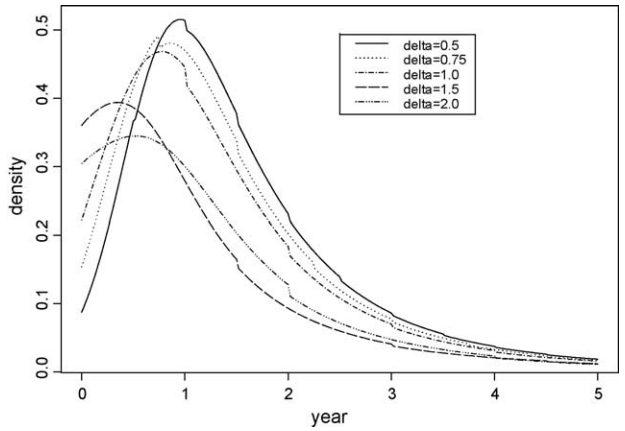

Fig. 3. The probability density curve of the lead time for female participants.

estimated the FOBT mass-screening sensitivity to be about 50%, using the data in France, however, their estimated MST was higher, between 4.5 and 5 years for all combined cancer cases. Prevost et al. [10] compared different statistical approaches to estimate sensitivity and sojourn time for colorectal cancer. Their estimates of the MST were about 2, 3, and 6 years for age groups 45–54, 55–64 and 65–74 years olds, correspondingly, and their estimates of sensitivity were approximately 0.75, 0.50 and 0.40 for the respective age groups mentioned above. From their results, it seemed that the estimates of the sensitivity and the mean sojourn time were negatively correlated; we observed the same scenario in our simulations; this negative correlation was also pointed out by Walter and Day [11].

There were other ways to estimate the lead time. Prorok [12] derived the conditional distribution of the lead time given that someone was diagnosed with cancer at the *i*th screening exam. Our model includes his as a special example [1]. There were other papers on the estimation of the mean and the variance of the lead time for the screen-detected case, see [13,14] among others. Usually their model assumes that the sojourn time has an exponential distribution, hence the lead time has an exponential distribution as well, due to the memoryless property of the exponential random variable. Therefore these researchers really estimated the sojourn time (or the lead time), and focused on the screen-detected cases only. Our model includes both screen-detected cases and interval cases, and we also provide probability density for the lead time, no matter what kind of distribution that the sojourn time takes; it is a more generalized probability model.

Our simulation results seemed to suggest adopting a short screening time interval for the FOBT test, especially for males. A recent Cochrane review paper showed that FOBT (Hemoccult) can significantly reduce the relative risk of colorectal cancer mortality [15]. However, the fecal occult blood test has undergone some big changes since the Minnesota screening study was done. As pointed out by an anonymous reviewer, the immunochemical FOBT has been found to have higher sensitivity and higher specificity than the traditional Hemoccult test [16]. From our simulation, usually higher sensitivity, longer sojourn time would contribute to longer lead time and higher probability of early-detection, therefore leading to less screening frequency. The methods presented in this paper can still be applied to evaluate screening trials. Under the conditions of the MCCCS trial, we have shown that the fecal occult blood test seemed to work better for females than for males. From the SEER Fast Stats Results [3], the probability of developing colorectal cancer for females is slightly lower than that of males for every age group of 5 years. To guarantee the chance of early detection to be around 90%, it seems necessary for males to take the test every 9 months, while females could have taken it annually to achieve the same result. However, shorter screening intervals may cause more false-positive cases and may bring a bigger burden to hospitals and individuals financially.

Conflict of interest statement

We declare that we have no conflict of interest.

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