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Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan

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ABSTRACT

Background: A screening program for lung cancer requires more empirical evidence. Based on the experience of the National Lung Screening Trial (NLST), we developed a method to adjust lead-time bias and quality-of-life changes for estimating the cost-effectiveness of implementing computed tomography (CT) screening in Taiwan.
Methods: The target population was high-risk (≥30 pack-years) smokers between 55 and 75 years of age. From a nation-wide, 13-year follow-up cohort, we estimated quality-adjusted life expectancy (QALE), loss-of-QALE, and lifetime healthcare expenditures per case of lung cancer stratified by pathology and stage. Cumulative stage distributions for CT-screening and no-screening were assumed equal to those for CT-screening and radiography-screening in the NLST to estimate the savings of loss-of-QALE and additional costs of lifetime healthcare expenditures after CT screening. Costs attributable to screen-negative subjects, false-positive cases and radiation-induced lung cancer were included to obtain the incremental cost-effectiveness ratio from the public payer's perspective.
Results: The incremental costs were US$22,755 per person. After dividing this by savings of loss-of-QALE (1.16 quality-adjusted life year (QALY)), the incremental cost-effectiveness ratio was US$19,683 per QALY. This ratio would fall to US$10,947 per QALY if the stage distribution for CT-screening was the same as that of screen-detected cancers in the NELSON trial.
Conclusions: Low-dose CT screening for lung cancer among high-risk smokers would be cost-effective in Taiwan. As only about 5% of our women are smokers, future research is necessary to identify the high-risk groups among non-smokers and increase the coverage.

1. Introduction

Lung cancer is the leading cause of cancer mortality worldwide [1]. Screening with low-dose computed tomography (CT) has been shown to reduce lung cancer mortality [2], and this method has drawn broad interests with regard to its cost-effectiveness for possible adoption in a national policy. Although the cost-effectiveness of CT screening for lung cancer has been analyzed in several previous studies [3–5], the results varied. Most studies applied transitional probabilities obtained from short-term observations for life-long simulations, which generally leave large ranges of uncertainties for stakeholders to judge. Recently, Black et al. used the National Lung Screening Trial (NLST) data and national life tables to extrapolate the survival to lifetime [6]; however, future healthcare costs were not included in their base case analysis. In

Abbreviations: CT, computed tomography; EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitor; EQ-5D, EuroQol five-dimension questionnaire; EYLL, expected years of life lost; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; NCKUH, National Cheng Kung University Hospital; NCR, National Cancer Registry; NELSON, Dutch-Belgian Lung Cancer Screening Trial; NHI, National Health Insurance; NLST, National Lung Screening Trial; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; QoL, quality-of-life; SD, standard deviation; SqCC, squamous-cell carcinoma; UKLS, UK Lung Cancer Screening Trial; VDT, volume doubling time

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addition, as age distribution at cancer diagnosis in the CT group might differ from that in the control group, potential lead-time bias might exist.

Different European and Asian countries have also conducted studies of CT screening programs for the high-risk population [7–9], and some of them explored the cost-effectiveness [9]. However, these programs varied in terms of recruitment, number of screening rounds, length of screening interval, nodule work-up strategies, and considerations of quality-of-life (QoL). Different costs of cancer care in different countries further complicate the issue. There is still a lack of consensus on adjustment of lead-time bias in evaluating the cost-effectiveness of different CT screening programs.

By assuming the same cumulative distributions of pathology and stage as those in the NLST, we conducted this study with a novel method to take account of lead-time bias in evaluating the cost-effectiveness of implementing three annual CT screenings for lung cancer in Taiwan.

2. Methods

This study received approval from the Institutional Review Board of National Cheng Kung University Hospital (NCKUH) before commencement (B-ER-103-354). The target population was high-risk (≥30 pack-years) smokers between 55 and 75 years of age, and the estimation can be summarized into three parts (Fig. 1). First, by linkages among Taiwan's nation-wide databases, we estimated the quality-adjusted life expectancy (QALE), loss-of-QALE, and lifetime healthcare expenditures per case of lung cancer stratified by pathology and stage. Second, we borrowed the cumulative stage distributions of screen-detected and non-screen-detected lung cancers from CT-screening vs. radiography-screening in the NLST, which were multiplied by the loss-of-QALE and lifetime healthcare expenditures for each specific pathology and stage to estimate the average loss-of-QALE and healthcare expenditures. We compared the savings of loss-of-QALE and additional costs of lifetime healthcare expenditures with and without CT screening. Third, we calculated the additional costs attributable to screening programs, which included expenditures on screen-negative subjects, false-positive cases, and radiation-induced lung cancer. The difference in overall costs (i.e., the incremental cost) was calculated, which was divided by the savings of loss-of-QALE to obtain the incremental cost-effectiveness ratio (ICER) from the public payer's perspective.

2.1. Lifetime healthcare expenditures and loss-of-QALE

We abstracted data by linking Taiwan National Cancer Registry (NCR) and National Mortality Registry for survival analysis. Survival was extrapolated to lifetime using a semiparametric method and simulation of age- and sex-matched referents from the national life tables of Taiwan. We adjusted the lifetime survival curve by the QoL function for lung cancer, as stratified by pathology and stage, and summed throughout life using the following equation [10]:

$$QALE = \int E[QoL(t/x)]S(t/x)dt,$$

where *E[QoL(t/x)]* denotes the expected value of the QoL function for condition *x* at time *t*, while *S(t/x)* represents the survival function for condition *x* at time *t*. Similarly, we multiplied the average survival rate by cost paid at time *t* and summed throughout life by:

$$LifetimeCosts = \int E[Cost(t/x)]S(t/x)dt,$$

where *E[Cost(t/x)]* denotes the expected healthcare expenditures of the cost function for condition *x* at time *t*. The estimations of lifetime healthcare expenditures and loss-of-QALE are detailed in the following paragraphs.

