Scheduling of the Upcoming Screening Exam using CT in Lung Cancer

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Abstract

We have applied a newly developed method on scheduling CT screening exam in lung cancer, based on an asymptomatic individual's current age, screening history, risk tolerance and other parameters. The probability of incidence was a function of the next screening time, so that the future screening time can be found by limiting this risk to a small value α. That is, with probability $1-\alpha$, one will not be a clinical incident case before the next exam. We estimated the lead time distribution and probability of overdiagnosis if one would be diagnosed with cancer at the next screening, so that predictive information could be provided to individuals on how early the disease could be detected and the risk of overdiagnosis. We applied the methods to two cohorts (male and female heavy smokers) in the National Lung Screening Trial using low dose computerized tomography (NLST-CT), comparing their future screening times, lead time and overdiagnosis by simulations. Under the same conditions, male heavy smokers need to schedule the next exam earlier than their female counterparts do; and older people should schedule it earlier than the younger ones. The mean lead time of female heavy smokers is longer than that of males; the risk of overdiagnosis is small for both genders, although it is a little bit higher in male than in female heavy smokers.

Key Words: Scheduling, incidence, sensitivity, sojourn time, overdiagnosis, lead time

1. Introduction

Early detection and effective treatments are vital to increase the cure rate and prolong survival of cancer patients. The primary technique for implementing early detection is screening exams, which seems effective in detecting tumors early before symptoms are present. Although numerous studies have been done in this area, it remains a fundamental challenge to schedule the upcoming screening exam: for a person who has just being screened with a *negative* result, when should he/she take the next exam? Using lung cancer incidence and screening as an example, we will provide a solution using probability modeling.

Lung cancer is the second most common form of cancer and the leading cause of cancer deaths for both genders in the US (see SEER Fast Stats Results). It occurs more often in older people: about 2/3 of people diagnosed with lung cancer are 65 or older, and less than 2% are younger than 45; the average age at diagnosis is around 70 (American Cancer Society). There are two major types of lung cancer: small cell (SCLC) and non-small cell (NSCLC). SCLC often spreads more quickly and accounts for 10-15% of lung cancer; while NSCLC grows at a slower rate and accounts for 85%. Clinical stage at diagnosis is a major determinant of survival after therapy (Mountain 1997, Henschke et al 2006); however, according to SEER Fast Stats Results, the average five-year survival rate for lung cancer patients is about 17.7%.

Several major randomized controlled lung cancer mass screening studies have been carried out in North America since the 1970s. The National Lung Screening Trial is the most recently finished study, which is designed to compare two different screening modalities for early detection: low-dose helical computed tomography (LDCT) and standard X-rays

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among heavy smokers (National Lung Screening Trial Research Team 2010, 2011). Results from the NLST seem to indicate that smokers screened by spiral low-dose computed tomography (LDCT) had a 20% lower chance of dying from lung cancer than those who were screened via chest X-rays. However, due to the complexities of lead time bias and overdiagnosis, no formal test has been shown to reduce lung cancer mortality. The United States Preventative Services Task Force (USPSTF) has recommended annual screening exams using low-dose CT for heavy smokers 55 to 80 years old since December 2013 (Moyer, VA. on behalf of the U.S. Preventive Services Task Force 2014).

Questions come concerning optimal scheduling with increased effort at early detection. However, there are limited research in this area. Some research using utility function (or cost) to find the optimal scheduling for $n + 1$ exms in a fixed age interval (Zelen 1993, Lee and Zelen 1998); and some other research focus on cancer risk modeling. These are valuable, even though the methods cannot be applied to schedule the next exam directly. Physicians observed that "intervals for screening tests should not be uniform" based on their daily practice (Lashner et al 1988).

