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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-