2.1.1. Taiwan national cancer registry for survival

We abstracted all lung cancer patients aged 55 and over during the period 2002–2012. Each patient underwent follow-ups from the day of diagnosis until the end of 2014. Because there are considerable differences in overall survival and management [11], lung cancer pathologies were classified into small-cell lung cancer, squamous-cell carcinoma (SqCC) and non-SqCC. Each patient's tumor stage was defined according to the classifications provided by the American Joint Committee on Cancer [12]. We verified the survival status by linking the patient's identification information to Taiwan National Mortality Registry.

2.1.2. Extrapolating the survival function to lifetime

After obtaining the survival data of the lung cancer cohort, we used a semiparametric method proposed by Hwang and Wang to extrapolate the survival to lifetime [13]. This approach assumes that the excess mortality generated from lung cancer approaches a constant value by the end of follow-up period. The calculation was carried out in the following three steps: First, we applied the life tables in Taiwan National Vital Statistics to generate an age- and sex-matched reference population, and used the Kaplan-Meier estimator, a non-parametric method, to estimate survival function for the reference. Second, we calculated the survival ratio between the lung cancer cohort and the referents at each time *t* and performed a logit transformation of the ratio. Third, the logit transformed relative survival was fitted with a simple linear regression, which is a parametric model, for a short time period near the end of the follow-up. The estimated straight line, together with the survival function of the reference population beyond the follow-up limit, was used to extrapolate the survival function of the lung cancer cohort over their lifetimes. In this manner, the life expectancy of the lung cancer cohort after diagnosis could be estimated. We defined expected years of life lost (EYLL) as the survival difference between the lung cancer cohort and the reference population [14]. This method has been demonstrated to be effective using computer simulations [13], proven mathematically [15], and corroborated by examples of lung cancer cohorts [16,17]. The iSQoL statistical package was used to carry out the computations [18].

2.1.3. Estimating the lifetime healthcare expenditures

We used the reimbursement data of Taiwan National Health Insurance (NHI) to obtain the spending details for all the lung cancer cases between 2002 and 2013. In Taiwan, all cancer cases verified by pathology could be registered as catastrophic illnesses and waived from copayments. All direct medical costs were reimbursed by the NHI, including out- and in- patient expenditures, and those spent for diagnosis and treatments. They were summed up to calculate the total monthly healthcare expenditures, whereas transportation costs, payments to caregivers and human capital loss were not taken into consideration in this analysis. Total monthly healthcare expenditures were divided by the effective sample size, namely, the number of patients who survived that month, to obtain the monthly healthcare expenditures per case. We adjusted all payments in different calendar years based on the related consumer price indices [19] and made equivalent to 2013 dollars. Moreover, we also adjusted the healthcare expenditures of future years using an annual discount rate of 3%. These values were subsequently multiplied by the corresponding monthly survival probabilities and summed to obtain the lifetime healthcare expenditures per case.

2.1.4. Estimating the QALE

From May 2011 to December 2014, we invited all lung cancer patients from the outpatient departments of NCKUH to participate in this study. Every interviewed patient provided written, informed consent. For some individuals, we performed QoL measurements repeatedly; however, each measurement was taken with a minimum three-month interval. The EuroQol five-dimension questionnaire (EQ-

