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Evaluating Long-Term Outcomes via Computed Tomography in Lung Cancer Screening

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Abstract

Objectives: Future outcomes of computed tomography in lung cancer screening were evaluated using recently derived probability formula in the disease progressive model, and the recently completed National Lung Screening Trial computed tomography (NLST-CT) data.

Methods: Every participant in a screening program would fall into one of the four disjoint groups eventually: symptom-free-life, no-early-detection, true-early-detection and overdiagnosis, depending on whether he/she would be diagnosed with cancer and whether symptoms would have appeared before death. The probability of each outcome was a function of an individual's current age, past and future screening frequency and the three key parameters: screening sensitivity, sojourn time and time in the disease-free state. The predictive probability was estimated for people with and without screening histories. Percentage of over-diagnosis among the screen-detected cases was also presented with human lifetime as a random variable.

Results: The probability of heavy smokers to live a lung-cancer-free life would depend on their current age; it was about 80%, 86% and 94% for the 60, 70, and 80 years old respectively. The probabilities of no-early detection and true-early-detection were determined by the future screening interval and the current age: the probability of no-early-detection would increase to about three times if the future screening interval changes from annual to biennial; while the probability of true-early-detection would decrease to about 75% if the future screening interval changes from annual to biennial. The probability of over-diagnosis among the screen-detected was increasing as people aging: ~3%, 5% and 9% for the 60, 70, and 80 years old correspondingly; this probability decreases slightly when the historic screening interval increases.

Conclusion: This research provided the estimated probabilities of the four outcomes in the future and the percentage of overdiagnosis among the screen-detected cases. It provided a practical approach on the evaluation of long-term outcomes via CT in lung cancer screening.

Keywords: True-early detection; No-early-detection; Over-diagnosis; Symptom-free life; Three key parameters; Computed Tomography (CT).

Introduction

Lung cancer is the second most common form of cancer and the leading cause of cancer deaths for both genders in the United States [1]. According to American Cancer Society's Cancer Facts & Figures 2016, there are 224,390 new cancer cases expected in 2016, accounting for about 14% of all cancer diagnoses; and there are 158,080 expected deaths of lung and bronchus cancers in 2016, accounting for about 1 in 4 cancer deaths [2]. The information posted by the SEER statistics fact sheets on lung and bronchus cancer is shocking, e.g., the number of new cases of lung and bronchus cancer was estimated 58.7 per 100,000 people per year; and the estimated deaths was 47.2 per 100,000 people per year [1]. And approximately 6.6 percent of men and women would be diagnosed with lung and bronchus cancer at some time during their lifetime, based on the 2010-2012 data. Clinical stage at diagnosis is a major determinant of survival after therapy [3]; however, the average five-year survival rate for lung cancer patients is only about 15% [4].

Several major randomized controlled lung cancer screening studies have been carried out in North America: the Mayo Lung Project, the Johns Hopkins Study, the Memorial Sloan-Kettering Study, the Early Lung Cancer Action Project, the PLCO, and the National Lung Screening Trial (NLST) [5-13]. Results from the NLST seem to indicate that smokers screened by spiral CT had a 20% lower chance of dying from lung cancer than those who screened via chest X-rays [14]. In December 2013, the United States Preventative Services Task Force (USPSTF) issued recommendations endorsing low-dose computed tomography (CT) screening for heavy smokers ages 55 to 80 years old, who have a 30 pack-year smoking history (A pack year is defined as smoking an average of one pack of cigarettes per day for one year, i.e., a person could have a 30 pack year history by smoking one pack a day for 30 years or two packs a day for 15 years) and is currently smoking, or who have quit smoking within the past 15 years [15].

The National Lung Screening Trial (NLST) enrolled 53,454 male and female heavy smokers aged 55 to 74 years old between August 2002 and April 2004 [13]. Participants were required to have a smoking history of at least 30 pack-years and were either current or former smokers without signs, symptoms, or history of lung cancer. The purpose of the NLST is to compare two different screening

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modalities for the early detection of lung cancer: low-dose helical computed tomography (often called spiral CT), versus standard chest X-ray. 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 randomly assigned to receive three annual screens with either spiral CT or standard chest X-ray. In both arms of the trial, the majority of positive screens led to additional tests, such as biopsy, to confirm the true disease status. The primary endpoint of the NLST is lung cancer mortality. Although the five-year survival rates approach 70% with surgical resection of stage IA (i.e., non-small cell lung cancer that is 3cm across or smaller) in the NLST, more than 75% of patients with locally advanced or metastatic cancer have a five-year survival of less than 5% [13]. Due to complexity of lead time bias and overdiagnosis, no formal test has been shown that screening will reduce lung cancer mortality so far [14].

