DECISION ANALYSIS OF THE EFFECTIVENESS OF LUNG CANCER SCREENING USING AUTOFLUORESCENCE BRONCHOSCOPY AND COMPUTED TOMOGRAPHY

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ABSTRACT

Background: Lung cancer (LC) is the leading cause of cancer death in the developed world. Most cancers are associated with tobacco smoking. A primary hope for reducing lung cancer has been prevention of smoking and successful smoking cessation programs. To date, these programs have not been as successful as anticipated.

Objective: The aim of the current study was to evaluate whether lung cancer screening combining low dose computed tomography with autofluorescence bronchoscopy (combined CT & AFB) is superior to CT or AFB screening alone in improving lung cancer specific survival. In addition, the extent of improvement and ideal conditions for combined CT & AFB screening were evaluated.

Methods: We applied decision analysis and Monte Carlo simulation modeling using TreeAge Software to evaluate our study aims. Histology- and stage specific probabilities of lung cancer 5-year survival proportions were taken from Surveillance and Epidemiologic End Results (SEER) Registry data. Screening-associated data was taken from the US NCI Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), National Lung Screening Trial (NLST), and US NCI Lung Screening Study (LSS), other relevant published data and expert opinion.

Results: Decision Analysis – Combined CT and AFB was the best approach at improving 5-year survival (Overall Expected Survival (OES) in the entire screened population was 0.9863) and in lung cancer patients only (Lung Cancer Specific Expected Survival (LCSES) was 0.3256). Combined screening was
slightly better than CT screening alone (OES = 0.9859; LCSES = 0.2966), and substantially better than AFB screening alone (OES = 0.9842; LCSES = 0.2124), which was considerably better than no screening (OES = 0.9829; LCSES = 0.1445). Monte Carlo simulation modeling revealed that expected survival in the screened population and lung cancer patients is highest when screened using CT and combined CT and AFB. CT alone and combined screening was substantially better than AFB screening alone or no screening. For LCSES, combined CT and AFB screening is significantly better than CT alone (0.3126 vs. 0.2938, p < 0.0001).

**Conclusions:** Overall, these analyses suggest that combined CT and AFB is slightly better than CT alone at improving lung cancer survival, and both approaches are substantially better than AFB screening alone or no screening.
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LIST OF ABBREVIATIONS

LC – Lung Cancer
LDCT – Low Dose Computed Tomography
AFB – Autofluorescence Bronchoscopy
SEER – Surveillance and Epidemiologic End Results
NCI – National Cancer Institute
BCCA – British Columbia Cancer Agency
PLCO – Prostate, Lung, Colorectal and Ovarian
NLST – National Lung Screening Trial
LSS – Lung Screening Study
OES – Overall Expected Survival
LCSES – Lung Cancer Specific Expected Survival
RCT – Randomized Controlled Trial
I-ELCAP – International Early Lung Cancer Action Program
USPSTF – United Stated Preventative Services Task Force
ACCP – American College of Chest Physicians
QALY – Quality Adjusted Life Year
CIS – Carcinoma In Situ
AdCA – Adenocarcinoma
SqCCA – Squamous Cell Carcinoma
ONSCLC – Other Non Small Cell Lung Cancer
SCLC – Small Cell Lung Cancer
CHAPTER I: INTRODUCTION

THEME

This thesis examines the potential impact that screening using low dose computed tomography (LDCT) and/or autofluorescence bronchoscopy (AFB) have on the survival of patients considered at high risk for lung cancer. By performing decision analysis and Monte Carlo simulation modeling, and using published data as well as expert opinion, we were able to carry out this analysis and draw conclusions. In addition, the extent of improvement and ideal conditions for screening were evaluated.

Lung cancer is currently one of the most common cancers worldwide and accounts for roughly one quarter of all cancer deaths in Canada and the United States (1-3). The probability of being diagnosed with lung cancer is highest among the elderly (individuals 70 years and older) and overall men are at higher risk than women (4). In North America, substantial declines in overall lung cancer rates have taken place over the last two decades, with the biggest improvements observed among middle aged adults (3).