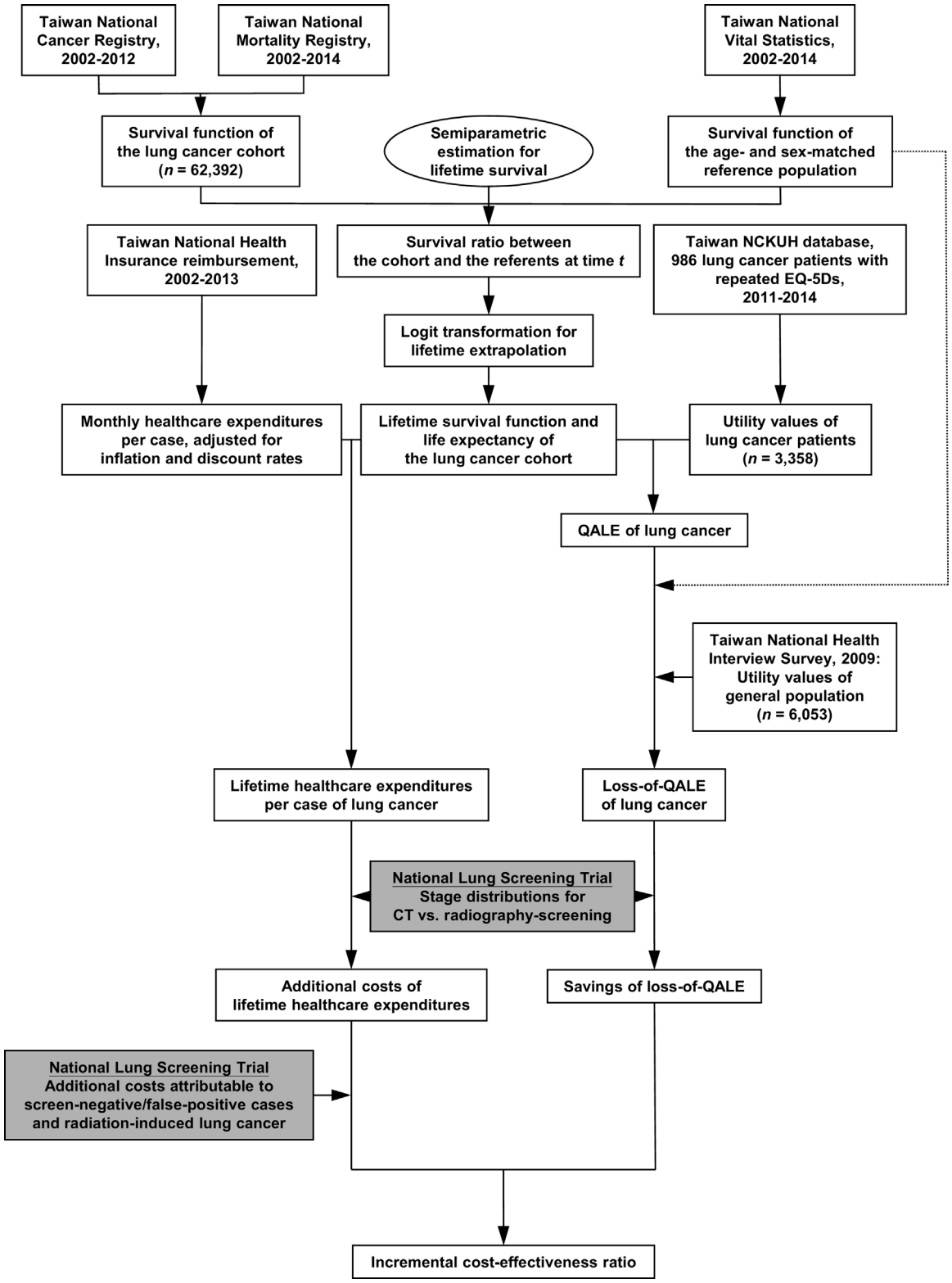

Fig. 1. Flow diagram of the inclusion of subjects and their relevant information for estimation. With lifetime horizon, this study first estimates the survival, cost, and quality-of-life data from Taiwan. A cost-effectiveness assessment is then conducted by adopting the stage shifting and potential adverse effects of CT screening from the National Lung Screening Trial (boxes highlighted with shadows). CT, computed tomography; EQ-5D, EuroQol five-dimension questionnaire; NCKUH, National Cheng Kung University Hospital; QALE, quality-adjusted life expectancy.

5D) was used to estimate the utility values of QoL [20]. Using the scoring function from Taiwan [21], we transformed the health state parameters into a utility value ranging from 0 to 1, where 0 represents death and 1 indicates full health. The duration-to-date for each measurement was defined as the period between the date of cancer diagnosis and that of interview. A kernel-smoothing method (i.e., a moving average of the nearby 10%) was used to estimate the mean QoL function along with time after diagnosis [10]. The utility values of QoL beyond the follow-up period were assumed to be the same as the average of the last 10% near the end of follow-up.

The lifetime survival function of the lung cancer cohort was adjusted using the corresponding mean QoL function to obtain a quality-adjusted survival curve, with the sum of the area under the curve being the QALE of lung cancer patients. We applied a 3% annual discount rate for calculation when the QALE values were employed in the estimation of ICER.

2.1.5. Estimating the loss-of-QALE to adjust for lead-time bias

We borrowed the utility values of age- and sex-matched referents from Taiwan National Health Interview Survey in 2009 to obtain a quality-adjusted survival curve for the referents. The loss-of-QALE was calculated by subtracting the area under the quality-adjusted survival curve of lung cancer patients from that of the referents.

Lead time denotes the period by which the disease diagnosed by screening advances routine diagnosis of the disease. The conventional method estimates lead time from volume doubling time (VDT), which could be influenced by different pathologies and stages of lung cancer [22,23]. While natural VDT for each specific type of lung cancer can only be measured without medical intervention, it is generally difficult to ensure the representativeness and accuracy of measured samples. We take an alternative approach – estimating the difference of life expectancy between a cancer case and his/her age- and sex-matched general population, or EYLL, after stratification for pathology and stage. The difference in differences between lung cancers detected by CT screening and those by radiography would account for the difference in age and sex at diagnosis. As people with the same age and sex usually share the same risk set [24], the difference in EYLLs would account for the lead-time bias in each specific pathology and stage. Similarly, loss-of-QALE is the expected lifetime utility loss from developing the disease, and is estimated by the difference in QALE between a lung cancer and age- and sex- matched general referents within a specific stratified group. The difference in loss-of-QALEs between lung cancer cases diagnosed with CT screening and those with radiography would be the health benefit of CT screening after correction of the difference in age and sex at diagnosis, namely, after adjustment for lead-time bias.

2.2. Additional costs of lifetime healthcare expenditures and savings of loss-of-QALE

Cumulative pathology and stage distributions of screen-detected and non-screen-detected lung cancers in the CT-screening and no-screening arms were assumed to be the same as those for CT-screening and radiography-screening in the NLST (Supplementary Fig. A1 and A2) [2]. The lifetime healthcare expenditures and loss-of-QALE for each specific pathology and stage were multiplied by the weights of the above two distributions and summed up to estimate the average lifetime healthcare expenditures and loss-of-QALEs for the comparison between CT-screening and no-screening.