We have developed a different approach to handle the scheduling of upcoming exam for chronic disease, such as cancer. We will not use weight, cost, nor utility functions; instead, we will directly calculate the risk of incidence before the next exam, given one's age, gender, screening history and other parameters; then the next screening time will be chosen, such that the incidence risk will be bounded by some (preselected) small value, such as 10% or less. Hence, with 90% or more possibility, a person at risk will not become a clinically incident case between two screening exams if s/he would follow this schedule. We also derive the lead time distribution and the probability of overdiagnosis, if one would be diagnosed with cancer at the next scheduled exam. This provides individuals predictive information regarding how early the diagnosis of cancer could be if one would develop cancer and would follow this schedule. This is a method that could be directly used by physicians/diagnostic radiologists to schedule a person's future exam. We have applied the method to women's breast cancer using the Health Insurance Plan of Greater New York data (Wu and Kafadar 2019). Now in this project, we will apply the existing methods to lung cancer scheduling for male and female heavy smokers, using low-dose CT, based on the National Lung Screening Trial (NLST) data.

2. Dataset and Methods

We will briefly describe the NLST dataset, and review the method that we have developed for optimal scheduling, lead time and overdiagnosis estimation.

2.1 The NLST Data

The National Lung Screening Trial (NLST) is the most recently finished study. The purpose of the project was to compare two different screening modalities for early detection: low-dose helical computed tomography (or spiral CT) with standard chest X-rays among heavy smokers (National Lung Screening Trial Research Team 2010, 2011). The spiral CT uses X-rays to obtain a multiple-image scan of the entire chest, while a standard chest X-ray produces a single image of the whole chest. Participants were either current or former heavy smokers, but were without signs, symptoms, or history of lung cancer (i.e. asymptomatic heavy smokers). There were 54,000 male or female heavy smokers enrolled in the study, with initial screening age between 55 and 74 in 33 centers across the United States, between August 2002 and April 2004. All participants were evenly randomized to one of two arms: chest X-ray arm or the low dose CT arm. Three annual screening exams were provided to

each participant in each arm. Although five-year survival rates approach 70% with surgical resection of stage IA lung cancer (NSCLC that is 3cm across or smaller), more than 75% of patients with locally advanced or metastatic lung cancer have a five-year survival of less than 5%. The primary endpoint of the NLST is lung cancer mortality, however, no test has been shown to reduce lung cancer mortality significantly so far.

Table 1. Overview of the NLST Data

Group within Study	[a]total subj.	[b]Screen-diag. No.	[c]Interval No.
The NLST: Chest X-ray			
Overall	26226	279	177
male smokers	15500	165	107
female smokers	10726	114	70
The NLST: Spiral CT			
Overall	26452	649	60
male smokers	15621	384	44
female smokers	10831	265	16

[a]Total number of people who ever received lung cancer screens.
[b]Total number of subjects diagnosed by regular screening.
[c]Total number of clinical incident cases between two regular screenings.

We summerized the NLST data in Table 1. It is obvious that more tumors were diagnosed in the low-dose CT arm than in the chest X-ray arm, which implies that the sensitivity of spiral CT may be higher than that of chest X-ray. Two cohorts from the CT arms (male vs. female heavy smokers) will be used in this project.

2.2 Methods

We briefly review the methods that we have developed regarding scheduling for the next exam in Wu and Kafadar 2019. The methods were originally developed using the Health Insurance Plan of Greater New York (HIP) of breast cancer screening as an example. We will apply the methods to the NLST low-dose CT arm data for male and female heavy smokers in this project.

A cohort of asymptomatic people are enrolled in a screening program to detect a specific disease. The disease progressive model $S_0 \rightarrow S_p \rightarrow S_c$ is exhibited in Figure 1. S_0 refers to the *disease-free state* or the state in which the disease cannot be detected; S_p refers to the *preclinical state*, in which an asymptomatic individual unknowingly has the disease that a screening exam can detect; and S_c refers to the *clinical state* at which the disease manifests itself in clinical symptoms. The progressive model describes the natural history of tumor growth (Zelen and Feinleib 1969). The goal of screening is to detect the disease in the preclinical state S_p. The time duration in S_p is called sojourn time. If one is screened and diagnosed with cancer at time $t \in (t_1, t_2)$, then $(t_2 - t)$ is called the lead time, the length of time that diagnosis is advanced by screening. Sensitivity is the probability that a screening result is positive, given that a person is in the preclinical stage Sp. Another important term is transition density, the probability density function (PDF) of the time duration in the disease-free state S_0. The sensitivity, the sojourn time, and the transition density are the three key parameters in screening, because all other terms can be expressed as functions of these three.