The purpose of this research was to investigate whether continued screening for old heavy smokers (i.e., 55 or older) would cause higher chances of overdiagnosis; hence probabilities of different outcomes in the future were estimated using the completed NLST-CT screening data. All initially superficially healthy participants would be separated into four mutually exclusive groups: symptom-free-life, no-early-detection, true-early-detection, and over-diagnosis. All screening participants would eventually fall into one of the four groups, depending on whether an individual would be diagnosed with lung cancer, and whether he/she would die from this cause. The probability of overdiagnosis among the screen-detected cases was also estimated using the NLST-CT data.

Methods

Model and probability formula

The commonly used disease progressive model $S_0 \rightarrow S_p \rightarrow S_c$ was assumed: S_0 represents the disease-free state; S_p represents the preclinical disease state, in which an asymptomatic individual unknowingly has the disease that a screening exam can detect; and S_c represents the clinical state at which the disease manifests itself in clinical symptoms. If a person enters the preclinical state S_p at age t_1, and his clinical symptoms present later at age t_2, then (t_2-t_1) is sojourn time in the preclinical state, with q(x) as the probability density function (PDF) of the sojourn time, and $Q(x)=\int_x^\infty q(t)dt$ as the survival function of the sojourn time. Sensitivity $\beta(t)$ is the probability that a screening result is positive when an individual is in the preclinical state at age t. Transition density $w(t)$ is the distribution of time duration in the disease-free state S_0; it is a sub-PDF because some people may stay in the disease-free state all their life and never transition into the preclinical state. The sensitivity $\beta(t)$, the survival function of the sojourn time Q(x), and the transition density $w(t)$ are called the three key parameters in a screening program, because all other model parameters are functions of these three key parameters.

To evaluate the long term outcomes of a screening program, all participants will be separated into four mutually exclusive groups, based on their ultimate diagnosis status and whether clinical symptoms would appear before their death or not. Here are the definitions of the four outcomes:

- Case 1 (Symptom-free-life): An individual who took part in screening exams, no lung cancer was diagnosed, and ultimately he/she died of other causes.
- Case 2 (No-early-detection): An individual who took part in screening exams, and who was a clinical incidence case between two regularly scheduled exams.
- Case 3 (True-early-detection): An individual who was diagnosed with lung cancer at a scheduled exam and whose clinical symptoms would have appeared before death.
- Case 4 (Overdiagnosis): An individual who was diagnosed with lung cancer at a scheduled exam, but whose clinical symptoms would NOT have appeared before death.

For an individual at age t_{K_1} currently, who has gone through K_1 exams with negative results at previous ages $t_0 < t_1 < \cdots < t_{K_1-1}$ (i.e., he/she has no lung cancer diagnosed so far), an event is defined with respect to his/her screening history:

H_{K_1} ={an individual underwent exams at ages $t_0 < t_1 < \cdots < t_{K_1-1}$, no lung cancer was diagnosed, and he/she is asymptomatic at his/her current age t_{K_1} }.

The probability of each case has been derived in Wu et al. [16-18], and the probability formulas are briefly summarized here. Let $\beta_i=\beta(t_i)$ be the screening sensitivity at age t_i, $i=0,1,2\ldots$, and let $t_{-1}=0$. The probability of the event H_{K_1} given that the lifetime T exceeds his/her current age t_{K_1}, is:

$$P(H_{K_1} \mid T \geq t_{K_1}) = 1-\int_0^{t_{K_1}} w(x)dx+\int_{t_{K_1-1}}^{t_{K_1}} w(x)Q(t_{K_1}-x)dx + \sum_{j=0}^{K_1-1}(1-\beta_j)\cdots(1-\beta_{K_1-1})\int_{t_{j-1}}^{t_j} w(x)Q(t_{K_1}-x)dx. \quad (1)$$

