Effectiveness of Lung Screening CT on Mortality Reduction for Lung Cancer
-Estimation Using a Mathematical Model

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Abstract:
Lung cancer is the most serious disease among cancers in Japan and Western countries. Although smoking cessation is the most important strategy, it is not enough because of long time lag. We have proposed Lung Screening CT for mass screening of lung cancer. In this article we estimate relative risk(RR) of lung cancer deaths using the data of Anti-Lung Cancer Association, Tokyo, and a mathematical model of steady state in stead of randomized controlled trials. It is shown that RR of CT screening compared with unscreened are between 0.42 and 0.54 assuming fatality rates of 26 and 30% and overdiagnosis rates of 0 and 30% respectively. If the CT screening is performed to Japanese population of 40-84y.o., we can save 24,924 to 31,317 persons compared with 65,608 persons lost in the unscreened population in 2007. We strongly recommend that CT screening for lung cancer should be introduced as the organized screening.
Keywords: Lung cancer, Lung Screening CT(LSCT), Anti-Lung Cancer Association(ALCA), Mathematical model

Introduction

Lung cancer is No.1 killer among cancers in Japan and in the western countries. In order to reduce the deaths due to lung cancer, the most important strategy is the primary prevention that is prohibition of smoking for Japanese male in which smoking rate is still high. However, smoking cessation only would not be enough since a long time lag exists between lung cancer incidence and smoking rates. So the secondary prevention is necessary together with smoking cessation. We propose the screening for lung cancer using Lung Screening CT(LSCT) of low dose as a powerful tool of secondary prevention.

In this article we show reduction of lung cancer deaths with LSCT screening using an observational data from Anti-Lung Cancer Association(ALCA) and a mathematical model of cancer screening in stead of randomized controlled trial.

Method-Description of model for cancer screening

Firstly, we define LSCT as follows: 1)a low dose CT in optimally achieved(Effective Dose 1-2mSv), 2)multi-detector CT more than 4 detector rows, and 3)computer-assisted diagnosis(CAD) system attached. Secondly, the lung cancer screening should be operated as a repeat screening for a fixed population with a regular interval so that effect of base-line screening is disappeared.

Then the efficacy of lung cancer screening is estimated by a simulation model of cancer screening with steady state. Since the model was described in detail in the previous report1), summary results are shown here. Variables used in the model are as follows：1)Number of deaths by lung cancer in screened population: As 2)Number of deaths by lung cancer in unscreened population: Ao (It is assumed both screened and unscreened population are identical) 3)Relative risk for mortality reduction: RR=As/Ao 4)Risk difference for mortality reduction: RD=Ao-As (It is number of saved life). 5)Number of screened population: Ps 6)Number of unscreened population: Po (It is assumed Ps=Po) 7)Incidence rate of lung cancer for the both population: D 9)Number of incidence of lung cancer: PsD=PoD 10)Sensitivity of screening test: Fs 11)Rate of recalled examinees who actually take detailed examination: S 12)Sensitivity of the detailed examination: Fd 13)Fatality rate of lung cancer patients who are screen-detected: Us 14)Fatality rate of lung cancer patients who are unscreened: Uo 15)Rate of overdiagnosis(OD): γ (if OD does not exist γ=1.0, but exists γ＞1.0).

The model for screening of one year interval shows that deaths due to lung cancer in screened population consist of following causes: (1)Deaths due to false-negative examinees in the screening test expressed as PsD(1-Fs)Uo. (2)Deaths due to recalled cancer examinees who do not take detailed examination as PsDFs(1-S)Uo. (3)Deaths due to false-negative examinees in the detailed examination expressed as PsDFsS(1-Fs)Uo. (4)Deaths due to screen-detected cancer examinees expressed as γPsDFsSFdUs. Here the rate of OD(γ) is introduced. Sum of the above four causes are total number of deaths in the screened population expressed as As=PsDUo-PsDFsSFd(Uo-γUs).

Deaths due to lung cancer in the unscreened population during one year is expressed as PoDUo, where number of incidence in the unscreened population is multiplied by fatality rate of the unscreened and Po is assumed to be equal to Ps. Thus Ao=PoDUo=PsDUo.

Relative Risk(RR) for lung cancer deaths is expressed as As/Ao=1-FsSFd(1-γUs/Uo).

Risk Difference(RD) for lung cancer deaths is expressed as Ao-As=PDFsSFd(Uo-γUs) which is equivalent to the number of saved lives from lung cancer.