Consider an asymptomatic individual who has gone through a series of exams at her ages $t_0 < t_1 < \cdots < t_{K-1}$, and got all negative screening results, and her current age is t_{K-1}. We use $\beta_i = \beta(t_i)$ to represent screening sensitivity at age t_i. We let $q(x)$ be the probability density function (PDF) of sojourn time in S_p; and let $Q(y) = \int_y^\infty q(x)dx$ be

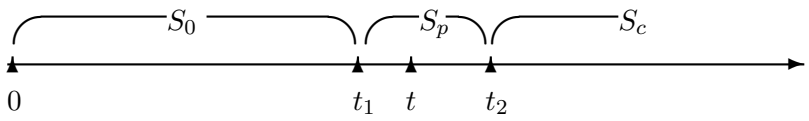

Figure 1: Disease states and the lead time.

the survival function of sojourn time. And we define $w(t)$ as the PDF of time duration in the disease-free state S_0. Suppose she will take the next exam at time t_x, that is, at her age $t_{K-1} + t_x$, where t_x is unknown. See Figure 2 (Wu et al 2018),

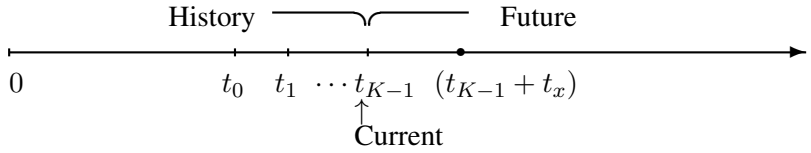

Figure 2: Screening history and future events

We define four events H_K, I_K, D_K and A_K based on her screening experience and future events:

$$\begin{aligned}
H_K &= \left\{ \begin{array}{l} \text{one is asymptomatic in } [0, t_{K-1}] \text{ after} \\ \text{taking } K \text{ exams at ages } t_0 < t_1 < \cdots < t_{K-1} \end{array} \right\}, \\
I_K &= \{ \text{ one will be a clinical incident case first time in } (t_{K-1}, t_{K-1} + t_x)\}, \\
D_K &= \{ \text{ one will be diagnosed with cancer at } (t_{K-1} + t_x) \text{ for the first time}\}, \\
A_K &= \{ \text{ one will be asymptomatic in } (t_{K-1}, t_{K-1} + t_x]\}.
\end{aligned}$$

The three mutually exclusive events (I_K, D_K, A_K) define what would happen before and at the next exam; and they include all possible outcomes in $(t_{K-1}, t_{K-1} + t_x]$, i.e., they form a partition of the sample space

$$I_K \cup D_K \cup A_K = H_K.$$

Notice that her risk of cancer before the next exam is composed of two events I_K or D_K, and the probability of incidence before the next screening exam is:

$$P(I_K | I_K \cup D_K, H_K) = \frac{P(I_K \cap H_K)}{P(H_K) - P(H_{K+1})}, \tag{1}$$

where $P(H_K)$ and $P(I_K \cap H_K)$ are (Wu and Kafadara 2019):

$$\begin{aligned}
P(H_K) &= 1 - \int_0^{t_{K-1}} w(x)dx \qquad (2) \\
&+ \sum_{i=0}^{K-1} (1-\beta_i) \cdots (1-\beta_{K-1}) \int_{t_{i-1}}^{t_i} w(x) Q(t_{K-1} - x) dx \\
P(I_K \cap H_K) &= \sum_{i=0}^{K-1} (1-\beta_i) \cdots (1-\beta_{K-1}) \int_{t_{i-1}}^{t_i} w(x) [Q(t_{K-1} - x) - Q(t_K - x)] dx \\
&+ \int_{t_{K-1}}^{t_K} w(x)[1 - Q(t_K - x)]dx, \qquad (3)
\end{aligned}$$

And $P(H_{K+1})$ is just changing the index of K to $K+1$ in equation (2).

This probability of incidence $P(I_K|I_K \cup D_K, H_K)$ is monotonically increasing as the upcoming screening time interval t_x increases. Therefore, for any pre-selected small value α, there exists a unique numerical solution t^*, that satisfies

$$P(I_K|I_K \cup D_K, H_K) = \frac{P(I_K \cap H_K)}{P(H_K) - P(H_{K+1})} = \alpha. \tag{4}$$

That is, with probability $(1-\alpha)$, she will NOT be a clinical cancer case before her next screening exam at her age $(t_{K-1} + t^*)$, where t_{K-1} is her current age. One may choose $\alpha = 0.05$ or 0.10, or, any risk level that she is comfortable with.