If he/she has a future plan of exams at ages $t_{K_1} < t_{K_1+1} < \cdots < t_{K_1+K-1} < \cdots$, the probability of each outcome when his/her lifetime T is a fixed value and $T = t_{K_1+K} (> t_{K_1+K-1})$ is:

$$P(Case\ 1, H_{K_1} \mid T = t_{K_1+K}) = 1-\int_0^{t_{K_1+K}} w(x)dx+\int_{t_{K_1+K-1}}^{t_{K_1+K}} w(x)Q(t_{K_1+K}-x)dx + \sum_{j=0}^{K_1+K-1}(1-\beta_j)\cdots(1-\beta_{K_1+K-1})\int_{t_{j-1}}^{t_j} w(x)Q(t_{K_1+K}-x)dx. \quad (2)$$

$$P(Case\ 2, H_{K_1} \mid T = t_{K_1+K}) = \sum_{j=K_1+1}^{K_1+K}\left\{\sum_{i=0}^{j-1}(1-\beta_i)\cdots(1-\beta_{j-1})\int_{t_{i-1}}^{t_i} w(x)[Q(t_{j-1}-x)-Q(t_j-x)]dx+\int_{t_{j-1}}^{t_j} w(x)[1-Q(t_j-x)]dx.\right\} \quad (3)$$

$$P(Case\ 3, H_{K_1} \mid T = t_{K_1+K}) = \sum_{j=K_1}^{K_1+K-1}\beta_j\{\sum_{i=0}^{j-1}(1-\beta_i)\cdots(1-\beta_{j-1})\int_{t_{i-1}}^{t_i} w(x)[Q(t_j-x)-Q(t_{K_1+K}-x)]dx + \int_{t_{j-1}}^{t_j} w(x)[Q(t_j-x)-Q(t_{K_1+K}-x)]dx\}. \quad (4)$$

$$P(Case\ 4, H_{K_1} \mid T = t_{K_1+K}) = \sum_{j=K_1}^{K_1+K-1}\beta_j\{\sum_{i=0}^{j-1}(1-\beta_i)\cdots(1-\beta_{j-1})\int_{t_{i-1}}^{t_i} w(x)Q(t_{K_1+K}-x)dx + \int_{t_{j-1}}^{t_j} w(x)Q(t_{K_1+K}-x)dx\}. \quad (5)$$

For an individual at current age t_{K_1}, since his/her lifetime is a random variable, the number of future screenings K is unknown. However, if he/she plans to follow a future screening schedule at ages $t_{K_1} < t_{K_1+1} < \cdots$, then the number of his/her future screening exams is $K=n$, if $t_{K_1+n-1} < T < t_{K_1+n}$. The probability of each outcome can be obtained by the weighted average:

$$P(Case\ i, H_{K_1} \mid T \geq t_{K_1}) = \int_{t_{K_1}}^{\infty} P(Case\ \ i, H_{K_1} \mid K = K(t), T = t) f_T(t \mid T \geq t_{K_1})dt,\ i = 1,\ 2,\ 3,\ 4. \quad (6)$$

Where the lifetime distribution $f_T(t \mid T \geq t_{K_1}) = \frac{f_T(t)}{1-F_T(t_{K_1})}$ if $t \geq t_{K_1}$. And it was proved that: $\sum_{i=1}^{4} P(Case\ \ i \mid H_{K_1}, T \geq t_{K_1}) = \sum_{i=1}^{4}\frac{P(Case\ i, H_{K_1} \mid T \geq t_{K_1})}{P(H_{K_1} \mid T \geq t_{K_1})} = 1$, for any $K_1 \geq 0$, $K \geq 1$. Therefore the derived probability formulas are correct. The probability of over diagnosis among the screen-detected cases is:

$$P(OverD \mid D) = \frac{P(Case4 \mid T \geq t_{K_1}, H_{K_1}, DATA)}{P(Case3 \mid T \geq t_{K_1}, H_{K_1}, DATA) + P(Case4 \mid T \geq t_{K_1}, H_{K_1}, DATA)} \quad (7)$$

The probability of each outcome without any screening history can be considered as a special case and obtained by letting K_1=0 in the above formulas.