By far, the most important risk factor for lung cancer is smoking. In Canada, it is estimated that 21 032 new cases of lung cancer will be diagnosed among individuals with a smoking history (either current or former smokers) in 2008 (Canadian Cancer Society, Canadian Cancer Statistics, 2008). Currently, only 10% of men and 15% of women who develop lung cancer are considered never smokers (5). Current hopes for reducing lung cancer mortality rest primarily on the implementation of successful smoking cessation programs,
which unfortunately have not enjoyed the level of success originally anticipated (6). Compared to never smokers, former smokers remain at a significantly elevated risk for developing lung cancer (6-8) and currently represent a sizeable proportion (approximately half) of newly diagnosed cases (6). To reduce lung cancer mortality among former smokers, current anti-smoking campaigns provide little benefit, while an alternative control strategy is needed. Many experts believe that screening high risk individuals has the best potential to reduce lung cancer mortality, but this has yet to be proven.

Currently, the majority of lung cancers are diagnosed at late stage and despite modest improvements in treatment, prognosis is still very poor (4). Overall, the 5-year survival rate for lung cancer remains only at approximately 16% (9). However, if a patient is diagnosed with early stage lung cancer; i.e., stage 1, the overall 5-year survival is higher than 70% (10, 11). This suggests that lung cancer would make an ideal candidate for screening based on the premise that most cases of lung cancer that would have caused death would now be diagnosed at an earlier and more curable stage through screening.

The idea of screening for lung cancer is not something new. Beginning in the 1960s, several randomized controlled trials (RCTs) using chest radiograph and/or sputum cytology were carried out to test this hypothesis, but none were able to detect any significant benefit in lung cancer mortality. Although screening did lead to more cancers being detected, it did not result in a reduction in lung cancer mortality (12-17). These early trials have since been criticized on many grounds; and, because of their limited power alone, they are unable to detect a
lung cancer mortality reduction in the range of 10–20% (9). Other important criticisms include employment of insensitive screening devices (9, 18) and serious methodological flaws in study design (13). Recently, with the advent of newer and more sensitive imaging technology, there has been renewed interest in lung cancer screening. Low-dose computed tomography and autofluorescence bronchoscopy are two such technologies and are highly sensitive in the detection of peripheral and central airway cancers, respectively. Both are considered useful in screening because of their improved ability to detect small lung cancers and at an earlier stage than conventional chest x-ray and sputum cytology (10, 19).

In order for screening to benefit patients, these additional early lung cancers that are detected must be considered reasonably likely to progress to advanced disease and must be sensitive in detecting lung cancers that advance rapidly (20). Unfortunately, at this time, previous screening trials do not support these benefits and it is speculated that the majority of additional small cancers that are detected through screening are actually only indolent cases that would never have progressed to invasive disease if they had been left and watched (referred by some as “pseudodisease”; a term which refers to abnormalities detected by screening, which meet the pathologic definition of cancer, but that will never progress to cause symptoms) (21, 22). In the context of screening, this is referred to as overdiagnosis bias. Until recently, overdiagnosis had received relatively little attention, but it is thought by some to be an important source of cost and harm involved with cancer screening (9).
Other biases that are important are *length* and *lead-time biases*. Length bias pertains to comparisons that are not adjusted for the rate of disease progression. The probability that a case will be detected by screening is directly proportional to the length of its detectable pre-clinical phase, which is inversely related to its rate of progression. This implies that cases detected by screening are inherently less likely to be aggressive when compared to disease that presents clinically. Also, because survival is often measured from the time of diagnosis, any screening test that advances the time of diagnosis introduces lead-time bias. Unfortunately, adjusting for lead time is often problematic because it is usually unknown and variable (9).

These biases must be considered and taken into account when attempting to determine the cost-effectiveness of lung cancer screening. To date, there have been several cost-effectiveness analyses of CT screening for lung cancer that have been published and results range from very favourable to marginal, depending on how well they adjusted for overdiagnosis, quality of life, and other factors (9). If a screening regime can be developed that is sensitive in detecting early aggressive lung cancer, and specific so as to limit overdiagnosis, then it is possible that screening will become cost-effective and should be recommended. However, before a screening strategy can be considered cost-effective, it first needs to be proven that it is in fact effective.

Using decision analysis, this study seeks to evaluate whether a proposed screening strategy for lung cancer is effective in reducing lung cancer specific mortality (how we evaluate effectiveness is discussed in greater detail in the
following sections), and by which application or combination of applications screening is most effective.