2.3. Additional costs attributable to screen-negative/false-positive cases and radiation-induced lung cancer

We obtained the 2013 payment prices of the NHI to estimate the unit costs for CT screening, diagnostic follow-ups, and complications. Because no specific code has been set for low-dose CT, we used the reimbursement rate for non-contrast chest CT as a proxy for this. Additional costs attributable to screen-negative subjects and false-positive cases consist of the product of unit cost multiplied by the additional number of resources consumed, which are the numbers of CT screenings, diagnostic follow-ups, and complications per case of newly-diagnosed lung cancer based on the results of the NLST (Supplementary Fig. A1) [2]. Similarly, additional costs attributable to radiation-induced lung cancer consist of the average lifetime healthcare expenditures in the radiography group multiplied by the incidence of radiation-induced lung cancer deaths, which is the number of radiation-induced lung cancer deaths per case of newly-diagnosed lung cancer. The number of radiation-induced lung cancer deaths was modeled by the Fred Hutchinson Cancer Research Center and Massachusetts General Hospital simulating eligible criteria and annual screening in the NLST [25].

We summed up all the above costs of lifetime healthcare expenditures, costs attributable to screen-negative subjects and false-positive cases, and those of radiation-induced lung cancer for comparison to obtain the difference in total costs for the two arms. This was then divided by the difference in overall loss-of-QALEs between the two arms, which was also adjusted for the QALY lost from radiation-induced lung cancer, to determine the ICER.

2.4. Sensitivity analyses

We performed one-way sensitivity analyses of the additional numbers of diagnostic follow-ups, the costs of CT and surgery, and the stage distributions for CT-screening obtained from the Dutch-Belgian Lung Cancer Screening Trial (NELSON) [26] and UK Lung Cancer Screening Trial (UKLS) [27]. Adopting the cumulative stage distributions and additional resource uses attributable to radiography screening and CT screening in the NLST (Supplementary Fig. A1 and A2) [2], we further took the stage distribution of no-screening cohort in our NCR as a baseline comparison for both to examine the cost-effectiveness.

A probability sensitivity analysis was conducted. In this analysis, we assumed gamma distribution to additional costs, with means set to the base-case values and standard deviations (SDs) set to 40% of the means divided by (2×1.96). Pathology and stage specific proportions were assumed Dirichlet distribution, with mean set to the base-case value (p) and SD set to the square root of $p(1\text{-}p)/n$, where n denotes the number of lung cancer cases. Scatter plots were developed to represent uncertainty.

3. Results

The lung cancer cohort established from Taiwan NCR for survival estimation consisted of 62,392 patients (Fig. 1). Taiwan NHI reimbursement data included details of healthcare expenditures for every one of these cases. A total of 986 lung cancer patients with 3,358 repeated EQ-5D measurements were assessed at NCKUH. Supplementary Table A1 compares Taiwan NCR for the survival function with NCKUH database for the utility values.

3.1. Additional costs of lifetime healthcare expenditures and savings of loss-of-QALE

Fig. 2 shows the loss-of-QALE, which is the difference between the area under the quality-adjusted survival curve of the lung cancer cohort and that of the age- and sex-matched referents.

The EYLL, loss-of-QALE and lifetime healthcare expenditures for lung cancer in Taiwan, as stratified by pathology and stage, are summarized on Table 1. Fig. 3 shows how lead-time bias would be adjusted by comparing the difference in EYLLs for lung cancers diagnosed at stage I versus IV. Because the EYLL is adjusted for different ages at diagnosis, the difference of EYLLs would also be adjusted for such a confounder. According to Table 1, the difference in EYLLs between stages I and IV would be 12.62–4.65 = 7.97 years, indicating adjustment for lead-time bias between two different ages of diagnosis. Loss-of-QALE indicates loss of health benefits by taking both life expectancy and changes of QoL into account.

The pathology and stage specific proportions (or weights) for CT-screening and radiography-screening (Supplementary Fig. A1 and A2) [2] were multiplied by the lifetime healthcare expenditures and loss-of-QALE for each stratum and summed up for comparison of the two arms (Table 2 [28]).