From these formulas, it is known that the probability of each outcome is a function of the three key parameters $(\beta(t), Q(x), w(t))$, an individual's current age t_{K_1}, one's screening history $t_0 < t_1 < \cdots < t_{K_1-1}$ and one's future screening plan $t_{K_1} < t_{K_1+1} < \cdots$. Since human lifetime is a random variable, the distribution of lifetime can be obtained by transforming the actuarial life table from the US Social Security Administration's website [19]. For details about how to transform the period life table into the probability density function (PDF), see Wu et al 2012 [21]. The conditional PDF for the overall lifetime combining both genders was plotted in Figure 1.

Data preparation and Bayesian inference

In this project, we focus on evaluating long term outcomes via CT screening only. To make predictive inference using the NLST-CT arm data, accurate estimation of the three key parameters (i.e., the sensitivity $\beta(t)$, the survival function of the sojourn time Q(x), and the transition density $w(t)$) must be obtained first, then estimation of the three key parameters were plugged into the derived probability formulas to estimate the probability of the four outcomes $P(Case\ i \mid H_{K_1}, T \geq t_{K_1})$ for i=1,2,3,4, and to estimate the probability of over diagnosis among the screen-detected *P (0ver D/D)*.

For accurate estimation of the three key parameters, the likelihood method developed by Wu et al. 2005 [19] was used, the data to be used in the likelihood were simple: at each screening, the total number of people being screened was recorded, the number of confirmed cancer cases (true positive), and the number of clinical incident cases before the next exam were also recorded. These data were stratified by initial age at the study entry, and ranged from 55 to 74 years old in the NLST CT data [13]. And there were three annual screenings in the NLST [19].

The three key parameters were estimated using the following parametric models: the sensitivity $\beta(t) = [1 + \exp\{-b_0 - b_1(t-m)\}]^{-1}$, where m=64.5 is the average age at the study entry, the transition density $w(t) = 0.3 \cdot \exp[-(\log t - \mu)^2 / (2\sigma^2)] / (\sqrt{2\pi}\sigma t)$ is a log normal PDF with 0.3 as its upper bound. The reason to pick 0.3 is that according to Villeneuve and Mao 1994 [21], the life time risk of developing lung cancer for male smokers is 17.2%; the transition density should be higher than the life time risk, therefore 0.3 were picked as a reasonable upper limit. The sojourn time distribution is the Weibull distribution, where the survival function of the sojourn time is: $Q(x) = \exp(-\lambda x^{\alpha}), x > 0, \alpha > 0, \lambda > 0$, for mathematical convenience.

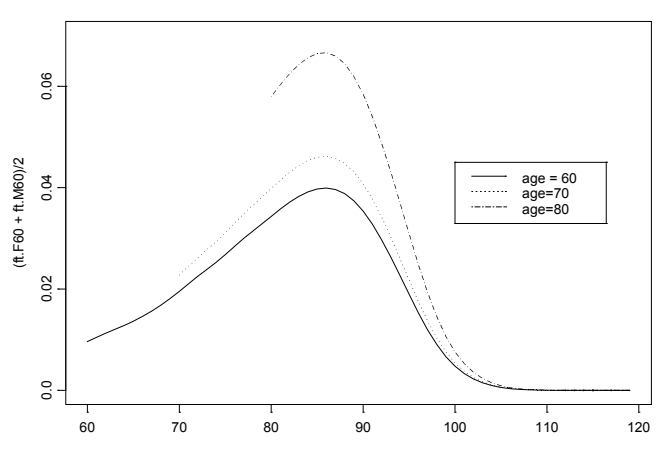

Figure 1: The conditional PDF for the overall lifetime combining both genders.