**STUDY AIMS**

Using decision analysis and Monte Carlo simulation modeling we attempt

1. To evaluate whether screening for lung cancer using (1) AFB and/or (2) low dose CT can improve screening performance compared to no screening as measured by reduced 5-year lung cancer specific mortality, and

2. To determine the CT and AFB test parameters and screening conditions required to optimize overall lung cancer screening performance (measured by reduced 5-year lung cancer specific mortality) by comparing alternative combinations of application.
BACKGROUND

Lung cancer is a serious public health problem that is not expected to go away anytime soon. It is currently the most commonly diagnosed cancer worldwide and kills more men than women (23, 24). Smoking is the number one risk factor for lung cancer. It is responsible for 88% of the problem and is associated with all histological types of lung cancer (1, 5). Currently the majority of public health efforts aimed at reducing lung cancer mortality have targeted quitting smoking, but success has been limited. During the 1980s it was estimated that approximately 1.3 million people in the US quit smoking each year and it was hoped that this would reflect favourably on lung cancer mortality (25). Unfortunately, we now know that quitting smoking does not eliminate one’s risk of developing lung cancer and today former smokers are the source of approximately half of new lung cancers (6, 26, 27). To quantify risk of lung cancer in former smokers, Peto and colleagues (7) recently published findings from a large cohort study performed in the UK and found that cessation at age 60, 50, 40, or 30 years resulted in cumulative risks of lung cancer of 10, 6, 3 and 2%, respectively. Beyond current and former smoking status, we now know that smoking duration is a more important risk factor than smoking intensity (24, 26).

In addition to active smoking, other known risk factors for lung cancer include exposure to secondhand smoke, diet, physical activity, exposure to asbestos, radiation exposure, air pollution, family history of lung cancer, presence of acquired lung disease, and genetic factors (24, 28-31). There are
also many exposures in the workplace that are known to cause lung cancer and some of these include arsenic, chromium, cadmium and nickel. Exposure to tar and soot (which contains benzo[a]pyrene) in concentrations higher than what is present in urban air also elevates one’s risk of developing lung cancer (24). Low socio-economic status has also been linked to lung cancer. Risk of being diagnosed with lung cancer has been found to be inversely associated with income, education and social class, and this is even after adjustment for smoking (24, 32, 33). Although it is important to recognize these other risk factors, they are relatively unimportant in comparison to smoking.

**Screening for Lung Cancer**

Lung cancer satisfies most of the conditions put forth by Wilson and Jungner that would make it an ideal candidate for screening (34). It is a major public health problem, but if detected early, there is a good chance for a cure. The major problem with lung cancer is that there is currently no effective method to screen for early stage disease among the high-risk population (11). Although screening has proven to be successful in reducing the incidence and mortality of other cancers (e.g., cervix, breast and colon cancer) (35-38), it has not yet been proven effective for lung cancer (18).

To date, several large randomized trials using chest radiography and/or sputum cytology to screen for lung cancer have been conducted (11 – 16). Although some of these studies found a higher incidence of disease in the screened population, none demonstrated any significant reduction in lung cancer
mortality. Unfortunately, these studies possessed some serious methodological flaws in their design, which now makes them difficult to interpret (13). Included in the criticisms are lack of sufficient study power (9) and employment of insensitive screening devices (9, 18).

**Screening Using CT**

Despite a lack of evidence supporting lung cancer screening, there are still many good reasons to remain optimistic about using low dose CT. For one, CT is noninvasive and can be performed in a short period of time. A low-resolution image of the entire thorax can be obtained with low radiation exposure and within a single breath hold using low-dose CT (39). It has been reported that the radiation dose for a single examination is only slightly more than the United States average annual effective dose equivalent per person from natural sources, and this dose is expected to decrease by an order of magnitude in the near future, eventually making it even more safe (9). Also, since the population that is at greatest risk for lung cancer can be identified on the basis of age, smoking history and other factors (e.g., occupation, family history), we can selectively screen only high risk individuals and hopefully limit the amount of unnecessary exposure to radiation and other harms.

Perhaps the best reason to remain optimistic about screening is that CT is much more sensitive than chest radiograph and sputum cytology. In 1993, the Early Lung Cancer Action Project (ELCAP) was created and in 1999, Henschke et al. (40) published its first report on the progress of lung cancer screening.
They presented findings from 1000 high risk individuals that were screened using low-dose CT and found that CT detected about 6 times as many stage I lung cancers as chest radiography, and that the majority of these tumors measured ≤ 1 cm in greatest dimension. They concluded that screening using low-dose CT improves the likelihood of detecting lung cancer, and at an earlier and potentially more curable stage (40).