After t^* is found, we can calculate the distribution of lead time and probability of overdiagnosis (and true-early-detection) at $t_K = t_{K-1} + t^*$, if one were diagnosed with cancer at t_K.

We let L be the lead time, and $t_K = t_{K-1} + t^*$, then the conditional probability density function (PDF) of the lead time given the event D_K is

$$f_L(z|D_K) = \frac{f_L(z, D_K)}{P(D_K)}, \qquad \text{for } z \in (0, \infty). \tag{5}$$

Where

$$\begin{aligned} P(D_K) &= \beta_K \left\{ \sum_{i=0}^{K-1} (1-\beta_i) \cdots (1-\beta_{K-1}) \int_{t_{i-1}}^{t_i} w(x) Q(t_K - x) dx \right. \\ &+ \left. \int_{t_{K-1}}^{t_K} w(x) Q(t_K - x) dx \right\}. \end{aligned} \tag{6}$$

$$\begin{aligned} f_L(z, D_K) &= \beta_K \left\{ \sum_{i=0}^{K-1} (1-\beta_i) \cdots (1-\beta_{K-1}) \int_{t_{i-1}}^{t_i} w(x) q(t_K + z - x) dx \right. \\ &+ \left. \int_{t_{K-1}}^{t_K} w(x) q(t_K + z - x) dx \right\}. \end{aligned} \tag{7}$$

This is a valid PDF since $\int_0^\infty f_L(z|D_K)dz = 1$. And $f_L(z|D_K)$ is a smooth function of the lead time z.

To calculate the probability of overdiagnosis and true-early-detection at the future time point t^*, we first let the lifetime T to be a fixed value, then let it to be random. Given one would be diagnosed at $t_K = t_{k-1} + t^*$, with a fixed lifetime $T = t (> t_K)$, the probability of overdiagnosis and true-early-detection are:

$$\begin{aligned} P(\text{OverD}|D_K, T = t) &= \frac{P(\text{OverD}, D_K|T = t)}{P(D_K|T = t)}, \\ P(\text{TrueED}|D_K, T = t) &= \frac{P(\text{TrueED}, D_K|T = t)}{P(D_K|T = t)}. \end{aligned}$$

Where $P(D_K|T = t) = P(D_K)$ as in equation (6), and

$$\begin{aligned} &P(\text{OverD}, D_K|T = t) \\ &= \beta_K \left\{ \sum_{i=0}^{K-1} (1-\beta_i) \cdots (1-\beta_{K-1}) \int_{t_{i-1}}^{t_i} w(x) Q(t - x) dx \right. \\ &+ \left. \int_{t_{K-1}}^{t_K} w(x) Q(t - x) dx \right\}. \end{aligned} \tag{8}$$

$$
\begin{aligned}
&P(\text{TrueED}, D_K|T=t) \\
&= \beta_K \left\{ \sum_{i=0}^{K-1} (1-\beta_i)\cdots(1-\beta_{K-1}) \int_{t_{i-1}}^{t_i} w(x)[Q(t_K-x)-Q(t-x)]dx \right. \\
&+ \left. \int_{t_{K-1}}^{t_K} w(x)[Q(t_K-x)-Q(t-x)]dx \right\}. \qquad (9)
\end{aligned}
$$

And it can be verified that

$$P(\text{TrueED}|D_K, T=t) + P(\text{OverD}|D_K, T=t) = 1.$$

Now we allow human lifetime T to be random, and let $f_T(t|T>t_k)$ be the conditional PDF of the lifetime T, derived from the actuarial life table: US Social Security Administration, http://www.ssa.gov/OACT/STATS/table4c6.html (Wu et al 2012). Then,

$$
\begin{aligned}
P(\text{OverD}|D_K, T>t_K) &= \int_{t_K}^{\infty} P(\text{OverD}|D_K, T=t) f_T(t|T>t_K)dt, \\
P(\text{TrueED}|D_K, T>t_K) &= \int_{t_K}^{\infty} P(\text{TrueED}|D_K, T=t) f_T(t|T>t_K)dt.
\end{aligned}
$$