95% confidence interval of RR is expressed as $(RR)\exp\{\pm 1.96(1/As+1/Ao)^{1/2}\}$

Results-1：Relative Risk for lung cancer death by screening

1)Numerical values introduced to the model

As a subject, average Japanese male of age 60-64 years old are selected. Number of screened population(Ps) for CT and XP is 100,000 persons each and those of unscreened population(Po) is 100,000 persons who are assumed to be identical to the screened population. Incidence rate of lung cancer(D) of this population is 118 persons/100,000 in a year and number of incidence is 118 persons/year which is identical in screened and unscreend populations (PsD=PoD).

Sensitivity of the screening test(Fs) is assumed to be 95% for LSCT and 75% for chest X-ray(XP)2). Rate of recalled examinees who take detailed examination(S) is assumed to be 90% for LSCT and XP. Sensitivity of the detailed examination(Fd) is assumed to be 95% for LSCT and XP. Fatality rates of lung cancer patients who are screen-detected(Us) are 30-26% for LSCT and 48% for XP. These values are observed in the repeated screening of CT and XP groups in ALCA3). Fatality rate of the unscreened group(Uo) is 90%4). Finally, OD is assumed to be none in XP screening and 30% increase in CT screening, that is γ=1.0 in XP and γ=1.0 or 1.3 in CT.

2) XP screening

Using the values mentioned above, the following results are obtained.

Total number of deaths in the screened population consist of four causes mentioned above.

(1)Deaths due to false-negative examinees in the screening test: 118*(1-0.75)*0.9=26.55persons

(2)Deaths due to recalled examinees who had cancer, but did not take detailed examination:

118*0.75*(1-0.90)*0.90=7.97persons

(3)Deaths due to false-negative examinees in the detailed examination:

118*0.75*0.90*(1-0.95)*0.90=3.58persons

(4)Deaths due to screen-detected cancer examinees: 1.0*118*0.75*0.90*0.95*0.48=36.32persons

Where γ=1.0, no OD is assumed in XP screening.

(5)Total number of deaths in the screened population is the sum of the four: 74.42persons

(6)Number of deaths due to lung cancer in the unscreened population: 118*0.9=106.2 persons
(7)Relative risk(RR) for lung cancer death: 74.42/106.2=**0.701**
(8)Risk difference for lung cancer deaths: 106.2-74.4=**31.8/100,000** persons
(9)95% CI of RR: 0.701*EXP{±1.96(1/74.4+1/106.2)$^{1/2}$}= 0.92-0.50

3)LSCT Screening (Best estimation)

Here we calculate the best estimation in CT screening where Us for CT is 26% and no OD is assumed, that is γ =1.0.
(1)Deaths due to false-negative examinees in the screening test: 118*(1-0.95)*0.9=5.31persons
(2)Deaths due to recalled examinees who had cancer, but did not take detailed examination:
118*0.95*(1-0.90)*0.90=10.09persons
(3)Deaths due to false-negative examinees in the detailed examination:
118*0.95*0.90*(1-0.95)*0.90=4.54persons
(4)Deaths due to screen-detected cancer examinees: 1.0*118*0.95*0.90*0.95*0.26=24.92persons
Where γ =1.0, no OD is assumed in this case.
(5)Total number of deaths in the screened population is the sum of the four: 44.86persons
(6)Number of deaths due to lung cancer in the unscreened population: 118*0.9=106.2 persons
(7)Relative risk(RR) for lung cancer death: 44.86/106.2=**0.422**
(8)Risk difference for lung cancer deaths: 106.2-44.9=**61.3/100,000** persons
(9)95% CI of RR: 0.701*EXP{±1.96(1/44.9+1/106.2)$^{1/2}$}=0.60-0.30

4)LSCT Screening (Worst estimation)

Here we calculate the worst estimation in CT screening where Us for CT is 30% and OD is assumed to be 30% that is γ =1.3.
(1)Deaths due to false-negative examinees in the screening test: 118*(1-0.95)*0.9=5.31persons
(2)Deaths due to recalled examinees who had cancer, but did not take detailed examination:
118*0.95*(1-0.90)*0.90=10.09persons
(3)Deaths due to false-negative examinees in the detailed examination:
118*0.95*0.90*(1-0.95)*0.90=4.54persons
(4)Deaths due to screen-detected cancer examinees: 1.3*118*0.95*0.90*0.95*0.30=37.38persons
Where γ =1.3, OD is assumed to be 30%.
(5)Total number of deaths in the screened population is the sum of the four: 57.32persons
(6)Number of deaths due to lung cancer in the unscreened population: 118*0.9=106.2 persons
(7)Relative risk(RR) for lung cancer death: 57.32/106.2=**0.540**
(8)Risk difference for lung cancer deaths: 106.2-57.3=**48.9/100,000** persons
(9)95% CI of RR: 0.701*EXP{±1.96(1/57.3+1/106.2)$^{1/2}$}=0.74-0.39
The summary of results described above are shown in Table 1.