At about the same time that this first ELCAP study was published, researchers in Japan came out with similar results, demonstrating that low-dose CT scans were very effective in detecting early lung cancers (41, 42). Kaneko et al. (41) evaluated chest radiograph and CT scans in a population of over 1300 high risk patients and compared the two tests efficacy. A total of 15 lung cancers were detected by CT, but only 4 were detected by chest radiography, which means that 11 potentially deadly lung cancers were missed by chest x-ray.

In another study at the Mayo Clinic, CT screening was found successful in detecting all lung cancers that measured ≥ 8 mm (43). This provides further support for screening using low-dose CT. Because stage I lung cancer is the most curable form of the disease, and considering the evidence that CT is effective at detecting disease at this stage, proponents of lung cancer screening believe that an increase in the detection of early stage disease will ultimately result in a decrease in lung cancer related mortality. Unfortunately, this may not necessarily be the case, and there are also reasons for healthy skepticism about CT screening for lung cancer (to be discussed later). As it stands, we do not know whether CT screening for lung cancer reduces lung cancer mortality.
Although high rates of survival have recently been reported for screen detected lung cancers, such as in the international ELCAP (I-ELCAP) study (44) a reduction in lung cancer mortality has not been demonstrated (median follow-up = 40 months).

As mentioned previously, ELCAP was originally established in 1993 at Cornell University Medical Centre and since this time, experts from various other institutions from around the world have joined forces to collaborate on this project (now referred to as the I-ELCAP study). In 2006, Henschke and colleagues published findings from this study in the New England Journal of Medicine (44). The purpose of this investigation was to determine the outcome of patients with CT detected stage I lung cancer and employed a case series study design without a control group. Researchers found that of the 31 567 asymptomatic high risk individuals screened using low dose CT, 484 were diagnosed with lung cancer, and of these 412 (85%) had clinical stage I lung cancer. The reported 10-year survival rate for patients with confirmed stage I lung cancer in this study was 88%, and for those who underwent resective surgery within 1 month of diagnosis, the survival rate was 92% (44). Upon publication, this article received considerable media attention and some felt that it should be used as strong evidence to support immediate initiation of lung cancer screening. At the present, the Lung Cancer Alliance, a major patient advocacy group is lobbying congress and the US president to make early detection of lung cancer a national priority by encouraging CT screening as a way to save lives, using I-ELCAP study data as evidence to support their stance and using popular sports
celebrities in advertisements that encourage the public to take the initiative by getting themselves screened (45).

In a recent article published in Archives of Internal Medicine, Welch et al. (45) caution heavily against interpreting results from the I-ELCAP study as support for screening. Their main concern is that the I-ELCAP study had no control group and contends that, only a control group can provide insight into what would happen in the absence of screening. They also point out that the use of 10-year survival as an outcome measure is biased. Survival does not take into account the influence of lead time or overdiagnosis and these are two important sources of bias that are known to exist in lung cancer screening, and that should not have been overlooked (45).

Since survival is measured from the time of diagnosis, any screening test that advances the time of diagnosis introduces lead-time (Figure 1). Figure 1 illustrates the danger in not correcting for lead-time when reporting 10-year survival rates with and without screening.
Figure 1. Lead-time bias. Any screening test that advances the time of diagnosis introduces lead-time bias. Even if death is not delayed at all, screening may appear to be extremely successful. In this example, even though the 10-year survival rates have changed dramatically (0% without screening vs 100% with screening), nothing has changed about the time of death. That is, whether diagnosed at age 67 years or at 59 years, all patients die at age 70 years.

(Adapted from Welch et al., 2007) (45)

Overdiagnosis is the second phenomenon associated with screening that may produce bias if not adjusted for in analysis. It refers to abnormalities detected by screening which meet the pathologic definition of cancer but that will never progress to cause symptoms. Welch et al. (45) attempt to explain the concept of overdiagnosis bias by using the following hypothetical example. Imagine that 1000 patients are diagnosed with lung cancer and without pseudodisease and of those 100 are alive 10 years later. However, using spiral CT an additional 4000 are diagnosed with pseudodisease, all of whom survive 10 years later. Notice that although the survival rate changes dramatically (82% compared to 10%), the number of people who die does not change (Figure 2).
Figure 2. Overdiagnosis bias. The diagram shows how the detection of pseudodisease inflates the survival statistic even when the number of deaths stays the same.