Where

$$
f_T(t|T\geq t_K) = \begin{cases} \frac{f_T(t)}{P(T>t_K)} = \frac{f_T(t)}{1-F_T(t_K)}, & \text{if } t \geq t_K, \\ 0, & \text{otherwise.} \end{cases}
$$

3. Application to the NLST-CT Data

We now apply the method of scheduling to the NLST low-dose CT arm data for male and female heavy smokers. After we found the schduling time t^*, we will use it to estimate the lead time and probability of overdiagnosis and true-early-detection.

From the two cohorts (male and female heavy smokers) in the NLST CT data, we first estimated the three key parameters: sensitivity $\beta(t)$, PDF of sojourn time $q(x)$, and transition density $w(t)$. These three key parameters are critical since the probability of incidence in equation (1) is a function of these three key parameters. We used a likelihood function and parametric modeling to estimate these three from the NLST CT arm data (Liu etal 2015), where

$$
\begin{aligned}
\beta(t|b_0, b_1) &= \frac{1}{1+\exp(-b_0-b_1*(t-m))}, \\
w(t|\mu, \sigma^2) &= \frac{0.3}{\sqrt{2\pi}\sigma t} \exp\left\{-(\log t-\mu)^2/(2\sigma^2)\right\}, \\
Q(x|\lambda, \alpha) &= \exp(-\lambda x^{\alpha}), x>0, \lambda>0, \alpha>0.
\end{aligned}
$$

The unknown parameters in the likelihood is $\theta = (b_0, b_1, \mu, \sigma^2, \lambda, \alpha)$. Using Markov Chain Monte Carlo (MCMC) with Gibbs sampler, 130,000 samples were generated; after 30,000 burn-in and thinning every 200 iterations, we obtained a sample of 500 from each chain. Runing two initially over-dispersed chains provide 1000 Bayesian posterior samples (θ_j^*) for each gender. For more details, see Liu et al 2015.

We designed hypothetical cohorts in our simulation: For each gender, we have three big cohorts according to the initial screening age t_0 and current age t_{K-1}: $(t_0, t_{K-1}) = (56, 62), (62, 68)$ and $(68, 74)$. Then within each age cohort, we split it into three smaller groups, by assuming that the historical screening time interval Δ from t_0 to t_{K-1} was 1, 2 or 3 years. So, there were 9 cohorts for each gender in the simulation. Then we used the 1000 posterior samples $\theta_j^*, j = 1, 2, \ldots, 1000$ from the MCMC for each gender to make Bayesian inference on optimal scheduling.

For each θ_j^*, using $P(I_K|I_K \cup D_K, H_K, \theta_j^*) = \alpha$, a scheduling time $t_j^*(j = 1, 2, \ldots, 1000)$ can be found; We calculated the mean and 95% Confidence Interval (CI) of the future screeing time interval t_j^* (in years) and summerized the results in Table 2.