The six unknown parameters $\theta=(b_0, b_1, \mu, \sigma^2, \lambda, \alpha)$ in the parametric model were estimated using the NLST-CT data in Liu et al. 2015 [22]. Markov Chain Monte Carlo (MCMC) was used to generate posterior samples from the joint posterior distribution of the parameters for a Bayesian inference. The posterior simulation was partitioned into 3 sub-chains, and Gibbs sampling was used to sample the posteriors for $\theta=(b_0, b1), (\mu,\sigma)^2, (\lambda,\alpha)$ separately. For detailed information about the simulation procedure and the posterior estimates for parameters θ and the standard errors [22], We used the posterior samples θ_j^* to estimate the probability of each outcome $P(Case\ i \mid H_{K_1}, T \geq t_{K_1})$. Given the NLST-CT arm data, the posterior predictive probability of each outcome can be estimated by:

$$P(Case\ \ i \mid T \geq t_{K_1}, H_{K_1}, NLST\ data) = \frac{1}{n}\sum_{j=1}^{n} P(Case\ \ i \mid T \geq t_{K_1}, H_{K_1}, \theta_j^*) \quad (8)$$

Where $P(Case\ \ i \mid T \geq t_{K_1}, H_{K_1}, \theta_j^*) = P(Case\ i, H_{K_1} \mid T \geq t_{K_1}, \theta_j^*) / P(H_{K_1} \mid T \geq t_{K_1}, \theta_j^*)$ was provided in the equations (1)-(6) in the Method section, and θ_i^* is the 1000 posterior samples from the MCMC simulation after 30,000 burn-in steps and thinning at every 200 steps from two converged chains.

Results

We applied the above method to make Bayesian inference on three hypothetical cohorts of asymptomatic heavy smokers with current age 60, 70 and 80, assuming that either they started their initial CT screening at their age 50, or they have never taken any screening exam until their current age now. That is, within each cohort, it is assumed that there are three scenarios in the participants' past: annual screening, biennial screening, or no screening at all, represented correspondingly by: Δ_1=1,2,∞ years; where, ∞ means one has never been screened until the current age in the simulation. These are called hypothetical cohorts, because it is assumed that some people may never have screening at their current age (i.e., Δ_1=∞) or they may have some screening annually or biennially; in any case, they would share the same three key parameters (i.e., screening sensitivity, sojourn time and transition density) as those participants in the NLST-CT study. For future planning, both annual and biennial screenings in the future were considered, that is, Δ_2=1,2 years. The simulation results were summarized in Tables 1 and 2.

Table 1 reported the estimated probability (in percentage) of each outcome with its corresponding standard error. The probability of symptom-free-life is quite high, about 80% for the currently 60-years-old, and it is increasing as people are aging: ~86% for the 70-years-old and ~94% for the 80-years-old. It is almost unchanging when the screening interval in the past and in the future changes. So we can consider that the probability of symptom-free-life is not affected by past or future screening intervals, but it is mainly affected by a heavy smoker's current age.

The probability of no-early-detection is mainly determined by the future screening interval $\Delta_2$and individual's current age, ranging from 0.55% (with initial screening at age 50, current age 80, and annual exams in the past and future) to 6.31% (with current age 60 and screening changes from annual to biennial). The probability increases as the future screening interval increases, and it decreases when one's current age increases. It depends less on the past screening interval,