(Adapted from Welch et al., 2007) (45)

Despite some very convincing evidence that CT is much more sensitive in detecting early stage lung cancer than chest x-ray, this alone does not serve as proof that CT is effective in reducing lung cancer mortality. While screening over 5400 volunteers, Japanese investigators found that CT was able to detect 10 times more lung cancer than chest x-ray; but oddly, incidence was virtually the same in smokers and in nonsmokers (those who have never smoked) (42). Because we know that incidence and risk of dying from lung cancer is much greater for smokers than for nonsmokers, this data provides powerful evidence that overdiagnosis can be a major problem in screening for lung cancer, and this is now well established in the literature (46-50).
Overdiagnosis results in patients being treated who do not have a disease to be cured. These patients do not benefit from treatment because their “disease” posed no threat; however, the harms associated with treatment as a result of overdiagnosis are numerous. Unneeded radiation, emotional and psychological harm are all important harms that are associated with overdiagnosis (51), but the most significant harm is the mortality associated with resective surgery. Recent reports from the I-ELCAP indicate that over three quarters of lung cancers are diagnosed in the elderly (individuals > 60 years of age) (44) and this is important because risk of operative mortality associated with lobectomy increases with age. In the Medicare population aged 65 to 79 years, the 30-day mortality rate for lobectomy ranged from 3.6% (for those aged 65-69 years) to 6.1% (for those aged 75-79 years) (52). But considering that risk of mortality associated with lobectomy extends far beyond 30 days, the rates presented here are likely an underestimate of the true mortality rate for these populations.

To assess whether routine CT screening can significantly reduce lung cancer mortality, Bach and colleagues recently conducted a controlled observational study (based on 3 single-arm studies) to evaluate the effectiveness of low-dose CT in a group of high risk patients (53). Specifically, they used a validated lung cancer prediction model to estimate the expected numbers of various lung cancer outcomes among a combined cohort of 3246 participants, and then compared the observed numbers of lung cancer outcomes with the numbers of expected cases. They found that while screening increases the rate
of lung cancer diagnosis (144 observed vs. 44.5 expected) and treatment (109 observed vs. 10.9 expected), it does not reduce advanced lung cancer (42 observed vs. 33.4 expected), or death from lung cancer (38 observed vs. 38.8 expected) (53). While this study provides some compelling evidence against lung cancer screening using CT, it is important to keep in mind that RCTs are the most reliable method for obtaining accurate assessments of the benefits and harms of screening.

Currently there are two major RCTs of low-dose CT underway and these are the National Lung Screening Trial (NLST) and the NELSON trial. The NLST is funded by the National Cancer Institute and has randomly assigned 50,000 high-risk smokers (between 55 and 74 years of age) to receive annual screening with either low-dose CT or with chest radiograph. This is a multi-centre study and is designed to have 90% power to detect a lung cancer mortality reduction of 20% over about 6 years. Results from this trial are expected to be ready by 2010 (11). The NELSON trial (54) is also a multi-centre study that is a collaboration between the Netherlands and Belgium. In this study, investigators have randomly assigned 16,000 high risk individuals to receive either low-dose CT screening, or usual care and advice on smoking cessation. This study is powered to detect a mortality reduction of 25% or more over 10 years, but results are not expected until 2016. The primary objective of both these trials is to provide high quality information regarding whether screening using low-dose CT reduces lung cancer mortality; and if it does, by how much and at what potential cost. In the future, results from these trials will provide important evidence in
guiding policy maker’s decisions on whether lung cancer screening should be recommended. But, even if the benefits do outweigh the harms, it is important to remember that the cost-effectiveness of CT screening will still need to be considered in the context of other healthcare alternatives.

Current Recommendations

The US Preventative Services Task Force (USPSTF) and the American College of Chest Physicians (ACCP) are two of the most authoritative organizations in the US that make recommendations on cancer screening, and both state that at the moment evidence is not sufficient to recommend in favour of lung cancer screening (20, 55). Both the ACCP and the USPSTF acknowledge that the results of ongoing RCTs will provide indispensable evidence in guiding the decision on whether lung cancer screening should be recommended in the future.