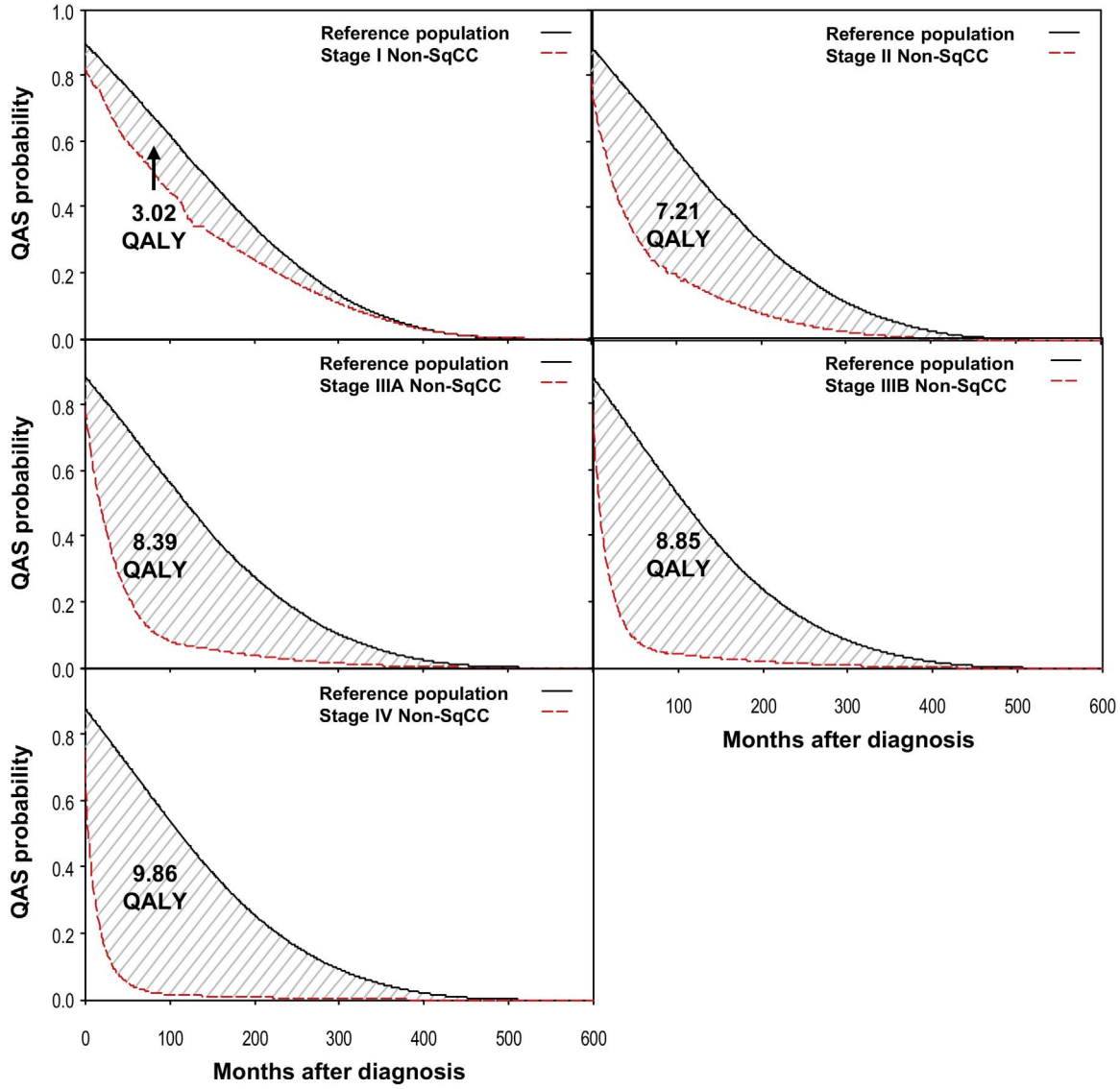

Fig. 2. Quality-adjusted survival (QAS) curves of patients and the corresponding referents stratified by stage. The shaded area is the loss-of-QALE (quality-adjusted life expectancy) (see Table 1). QALY, quality-adjusted life year; SqCC, squamous-cell non-small-cell carcinoma.

3.2. Additional costs attributable to screen-negative/false-positive cases and radiation-induced lung cancer

Table 2 also shows the additional costs attributable to screen-negative subjects, false-positive cases, and radiation-induced lung cancer. We added the additional costs of lifetime healthcare expenditures (US$2,407) to the sum to obtain the difference in overall costs between the two arms, which were divided by the savings of loss-of-QALE (1.16 QALY) to obtain the cost per savings of loss-of-QALE (US $19,683/QALY). Compared with the traditional method using incremental QALE (1.43 QALY) as the denominator, the savings of loss-of-QALE are lower. In other words, the ICER would have been underestimated (cost per incremental QALE = US$15,883/QALY) if we had not adjusted for lead-time bias.

3.3. Sensitivity analyses

In the sensitivity analyses, the ICER became US$29,349 per QALY when we doubled the additional number of diagnostic follow-ups (Fig. 4); it became US$31,066 per QALY and US$22,717 per QALY, respectively, when we doubled the costs of CT and surgery. However, if the stage distributions for CT-screening were equal to those of screen-detected cancers after the first three rounds of NELSON and cancers detected in the prevalence screen of UKLS, the ICER would fall to US $10,947 and US$11,575 per QALY, respectively. Taking the actual stage distribution of no-screening cohort in our NCR to compare with those of radiography screening and CT screening in the NLST, the ICER would become US$15,680 and US$11,367, respectively (Supplementary Table A2). Under these circumstances, the incremental costs would be underestimated because we compared non-screened general population to non-screened heavy smokers. In general population, the prevalence rate of lung cancer would be lower and the number of false-positive cases may be higher than those in heavy smokers. As a result, the amount of associated costs would be larger than we estimated.

Supplementary Fig. A3(A) shows the results of probability sensitivity analysis. Among 1,000 iterations, 77.1% could be considered cost-effective by falling to the right of the diagonal line, which represented per QALY cost of 1 gross-domestic product (GDP) per capita of Taiwan in 2013 (US$20,925) [29]. When we doubled the SD for Dirichlet distribution, the percentage became 67.3% (Fig. A3(B)).

Table 1
Loss-of-QALE and lifetime healthcare expenditures per lung cancer case aged 55 and over, follow-up for 13 years.