[a](Δ1,Δ2)	P(SympF)	P(NoED)	P(TrueED)	P(OverD)
Initial screening age t_0=50, current age $t_{K_1}=60$				
(1 yr, 1 yr)	80.26 (0.57)	1.86 (0.28)	17.19 (0.60)	1.01 (0.20)
(2 yr, 1 yr)	80.05 (0.56)	1.86 (0.27)	17.40 (0.60)	0.90 (0.19)
(∞, 1 yr)	80.01 (0.56)	1.86 (0.27)	17.44 (0.59)	0.66 (0.09)
(1 yr, 2 yr)	80.50 (0.57)	6.31 (0.63)	12.74 (0.55)	0.81 (0.17)
(2 yr, 2yr)	80.29 (0.57)	6.30 (0.63)	12.96 (0.56)	0.74 (0.16)
(∞, 2 yr)	80.25 (0.56)	6.30 (0.63)	13.00 (0.57)	0.43 (0.08)
Initial screening age t_0=50, current age $t_{K_1}=70$				
(1 yr, 1 yr)	86.13 (0.39)	1.30 (0.24)	11.90 (0.42)	0.67 (0.09)
(2 yr, 1 yr)	85.64 (0.42)	1.31 (0.24)	12.38 (0.44)	0.67 (0.09)
(∞, 1 yr)	85.53 (0.43)	1.31 (0.24)	12.49 (0.44)	0.67 (0.09)
(1 yr, 2 yr)	86.38 (0.39)	4.33 (0.44)	8.86 (0.45)	0.42 (0.08)
(2 yr, 2 yr)	85.88 (0.41)	4.33 (0.44)	9.36 (0.50)	0.43 (0.08)
(∞, 2 yr)	85.78 (0.43	4.32 (0.44)	9.47 (0.53)	0.43 (0.08)
Initial screening age t_0=50, current age $t_{K_1}=80$				
(1 yr, 1 yr)	94.20 (0.26)	0.55 (0.16)	4.73 (0.23)	0.52 (0.08)
(2 yr, 1 yr)	93.75 (0.30)	0.57 (0.17)	5.16 (0.27)	0.53 (0.09)
(∞, 1 yr)	93.65 (0.35)	0.57 (0.17)	5.27 (0.30)	0.53 (0.09)
(1 yr, 2 yr)	94.38 (0.25)	1.75 (0.21)	3.54 (0.26)	0.34 (0.07)
(2 yr, 2 yr)	93.92 (0.28)	1.76 (0.23)	3.97 (0.31)	0.36 (0.07)
(∞, 2 yr)	93.84 (0.33)	1.76 (0.23)	4.08 (0.35)	0.36 (0.08)

[a]$\Delta=t_i-t_{i-1}$ is the proposed time interval between screenings.
The mean probability and its standard error are reported in percentages (%) in columns 2-5.

Table 1: Probability and its standard error of the four outcomes using the NLST-CT data.

(Δ1,Δ2)	[b]P(TrueED|D)	P(OverD|D)
Initial screening age t_0=50, current age $t_{K_1}=60$		
(1 yr, 1 yr)	96.31 (95.10, 97.12)	3.69 (2.88, 4.90)
(2 yr, 1 yr)	96.35 (95.17, 97.15)	3.65 (2.85, 4.83)
(∞, 1 yr)	96.36 (95.20, 97.15)	3.64 (2.85, 4.80)
(1 yr, 2 yr)	96.78 (95.62, 97.51)	3.22 (2.49, 4.38)
(2 yr, 2yr)	96.83 (95.70, 97.54)	3.17 (2.46, 4.30)
(∞, 2 yr)	96.84 (95.74, 97.55)	3.16 (2.45, 4.26)
Initial screening age t_0=50, current age $t_{K_1}=70$		
(1 yr, 1 yr)	94.68 (93.01, 95.79)	5.32 (4.21, 6.99)
(2 yr, 1 yr)	94.85 (93.26, 95.90)	5.15 (4.10, 6.74)
(∞, 1 yr)	94.89 (93.39, 95.92)	5.11 (4.08, 6.61)
(1 yr, 2 yr)	95.45 (93.87, 96.46)	4.55 (3.54, 6.13)
(2 yr, 2yr)	95.62 (94.12, 96.58)	4.38 (3.42, 5.88)
(∞, 2 yr)	95.67 (94.26, 96.60)	4.33 (3.40, 5.74)
Initial screening age t_0=50, current age $t_{K_1}=80$		
(1 yr, 1 yr)	90.21 (87.32, 92.16)	9.79 (7.84, 12.68)
(2 yr, 1 yr)	90.71 (87.98, 92.51)	9.29 (7.49, 12.02)
(∞, 1 yr)	90.86 (88.43, 92.54)	9.14 (7.46, 11.57)
(1 yr, 2 yr)	91.29 (88.55, 93.06)	8.71 (6.94, 11.45)
(2 yr, 2yr)	91.82 (89.26, 93.44)	8.18 (6.56, 10.74)
(∞, 2 yr)	91.99 (89.69, 93.49)	8.01 (6.51, 10.31)

[b]The event D={the screen-detected cases}. The estimated probability was calculated by $p_i^*/(p_3^*+p_4^*), i=3,4,$ for each of 1000 posterior MCMC samples, then take the average. It is in percentage (%).