The ACCP is responsible for developing clinical practice guidelines for screening, as well as management of lung cancer and have recently published a series of reports on this (24, 56-62). Their recommendations on screening can be summarized as follows. They do not recommend that low-dose CT be used to screen for lung cancer except in the context of a well designed clinical trial; they recommend against the use of serial x-rays to screen for the presence of lung cancer; and they recommend against the use of single or serial cytologic evaluation to screen for lung cancer (20).
Several cost-effectiveness analyses of CT screening for lung cancer have been published (Table 1) and results have ranged from very favourable ($2500 per life-year saved (63)) to marginal (≥ $100 000 per quality-adjusted life-year saved (64, 65)), depending on how well investigators adjusted for known biases and other important factors (e.g., modeling assumptions and probabilities entered into the model). In Table 1, studies are listed in order of cost-effectiveness per life-year gained (lowest to highest). It is important that the reader recognize that the current investigation does not include cost-effectiveness analysis; however, because decision analysis and cost-effectiveness analysis are so closely related, it is important to present these studies in order to acquire a better understanding of the current state of knowledge on screening for lung cancer.

In a fairly recent study, Mahadevia et al. (64) stratified individuals by smoking status and used the Surveillance, Epidemiology, and End Results (SEER) national cancer database to obtain expected lung cancer incidence and mortality rates. Their model incorporated known biases such as length, lead-time, and overdiagnosis bias; and also took into account adherence to screening, cost of CT, and monitoring of indeterminate nodules. Success was modeled using stage shift and for current smokers this was modeled as a 50% shift and an associated lung cancer mortality reduction of 13% during the first 20 years. The incremental cost effectiveness per quality-adjusted life-year (QALY) gained for current, quitting and former smokers was determined to be $116 300, $558 600 and $2 322 700, respectively. In sensitivity analysis, investigators varied the
degree of stage shift and determined that in order for screening to cost less than $50 000 per QALY, current smokers needed a 91% stage shift. For quitting and former smokers, a 100% stage shift was by itself insufficient to reach $50 000 per QALY (64). It is important to note that this study examined costs over a very long time period and chose to include numerous costs which most other cost-effectiveness studies elected to omit. Because most other studies were not as inclusive as this one, the incremental cost-effectiveness estimates that they calculated were much lower, making screening appear much more attractive (63, 66-68). Recently, Manser et al. (65) performed a cost-effectiveness analysis of screening in the Australian setting and obtained quality adjusted estimates that were very similar to what Mahadevia et al. came up with. Both analyses made adjustments for overdiagnosis, effects of smoking on competing mortality, and other important factors and biases.

In June of 2008, Chien and Chen (69) published results from a decision analysis they performed comparing the effectiveness among different screening strategies for lung cancer. They compared CT, chest x-ray and observation and came to the conclusion that CT screening has the potential to advance the diagnosis of asymptomatic lung cancer by about one year compared to x-ray, and that a approximate 15% mortality reduction could be achieved by CT screening as compared with observation (10-year follow-up) (69). This study did not examine the potential impact of screening using AFB.

All of the analyses which have been presented so far are based on stage-shift models that have not been validated. Currently, more sophisticated models
which simulate the natural history of lung cancer are under development. An important concept that is relevant to screening and to the natural history of lung cancer is doubling rate. Evidence suggests that the doubling times of most lung cancers that cause death is approximately 40 to 70 days (20). It can be useful to determine the doubling rates of lung cancers detected by screening in order to evaluate whether these rates are consistent with the natural history of the disease.

Critical point is another important concept and is often defined as the point beyond which therapy is less effective (9). If the critical point occurs before the detectable preclinical phase, then screening will not be effective in detecting disease early and will likely not result in a reduction in lung cancer mortality. For most cancers the critical point occurs when the primary tumor metastasizes, and currently it is believed that some lung cancers (small cell lung cancers) metastasize when they are only about 1 mm in greatest dimension and difficult to detect (70). The ability to detect lung cancer before it metastasizes and the doubling rate of lung cancers detected via screening are important determinants of screening success and should be considered in future analyses of cost-effectiveness.
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<tr>
<td>Chirikos et al., 2002 (66)</td>
<td>Cohort characteristics modeled in treatment costs and life expectancy</td>
<td>High risk, 2.7%; low risk, &lt; 2.7%</td>
<td>Annual screening for 5 yr</td>
<td>50% localized disease (20% in the control arm)</td>
<td>15yr</td>
<td>291 (340-416)</td>
<td>46 513</td>
</tr>
<tr>
<td>Marshall et al., 2001 (68)</td>
<td>100 000 smokers; 60-74 yr old; median 45 pack-year smoking history; 45% male</td>
<td>High risk, 2.7%; low risk, 0.7%</td>
<td>One-time screening</td>
<td>85% stage I (21% in control arm)</td>
<td>15 yr</td>
<td>150 (not reported)</td>
<td>15 274</td>
</tr>
<tr>
<td>Wisnivesky et al., 2003 (63)</td>
<td>1 000 participants; ≥ 60 yr old; ≥ 10 pack-year smoking history</td>
<td>High risk, 2.7%; low risk, 1.0%</td>
<td>One-time screening</td>
<td>85% stage I (21% in control arm)</td>
<td>1 yr after diagnosis, including terminal care costs</td>
<td>165 (300)</td>
<td>2 500</td>
</tr>
</tbody>
</table>