Pathology	Stage distribution *number (%)*		Censored after F/U *%*	Mean age at diagnosis, *year (SD)*	Life expectancy, *life-year (SE)*	EYLL, *life-year (SE)*	QALE, *QALY (SE)*	Loss-of-QALE, *QALY (SE)*	Lifetime healthcare expenditures, *US$ (95% CI)*
SCLC	Limited	1,787 (2.9)	8.7	71.0 (8.5)	2.10 (0.06)	11.61 (0.06)	1.78 (0.11)	9.46 (0.11)	22,028 (20,719–23,387)
	Extensive	4,139 (6.6)	1.5	72.1 (8.6)	0.74 (0.02)	12.32 (0.03)	0.56 (0.03)	10.05 (0.03)	13,532 (12,937–14,100)
SqCC	I	1,591 (2.6)	40.4	72.4 (8.1)	7.12 (0.13)	5.68 (0.13)	5.51 (0.25)	4.90 (0.24)	35,273 (32,921–37,712)
	II	982 (1.6)	25.8	72.5 (8.6)	4.68 (0.16)	8.03 (0.16)	4.14 (0.18)	6.17 (0.18)	31,616 (28,249–34,345)
	IIIA	1,740 (2.8)	12.6	72.6 (8.5)	2.71 (0.07)	10.03 (0.07)	2.13 (0.09)	8.20 (0.09)	27,295 (25,877–29,256)
	IIIB	2,865 (4.6)	5.7	72.0 (8.5)	1.65 (0.04)	11.38 (0.05)	1.35 (0.05)	9.24 (0.05)	23,336 (21,924–24,671)
	IV	5,349 (8.6)	2.3	72.7 (8.6)	0.90 (0.02)	11.81 (0.03)	0.66 (0.03)	9.56 (0.04)	16,083 (15,402–16,829)
Non-SqCC	I	6,449 (10.3)	66.3	68.9 (8.7)	11.59 (0.07)	4.65 (0.07)	9.91 (0.14)	3.02 (0.14)	38,527 (36,546 − 40,968)
	II	1,510 (2.4)	38.5	70.3 (9.3)	6.01 (0.10)	9.14 (0.10)	4.77 (0.18)	7.21 (0.18)	48,262 (44,656–53,412)
	IIIA	2,923 (4.7)	25.3	71.0 (9.0)	4.09 (0.07)	10.52 (0.07)	3.15 (0.08)	8.39 (0.07)	43,472 (41,076–45,191)
	IIIB	5,799 (9.3)	8.9	72.2 (9.3)	2.22 (0.04)	11.36 (0.04)	1.79 (0.04)	8.85 (0.04)	32,663 (31,111–34,109)
	IV	27,258 (43.7)	6.7	71.7 (9.4)	1.50 (0.02)	12.62 (0.03)	1.15 (0.02)	9.86 (0.02)	26,581 (26,054–27,131)

CI, confidence interval; EYLL, expected years of life lost; F/U, follow-up; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year; SCLC, small-cell lung cancer; SD, standard deviation; SE, standard error of mean; SqCC, squamous-cell non-small-cell carcinoma.

4. Discussion

Before making any inferences, we must first examine if the ICER of US$19,683/QALY obtained in this study is plausible and accurate. First, we abstracted a nation-wide lung cancer cohort and followed them for 13 years to determine their lifetime survival function and reimbursement costs. Because the period of follow-up is longer than the usual life expectancy of lung cancer [16], and the extrapolation method [13] has been mathematically proved [15] and validated in Supplementary Table A3, we can be confident that the estimations would be accurate. Second, we also conducted 3,358 repeated measurements of QoL from 986 consecutive patients and applied kernel-smoothing to estimate the dynamic changes of QoL after lung cancer diagnosis, which were adjusted for survival probabilities at different durations after diagnosis. Although our patients were not randomly selected, the estimate of QALE would be more representative and accurate than simply taking a mean QoL utility value [10]. Third, all lung cancer cases were diagnosed during 2002–2012 and treated under the same guidelines required by the reimbursement of Taiwan NHI. Since lung cancer cases with a specific pathology and stage would share similar outcomes (Table 1), different time-point of diagnosis would not confound the results. Fourth, we have adopted a counter-factual viewpoint, stratified by pathology and stage, and compared our cohort with age- and sex-matched referents to estimate the loss-of-QALE. While the conventional method estimating lead time from VDT may account for lead-time bias, the variations for different pathologies and stages of lung cancer are usually large [22,23], and it is difficult to validate the estimation except under a natural experiment, or when there is no medical intervention. Our approach of counting the loss-of-QALE directly adjusts for the difference in sex and ages at diagnosis within each specific pathology and stage. Although this difference-in-differences approach has not yet taken other risk factors (e.g., smoking) into consideration for individual lung cancer cases, it accounts for the lead-time bias for people within the same risk set of age, sex, pathology and stage [24]. Fifth, additional costs related to screen-negative subjects, false-positive cases, and radiation-induced lung cancer were included in the estimation of incremental cost-effectiveness. Finally, the sensitivity analysis of varying parameter values of uncertainties seems to consistently show an ICER of around 1 GDP per capita per QALY. We thus tentatively conclude that implementing CT screening for lung cancer among high-risk smokers in Taiwan would be cost-effective according to the thresholds once proposed by the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) [30,31]. Of course, any result of health technology assessment must also consider fairness and legitimacy before adoption into policy [31,32].

Compared with studies using the same trial to examine the cost-effectiveness of CT screening [3,6], the lower estimate of ICER in our study could be partially explained by performing the cost-utility analysis from the public payer's perspective, in which out-of-pocket costs were not included in our estimation. Our previous study found that the out-of-pocket money paid by lung cancer patients, however, was about 1/4–1/2 of the overall medical costs [16] when epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR-TKIs) were restrictively reimbursed under second- or third-line treatment. Assuming that all these payments were covered, the cost-effectiveness ratio would be US$21,981 per QALY.