Table 2: Estimated posterior mean scheduling time t^* and 95% CI

$t_0 = 56, t_{K-1} = 62$						
	Female			Male		
$\alpha\backslash\Delta$	1.0	2.0	3.0	1.0	2.0	3.0
0.05	0.91(0.65,1.17)	0.75(0.23,1.08)	0.71(0.16,1.07)	0.62(0.23,0.92)	0.45(0.10,0.83)	0.42(0.10,0.82)
0.10	1.26(1.00,1.55)	1.18(0.86,1.48)	1.16 (0.77,1.46)	0.96(0.61,1.26)	0.84(0.26,1.17)	0.82(0.24,1.16)
0.15	1.52(1.25,1.89)	1.47(1.19,1.81)	1.46(1.17,1.78)	1.21 (0.91,1.52)	1.13(0.59,1.45)	1.12 (0.54,1.44)
0.20	1.75(1.43,2.16)	1.71(1.40,2.11)	1.70(1.40,2.09)	1.43 (1.15,1.76)	1.37(0.95,1.71)	1.36(0.88,1.70)
$t_0 = 62, t_{K-1} = 68$						
	Female			Male		
$\alpha\backslash\Delta$	1.0	2.0	3.0	1.0	2.0	3.0
0.05	0.89(0.50,1.18)	0.71(0.14,1.11)	0.66(0.11,1.10)	0.58(0.13,0.95)	0.43(0.10,0.86)	0.41 (0.10,0.86)
0.10	1.23(0.92,1.55)	1.13(0.55,1.48)	1.11(0.41,1.46)	0.90(0.33,1.28)	0.78(0.16,1.21)	0.75(0.15,1.20)
0.15	1.49(1.19,1.86)	1.43(0.99,1.80)	1.41(0.91,1.78)	1.15(0.58,1.52)	1.05(0.30,1.47)	1.03(0.27,1.46)
0.20	1.71(1.39,2.15)	1.67(1.29,2.10)	1.65(1.25,2.09)	1.36(0.84,1.76)	1.28(0.49,1.72)	1.27 (0.45,1.72)
$t_0 = 68, t_{K-1} = 74$						
	Female			Male		
$\alpha\backslash\Delta$	1.0	2.0	3.0	1.0	2.0	3.0
0.05	0.85(0.29,1.19)	0.68(0.10,1.13)	0.64 (0.10,1.13)	0.55(0.10,0.99)	0.42(0.10,0.91)	0.40(0.10,0.90)
0.10	1.20(0.69,1.55)	1.07(0.29,1.48)	1.04(0.24,1.48)	0.84 (0.18,1.30)	0.73(0.11,1.24)	0.70(0.10,1.22)
0.15	1.45(1.02,1.85)	1.37(0.66,1.80)	1.34(0.52,1.77)	1.08(0.31,2.53)	0.98(0.19,1.48)	0.96(0.17,1.48)
0.20	1.67(1.27,2.13)	1.61(1.01,2.09)	1.59(0.89,2.08)	1.29 (0.47,1.76)	1.20(0.28,1.73)	1.18(0.26,1.73)

This is how to read Table 2: under the big column "Female" and "$t_0 = 56, t_{K-1} = 62$", look at the row when $\alpha = 0.10$, it shows that if $\Delta = 1.0$ years (i.e., one had annual exam from 56 to 62 years old), then she should come back after 1.26 years (about 15 months) if she wants to have a probability of 90% early detection. From Table 2, we can see that the scheduling time t^* increases as the incidence risk α increases. i.e., heavy smokers can come back at a later time if they want to maintain a 80% early detection rather than a 90% early detection. The mean of t^* decreases as current age increases, i.e. older smokers should take the next exam earlier than younger ones when other conditions are the same. Under the same conditions, male heavy smokers should take the next exam earlier than their female counterparts. Historic screening interval and the future screening time are negatively correlated: shorter screening interval in the past means larger t^* for the upcoming test, and vise versa.

We then estimated the lead time and risk of overdiagnosis if one would be diagnosed with cancer at the future time point $t_K = t_{K-1} + t^*$. One lead time PDF can be obtained by using each pair of (θ_j^*, t_j^*), with $j = 1, 2, \ldots, 1000$, and the posterior distribution of the lead time is the average: $f_L(x|NLST) = \frac{1}{1000}\sum_{j=1}^{1000} f_L(x|\theta_j^*, t_j^*)$. We then calculate the mean, median, mode and standard deviation of the lead time using $f_L(x|NLST)$. The lead time density curves of the age group $(t_0, t_{K-1}) = (56, 62)$ under all combinations of α and Δ for the two genders are plotted in Figure 3.

The distribution of lead time changes with gender: male heavy smokers usually have a relatively shorter mean lead time than their female counterpart, if the t^* is adopted. If the current age is fixed, and let other parameters (α, Δ) change, the lead time curve would be almost the same for both genders. That is, one's current age won't affect the lead time much. That's why we only plotted the case of $(t_0, t_{K-1}) = (56, 62)$ in Figure 3. This maybe due to the fact that sensitivity of low-dose CT barely changes with one's age. However, there are some differences of the lead time between the two genders. The mean lead time for female is between 1.00 to 1.24 years, with a standard deviation (SD) of 0.66 to 0.71 years. The mean lead time for male is between 0.95 to 1.13 years, with a SD between 0.61 and 0.68 years. The median lead time for female is between 0.90 to 1.17 years; while the median for male is between 0.84 to 1.05 years. The mode of the lead time for female is between 0.66 and 1.08 years, and it is between 0.61 to 0.95 years for male. In summary, the mean, the median and the mode of the lead time for male heavy smokers is shorter/smaller than their female counterparts. And the mode is less than the median, and the median is less than the mean.