Table 2: The probability of over-diagnosis and true-early-detection among the screen-detected cases, with 95% credible intervals (C.I.).

and for those who have no screening history, the probability of no-early-detection is about the same as those who have annual or biennial screenings if their future screening schedules are the same. If we consider the ratio of this probability as a measure of relative risk when future screening interval Δ_2 changes from 1 year to 2 years, the ratio is 3.39, 3.31, 3.09 for the current age 60, 70 and 80 correspondingly, showing that doubling the future screening intervals will cause the probability of no-early-detection to increase about 3 times.

The probability of true-early-detection depends more on the future screening interval Δ_2 and the current age, than on the past screening experience Δ_2; it is ranging from 3.54% (with initial exam at 50 and current age 80, screening interval changes from annual to biennial) to 17.44% (with current age 60, no screening in the past and annual screening in the future). It increases when future screening interval decreases (i.e., more frequent screening), and it decreases as current age increases. The ratio of this probability between biennial and annual future screening interval $\Delta_2$is close to 75% for all three age groups, showing that the probability of true-early-detection would decrease to about 75% of what it was, if the future screening interval changes from annual to biennial.

The probability of over-diagnosis among all participants is very low; it is about 1% or less for all hypothetic cohorts. It is also slightly affected by the future screening interval and the current age.

The standard deviations (in percentage) were reported in parenthesis in Table 1. Each row in Table 1 should add to 100%, however, due to simulation accuracy, it is not exactly 100% sometimes.

Table 2 reported the predictive probability of true-early-detection and over-diagnosis among the screen-detected cases. These are the probabilities that most researchers are eager to explore and the general public wants to know. It shows that the probability of over-diagnosis is increasing when people are aging: ~3% for 60, ~5% for 70 and ~9% for 80 years old. It is slightly decreasing when the historic screening interval increases. Combining all cohorts, there seems to be only 3-10% of over-diagnosis among the screen-detected cases, while more than 90% are true-early-detection. This means, if left untreated, about 3-10% of patients may die of other causes before clinical symptom of lung cancer comes up, while more than 90% of the screen-detected cases are true-early-detection that needs treatment and intervention immediately. The 95% Credible Intervals (C.I.) are reported in Table 2 as well, ranging from 87% to 97% for the probability of true-early-detection; and 2% to 13% for over-diagnosis.

Discussion and Conclusion

The probability method in Wu et al 2014, 2016 [16-18] were applied to the NLST CT-arm data, and some useful information regarding long term outcomes for continued screening among heavy smokers were obtained. This research can provide policy makers important estimates of the probability of symptom-free-life, no-early-detection, true-early-detection, and over-diagnosis that result from a periodic screening program. Bayesian analysis was used because it can incorporate uncertainty and easy calculation of the variations and the credible intervals of the percentages.

According to the NIH SEER database [23-26], the lifetime risk for lung and bronchus cancer for both genders during their lifetime is 6.95% for all races, with a 95% C.I. (6.91%, 6.99%). In other words, the accepted lifetime risk of lung cancer is 1 in 14 during one's lifetime for general population. Our estimated probability of symptom-free-life is about 80%, 86% and 94% for heavy smokers if one' current age is 60, 70

or 80; that is, heavy smokers have a life time risk of 20%, 14% and 6% for lung cancer respectively corresponding to their current age; this is larger than the expected lifetime risk for the general population.

The proportion of over-diagnosis among the screen-detected cases is very small, about 3-10% among all age groups, showing that more than 90% of the screen-detected cases are true-early-detection cases, and immediate treatment is needed. The ultimate goal of a screening program in cancer is to reduce cancer mortality. We will explore whether early detection of lung cancer may or may not contribute to patient survival in our next project.

Our model contributes to the study of a screening program by providing a framework for the evaluation of long-term effects. The model can be used to evaluate and compare the outcomes of different cohort under different screening frequencies. For example, the model can be applied to data obtained from male and female non-smokers, or screened by other modalities, such as chest X-ray, etc., and provide answers to questions, such as what is the percentage of symptom-free-life in the cohort? What is the percentage of true-early-detection vs. over-diagnosis among the screen-detected cases? What is the percentage of no-early-detection for different screening schedules? We hope the general public can use this information in their decision making regarding their future screening intervals [27-29].

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Disclosure of Potential Conflicts of Interest

We authors declare that we have no conflict of interest.

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