* Estimates of cost-effectiveness are quality adjusted.
† All estimates include lead time of 1 to 1.5 years with the exception of the results from the Chirikos study, which do not adjust for lead time.
LYG = life-year gained

(Adapted from Bach et al., 2007) (20)
Lung Cancer Staging

The international system for staging lung cancer is a consistent method for classifying the extent of disease in patients with lung cancer and is currently the most valid indicator of prognosis (71). This system is applicable to all histological types of lung cancer and includes the following major stage groupings: stage 0 (carcinoma in situ), stage I, stage II, stage III, and stage IV (71). Stage 0 describes lung cancers that are localized and that have not penetrated the surface lining of the lungs (only found in the first few layers of the cells). Stage I describes lung cancers that have not metastasized and that are surrounded by normal tissue, stage II describes lung cancers that have spread to nearby lymph nodes, stage III describes lung cancers that have invaded mediastinal structures (esophagus, trachea, carina, heart, major vessels) or other nearby organs and may have spread to lymph nodes in the mediastinum, or the other side of the chest or neck. Stage IV indicates the most severe stage of disease and includes only patients with distant metastasis (71). For this investigation, lung cancer was staged according to SEER Historic Stage A classification system. Stage I lung cancer was referred to as localized, stage II and III as regional, and stage IV as distant.

Risk Prediction Models

Understanding that the risk of developing lung cancer is not identical among all high risk individuals (i.e., current and former smokers), Bach and colleagues developed and validated a risk prediction model to better estimate individual risk
Characteristics that they found significant and considered important to include in their model were: age, sex, exposure to asbestos, duration of quitting for former smokers, and duration of smoking and number of cigarettes smoked per day. In addition, Spitz et al. (75) recently published their own model which included other factors not considered by Bach (73). Variables that had a significant association with lung cancer and which were included in their model are: exposure to environmental tobacco smoke, family history of cancer, dust and asbestos exposure, history of respiratory disease, and smoking history. In order to acknowledge the important contribution that genetic susceptibility plays in lung cancer, Spitz mentions that in the future they plan to incorporate gene variation data into their model (75).

The concept of developing a model to estimate individual risk is not new for cancer. For example, the Gail model for predicting the absolute risk of invasive breast cancer was developed many years ago and this model has been a valuable resource for counseling patients and in designing intervention studies (76, 77). Like the Gail model, lung cancer prediction models are useful because they allow patients to locate themselves along the spectrum of lung cancer risk. This is important in the context of lung cancer screening trials because it allows investigators to identify subjects in whom lung cancer is most likely to develop. This strategy has the potential to reduce costs by reducing sample size or study duration without compromising statistical power. However, an important criticism of individual risk modeling is that for most diseases, and this includes lung cancer; there is a tremendous amount of overlap between the group that
eventually develops disease and the group that does not, regarding exposure to risk factors. And so, although clinicians are interested in providing patients with estimated personal risk of developing disease, risk prediction models should be applied only to aggregates of individuals and not be used for specific individuals (78).

**Role for Autofluorescence Bronchoscopy in Lung Cancer Screening**

It has now been well established that CT is sensitive in detecting small peripheral lung cancer nodules and at an earlier stage than traditional methods; however, its use in detecting central airway cancers is limited. In 1993, Lam and colleagues reported the early detection of central cancer using AFB (79), also known as Lung Imaging Fluorescence Endoscopy (or Laser Induced Fluorescence Endoscopy = LIFE), and today this technology is regarded as the best option in detecting radiographically occult central airway lung cancer (19, 80).