Finally, we used each pair (θ_j^*, t_j^*), $j = 1, 2, \ldots, 1000$, to estimate the probability of overdiagnosis; And of course, the probability of true-early-detection is 1 minus probability of overdiagnosis. The posterior mean and standard error are listed in Table 3. The probability of overdiagnosis is very low in the NLST-CT study ($< 3.91\%$). This risk slightly increases with one's current age for both

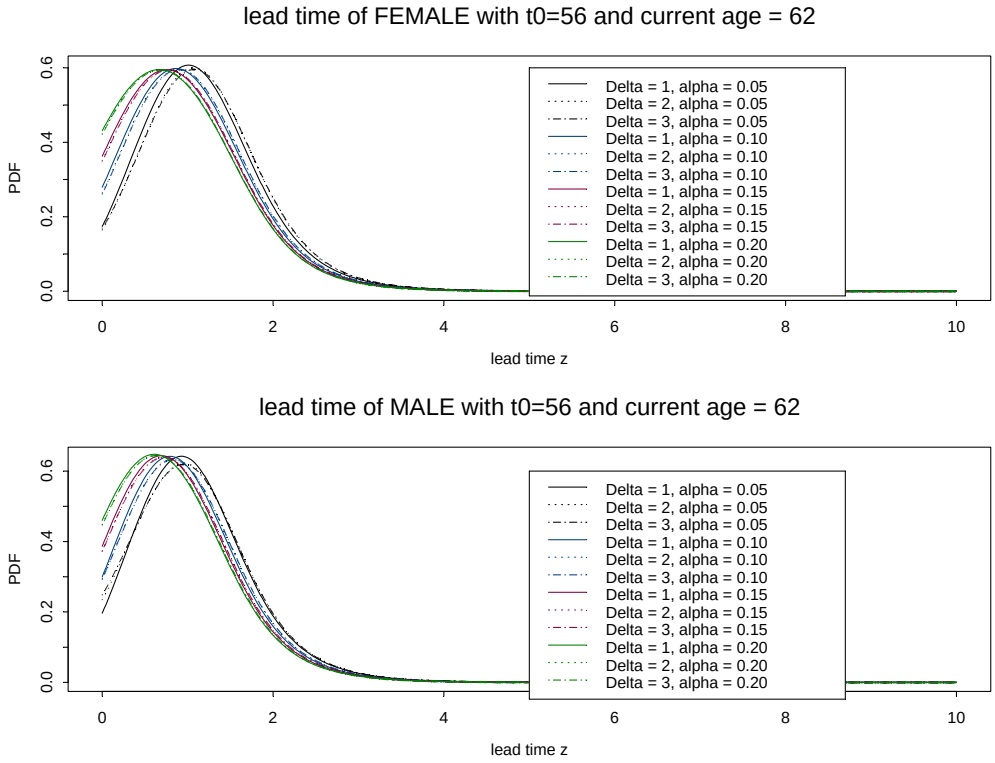

Figure 3: Lead time density curve

genders. And it is slightly higher for male heavy smokers than their female counterparts. It slightly decreases when α increases. The maximum probability of overdiagnosis is less than 6% for females and it is less than 7% for males in our simulation. In summary, Overdiagnosis is not a big issue using low-dose CT in lung cancer screening.

4. Discussion and Conclusion

Wu and Kafadar 2019 developed a probability method to dynamically schedule one's upcoming screening exam, based on one's past screen history, risk tolerance α, screening sensitivity, sojourn time distribution, etc., and have applied it to women's breast cancer screening. In this study, we applied the same method to lung cancer screening using low-dose CT for both males and females heavy smokers. In fact, the method can be applied to any kinds of screening for chronic disease, and it can handle any screening history $t_0 < t_1 < ...t_{K-1}$, including those not equally-spaced screening intervals.