While extrapolating the QoL function to lifetime, it was assumed that patients remained at the same level of QoL near the end of the follow-up period. Such an assumption could result in overestimated QoL scores because actual utility values usually decline with age and a further deterioration is expected towards the end-of-life. Hence, the QALE would be overestimated and the loss-of-QALE would be underestimated. These effects are more prominent in old or late-stage patients. As a result, the health benefits from CT screening would be underestimated and the ICER would be overestimated. However, patients with the above conditions also suffered from relatively short

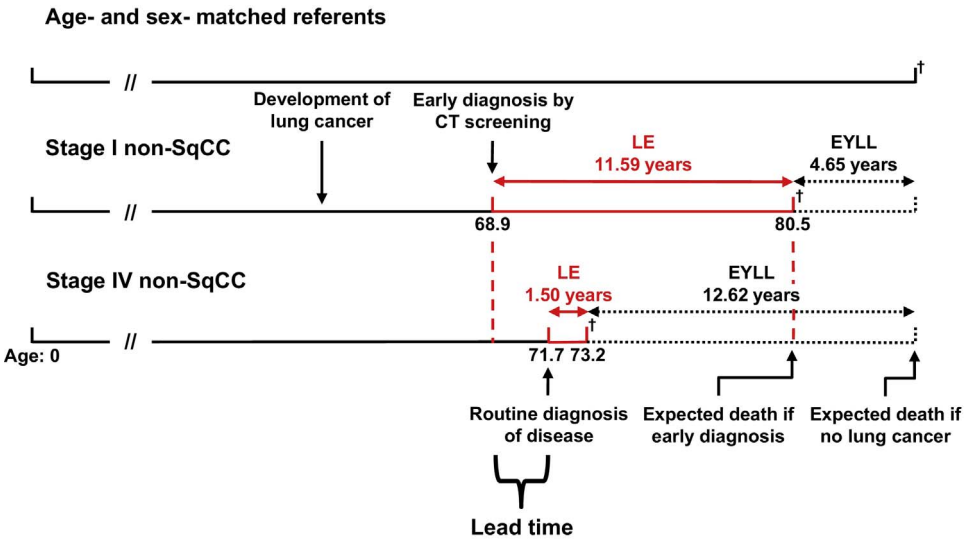

Fig. 3. Adjustment for lead-time bias: A case of stage IV non-SqCC is on average diagnosed at age of 71.7 (Table 1). If the patient is detected by CT at stage I (at age of 68.9), the gain in LE between stage I and IV would be 11.59–1.50 = 10.09 years. However, if we take two different ages of diagnosis into account by comparing the difference in EYLLs of the above two stages, the potential gain would be 12.62–4.65 = 7.97 years, and this number has been adjusted for lead-time bias between two ages of diagnosis. CT, computed tomography; EYLL, expected years of life lost; LE, life expectancy; SqCC, squamous-cell non-small-cell carcinoma. † indicates mortality.

Table 2
Incremental cost-effectiveness for computed tomography (CT) screening.

	Unit cost *(US$)*	Additional no. attributable to false-positive cases *(number)*	Additional costs attributable to CT screening *(US$)*
Low-dose CT (no. screen-negative subjects = 53.8)	127		6,820
No. false-positive cases		17.1	2,172
Diagnostic follow-up [a]:			
Clinical evaluation [b]	104	9.7	1,014
Chest radiography [b]	48	2.4	114
Chest CT [b]	508	8.2	4,167
FDG PET-CT	1,219	1.4	1,671
Transthoracic or extrathoracic biopsy	355	0.3	111
Bronchoscopy without biopsy	252	0.3	75
Bronchoscopy with biopsy	336	0.4	123
Mediastinoscopy or mediastinotomy	1,645	0.1	179
Thoracoscopy or thoracotomy	4,805	0.7	3,328
Other procedures [c]	405	0.3	123
Complications [a]:			
Major complications	1,921	0.1	156
Intermediate complications	880	0.1	114
Additional costs attributable to screen-negative and false-positive cases			20,167
Additional costs attributable to radiation-induced lung cancer			181
Additional costs of lifetime healthcare expenditures [d]			2,407
Incremental QALE [d], *QALY*			1.43
Savings of loss-of-QALE [d], *QALY*			1.16
ICER, cost per incremental QALE [d], *US$/QALY*			15,883
ICER, cost per savings of loss-of-QALE [d], *US$/QALY*			19,683

FDG PET, fluorodeoxyglucose-positron-emission tomography; ICER, incremental cost-effectiveness ratio; NLST, National Lung Screening Trial; QALE, quality-adjusted life expectancy; QALY, quality-adjusted life year.

[a] For those with false-positive findings on screening CT (false-positive rate of 96.4% in the NLST [2]).

[b] Unit cost including follow-ups at three months, nine months, 21 months and 33 months after positive findings on screening CT if no increase in size [28].

[c] Diagnostic pleurocentesis and thoracostomy.

[d] An annual discount rate of 3% for costs and QALY was applied.

survival, the magnitude of effect would generally be small.

The CT cost was one of the major determinants of ICER. Compared with the costs of chest CTs in other studies [3–6], the fee charged for a chest CT in Taiwan is lower (US$127), which contributes to the low ICER estimate in our study. However, because of the lower depreciation, the cost of a chest CT is higher than that of a low-dose CT several years after the screening program. The ICER we calculated would thus be higher compared with the true estimate. As expected, the ICER rose when we increased the number of diagnostic follow-ups. We also assumed the stage distribution for CT-screening equaled that of screen-detected cancers in the NELSON and UKLS. The ICER fell because interval cancers, most of which would be in later stages, were not included in the analysis.