Results-2：Estimates of lung cancer deaths for Japanese population

If the above results can be applied to whole Japanese population, we can calculate number of deaths due to lung cancer which can be reduced by XP and LSCT screening.
In 2007, number of deaths due to lung cancer in Japan is 65,608 persons for all age. For 40-84 years old, number of deaths is 54,182 persons and others are11,426 persons2).

1)XP Screening

If % of examinees is 100% for 40-84 y.o. , number of lung cancer deaths is estimated as follows:
54,182*0.701+11,426=49,408 persons will die and 16,200 persons will be saved.
If % of examinees is 50% for 40-84 y.o., number of deaths is as follows:
54,182*0.5*0.701+54,182*0.5+11,426=57,508 persons will die and 8,100 persons will be saved.

2)LSCT Screening (Best estimate)

If % of examinees is 100%, number of deaths is as follows.

54,182*0.422+11,426=34,291 persons will die and 31,317 persons will be saved.

If % of examinees is 50%, number of deaths is as follows.

54,182*0.5*0.422+54,182*0.5+11,426=49,949 persons will die and 15,659 persons will be saved.

3)LSCT Screening (Worst estimate)

If % of examinees is 100%, number of deaths is as follows.

54,182*0.540+11,426=40,684 persons will die and 24,924 persons will be saved.

If % of examinees is 50%, number of deaths is as follows.

54,182*0.5*0.540+54,182*0.5+11,426=53,146 persons will die and 12,462 persons will be saved.

The summary of results described above are shown in Table 2.

Discussion

There are several RCTs on CT lung cancer screening compared with XP screening in the world and a definite conclusion is not yet available as to the effectiveness of CT screening.5-9)

However, the recent result from the National Lung Screening Trial(NLST) shows that CT screening for smokers reduces lung cancer deaths by 20% compared to chest X-ray screening.10)

By the different approach, we try to estimate the relative risk(RR) of lung cancer deaths by XP and LSCT screening using the measured data of repeated screening of ALCA and a mathematical model of cancer screening. The RR for XP vs unscreened groups is 0.70 and RRs for LSCT vs unscreened groups are 0.42 for the best estimate and 0.54 for the worst estimate. The RR values are statistically significant for 100,000 population and LSCT is shown to be superior to XP.

There are several problems in this research. One is estimate of overdiagnosis(OD). We have used 30% increase of OD in which γ is 1.3, but this value seems to be large when repeated screening is employed in which image of the past screening is compared with the present image. We consider the OD is almost none in this case. However further study is needed. Second is the fatality rate of screen-detected lung cancer for LSCT screening. We used two values 26% and 30%. The former is a measured value in the repeated LSCT screening of ALCA and the latter is a calculated value using stage distribution of lung cancer of repeated LSCT screening. A value of 30% is the worst case, since screened population in ALCA includes more than 80% male smokers and thus is considered as a high risk group. Finally the sensitivity data of XP and LSCT screening are assumed to be 75% and 95% which will be reasonable.

In the future more study is planned to investigate the screening interval for LSCT screening according to the individual risk of screened population. For example, never-smokers can be screened less frequently and smokers should be screened once a year. Thus more cost-effective screening system may be established.

Conclusion

We have shown that lung cancer screening by LSCT is more effective than that by chest X-ray using data from Anti-Lung Cancer Association(ALCA) and mathematical model of steady state. We could achieve RR of 0.42 to 0.54 with LSCT screening and RR of 0.70 with XP screening compared to the unscreened group. We recommend the mass screening for lung cancer with LSCT as an organized screening throughout Japan in order to reduce the deaths due to lung cancer.

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Tables

Table 1. Summary of the results of XP and LSCT lung cancer screening

Type of Screening	Deaths due to screen-detected examinees	Relative Risk	Risk Difference	95% CI of RR	OD(γ)
XP Screening	$74.42/10^5$ persons	0.701	$31.8/10^5$persons	0.92- 0.50	1.0
LSCT Screening (Best)	$44.86/10^5$ persons	0.422	$61.3/10^5$persons	0.60 - 0.30	1.0
LSCT Screening (Worst)	$57.32/10^5$persons	0.540	$48.9/10^5$persons	0.74 - 0.39	1.3

Table 2. Estimates of lung cancer deaths for Japanese population(2007):Total No of death is 65,608 persons
Screening is performed for Japanese population of 40-84 years old. with 100% compliance..

Type of Screening	Deaths due to lung cancer	No. of saved lives
Unscreened	65,608 persons	0 persons
XP Screening	49,408 persons	16,200 persons
LSCT Screening(Best)	34,291 persons	31,317 persons
LSCT Screening(Worst)	40,684 persons	24,924 persons