Theoretically (and verified by simulations) the incidence risk increases as scheduling time for next exam increases. That is, for those who can tolerate higher incidence risk or consider themselves low risk for a specific cancer, they can come back for the next exam at a later date. The scheduling time decreases as one's current age increases if other conditions are the same; which means, older smokers should come back earlier than younger ones if other conditions are the same. And male heavy smokers should take their next exam earlier than their female counterparts. Simulation also shows that screening history, especially the length of past screening interval affects the timing of the next exam. Shorter screening interval in the past means one can come back later for the upcoming test.

Robbins et al 2019 analyzed participants who had negative CT results in the NLST study, and using their newly developed Lung Cancer Risk Assessment Tool + CT, they predicted short-term lung cancer risk following a negative CT screen. Their results support the idea "that many, but not all, screen-negatives might reasonably lengthen their CT screening interval." Our result seems to be

Table 3: Estimated mean probability of overdiagnosis and s.e. (in percentage) at t^*

$t_0 = 56, t_{K-1} = 62$						
	Female			Male		
$\alpha\backslash\Delta$	1.0	2.0	3.0	1.0	2.0	3.0
0.05	1.01(0.20)	1.03(0.20)	1.03(0.20)	1.52(0.28)	1.52(0.27)	1.51(0.26)
0.10	0.96(0.20)	0.96(0.20)	0.97(0.21)	1.44(0.28)	1.45(0.28)	1.45(0.27)
0.15	0.93(0.21)	0.93(0.20)	0.93(0.20)	1.38(0.28)	1.39(0.28)	1.39(0.28)
0.20	0.92(0.21)	0.92(0.21)	0.92(0.21)	1.35(0.28)	1.36(0.28)	1.36(0.28)
$t_0 = 62, t_{K-1} = 68$						
	Female			Male		
$\alpha\backslash\Delta$	1.0	2.0	3.0	1.0	2.0	3.0
0.05	1.75(0.35)	1.76(0.34)	1.75(0.34)	2.36(0.43)	2.32(0.43)	2.30(0.43)
0.10	1.65(0.35)	1.67(0.35)	1.67(0.35)	2.25(0.44)	2.25(0.43)	2.24(0.43)
0.15	1.60(0.35)	1.61(0.35)	1.61(0.35)	2.18(0.44)	2.18(0.44)	2.18(0.43)
0.20	1.57(0.36)	1.58(0.35)	1.58(0.35)	2.13(0.45)	2.13(0.44)	2.13(0.44)
$t_0 = 68, t_{K-1} = 74$						
	Female			Male		
$\alpha\backslash\Delta$	1.0	2.0	3.0	1.0	2.0	3.0
0.05	3.12(0.63)	3.09(0.63)	3.07(0.62)	3.91(0.74)	3.80(0.76)	3.77(0.74)
0.10	2.96(0.63)	2.98(0.62)	2.97(0.62)	3.77(0.73)	3.72(0.74)	3.71(0.73)
0.15	2.88(0.63)	2.89(0.63)	2.89(0.63)	3.66(0.74)	3.65(0.73)	3.64(0.73)
0.20	2.83(0.64)	2.84(0.64)	2.84(0.64)	3.59(0.74)	3.59(0.73)	3.58(0.73)

compatible with their findings.

Our approach also provides predictive information on the lead time and overdiagnosis if one were diagnosed with cancer at the future exam. This will provide predictive information for potential patients, regarding how early their diagnosis could be and the risk of overdiagnosis. From the NLST CT arm data, the average lead time is longer for female heavy smokers than males, while the risk of overdiagnosis for females is slightly lower than males; Overall, overdiagnosis is a very low percentage for both genders. Therefore, it is not a big concern using low-dose CT in lung caner screening.

Finally, we want to remind our readers that our modeling approach is just one way of thinking about the problem. Other models and approaches are possible. We have to consider other financial and emotional issues involved in screening too. Too many screening, especially screening with a false positive result not only hurts people emotionally, but may also causes unnecessary financial stress. The important point is to recognize that screening has outcomes and consequences that one should consider, especially for policy purposes. However, our method maybe the first step towards a personalized screening schedule in the near future.

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