Several limitations must be acknowledged in this study. First, the high-quality care and high screening-adherence rate in the NLST may not be easily achievable in routine clinical practice. For these reasons we examined the uncertainties in sensitivity analyses. Although the results appear similar, one must still be cautious with regard to generalizability. Second, we compared population-wide life expectancy to the life expectancy of screened smokers. Smokers' all-cause mortality may be increased because of diseases other than lung cancer, hence our method would potentially overestimate the savings of loss-of-QALE, or, the benefits of CT screening. Third, we did not analyze the data stratified by the time periods before and after EGFR-TKIs reimbursed as first-line treatment. In patients with advanced non-SqCC harboring exon 19 deletion, EGFR-TKIs are associated with better survival compared with chemotherapy [33], our method would thus overestimate the QALY gained and underestimate the ICER. On the other hand, however, increasing use of EGFR-TKIs also carries substantial costs [34] in patients with advanced non-SqCC, our method would thus overestimate the additional costs and the ICER. Fourth, the possibility of over-diagnosis could be a major concern in this analysis [35]. Over-diagnosis denotes that "indolent lung cancer" detected or identified by CT-screening might not necessarily progress to overt clinical disease in its natural course. In the past, it was not possible to be sure whether such cases would result in loss of life expectancy, because of the difficulty of following-up patients for lifetime, and such cases were called "over-diagnosis". In this study we took the opportunity to access a nation-wide database with 13 years of follow-up, for which stage IA non-mucinous bronchioloalveolar carcinoma could be the proxy to such cancers. The database collected 116 such patients from the 62,392 lung

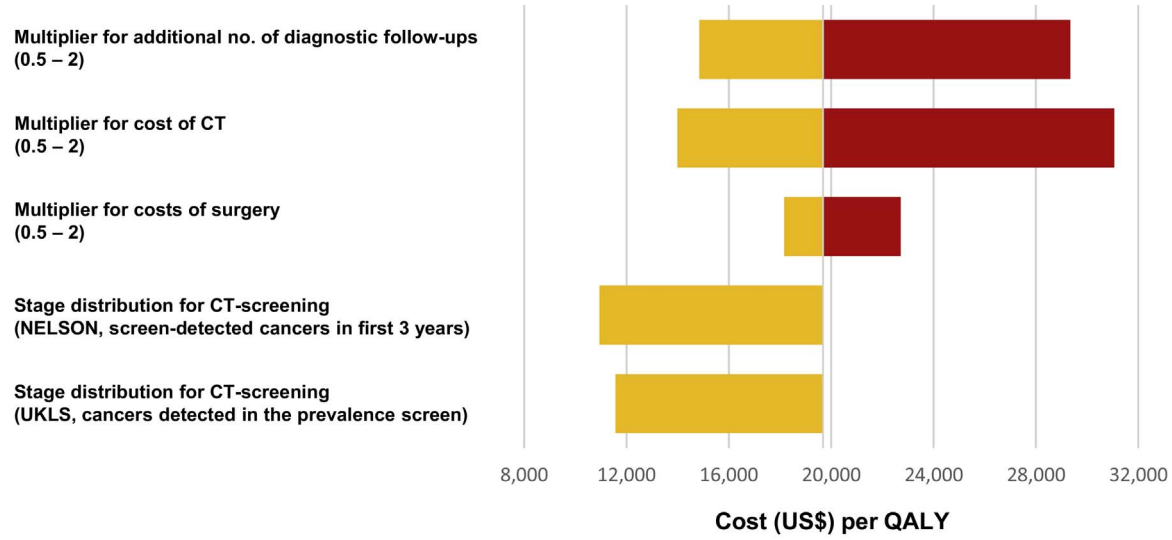

Fig. 4. Sensitivity analysis. CT, computed tomography; NELSON, Dutch-Belgian Lung Cancer Screening Trial; UKLS, UK Lung Cancer Screening Trial; QALY, quality-adjusted life year.

cancer cohort. Compared with the corresponding age- and sex-matched referents, the EYLL of patients with such an indolent lung cancer would be 1.56 life-years (Supplementary Fig. A4). This indicates that an excess mortality still exists in such lung cancer cases, namely, they would still die prematurely after a long-term period of follow-up.

The distributions of pathology and stage between our national cohort and the trial data are different. In Taiwan, more than two thirds of lung cancers are non-SqCC [36] and 43.7% are diagnosed at stage IV (Table 1). Such cases would generally be greatly benefited by the stage shifting of CT screening (Supplementary Figs. A1 and A2) [2]. Consequently, implementing CT screening in Taiwan would be more cost-effective than in Western countries. Nevertheless, since only 9–10% of females with lung cancer in Taiwan are smokers [37,38], the effectiveness of a screening program aimed at heavy smokers would be very limited for women. Future research is necessary to identify the high-risk groups among non-smokers to expand the coverage of CT screening.

5. Conclusions

In conclusion, the estimated cost per QALY gained by implementing CT screening for lung cancer among high-risk smokers in Taiwan would be around 1 GDP per capita. This methodology of using long-term big data to extrapolate survival and estimate QALE, loss-of-QALE, lifetime costs in a real-world setting could be applied to other screening programs for cost-effectiveness evaluations.

Conflict of interests

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2017.04.001.

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