Autofluorescence bronchoscopy employs the use of blue light rather than white light for detection of premalignant or malignant lesions (81). While normal bronchial mucosa emits fluorescent light with a major peak of about 520nm (green range) and a minor peak of about 630nm (red range), premalignant or malignant changes lead to an almost 10-fold reduction of total fluorescence and a change in the green/red ratio from 5:3 to 2:3 (81). AFB requires some learning and "getting used to" and while performing the procedure, care must be taken to avoid excessive suctioning or airway wall trauma, as this makes the interpretation
of the exam difficult. Feller-Kopman and colleagues (82) suggest that minimizing suction and using enough sedation and topical anesthetic is important to avoid excessive coughing during the bronchoscopy. They also suggest that the AFB examination be performed before any biopsies are taken or interventions are performed, as blood in the airways can make an AFB exam impossible. Individuals typically excluded from receiving AFB include those unable to medically tolerate the procedure or unable to medically tolerate treatment for lung cancer (83). In screening studies, individuals considered at low risk for lung cancer are also typically excluded from receiving AFB (83).

In a study conducted in the late 1990s, Japanese researchers evaluated whether AFB could improve the diagnostic rate of bronchial lesions, as compared with conventional bronchoscopy (84). A total of 158 patients were studied and selected among individuals meeting any one of the following criteria: (1) patients with cancer who were scheduled for endoscopic examination before treatment (68 cases), (2) patients with abnormal sputum findings with normal chest X-ray (42 cases), (3) patients who had undergone curative operation of stage I lung cancer scheduled for endoscopy for periodical follow-up (17 cases), or (4) smokers with respiratory symptoms (31 cases). Investigators found that sensitivity of AFB was greatly improved over conventional bronchoscopy (90% vs. 5%); however, specificity was only slightly better (66% vs. 62%) (84). It is important to consider that while specificity of AFB was low in this study, the patient population included those at extremely high risk for lung cancer. As a
result, these findings cannot be applied to an analysis of lung cancer screening of asymptomatic individuals.

In a preliminary report published by investigators from the Roswell Park Cancer Institute in Buffalo, Loewen and colleagues (83) discuss the efficacy of an ongoing lung cancer surveillance trial that incorporates AFB and low-dose CT scanning. AFB was also compared with conventional sputum cytology for the detection of malignancy and pre-malignant central airway lesions. To be eligible for this study, patients were required to have met at least two of four risk-factor eligibility requirements, which included: (1) ≥20 pack year history of tobacco use, (2) chronic obstructive pulmonary disease with a forced expiratory volume in 1 s (FEV₁) <70% of predicted, (3) asbestos-related lung disease on the chest radiograph, and (4) prior aerodigestive cancer treated with curative intent, with no evidence of disease for >2 years. So far in this cohort there have been 13 lung cancers detected in 169 subjects who have completed the surveillance procedures. Investigators found that sputum cytology missed 68% of the metaplasias and 100% of dysplasias detected by AFB, and also failed to detect any cases of carcinoma or carcinoma-in-situ (CIS). Researchers concluded by suggesting that AFB should be considered in high-risk patients, but also indicate that further research is needed in order to determine whether a surveillance strategy that incorporates both AFB and low-dose CT can assist in reducing lung cancer-related mortality (83).
Background to Decision Analysis

Decision analysis, in the context of healthcare evaluation is a quantitative method that assesses the relative value of different decision options and provides information for deciding how to manage an individual or guide an individual's decisions about therapies, or to formulate policy recommendations for groups (85, 86). Decision analysis evolved from game theory, which is a branch of applied mathematics that is commonly used in the context of economics and that was originally described by von Neumann in the 1920s (87). The first published application of decision analysis used to address a medical problem was in 1967, when Henschke and Flehinger (88) evaluated whether oral cancer patients with no palpable neck metastases should be recommended to undergo radical neck dissection. Since this time, decision analysis has been used to help address numerous other medical problems and is now considered commonplace in evidence based medical practice.

How it works: Decision analysis systematically breaks a problem into its component parts, usually using a decision tree to represent the decision options and components. Initial decision options are identified, outcomes are defined, component pathways connecting initial decisions and outcomes are identified, and then a decision tree is constructed that incorporates these features. Probabilities of a component step occurring or not occurring are estimated using reviews of the medical literature and expert opinion, and uncertainties in the components are identified. Values of the outcome are measured or inferred, and statistical computation produces the net value of the different decision options
relative to one another. The entire modeling process requires tremendous thought and effort and an outline of this procedure is presented below.

The specific methodology involved in conducting decision analysis has been explained by many authors; and although they do not describe the process in exactly the same way, all cover the same important concepts (86, 89-91). Sun and Faunce (90) recently produced a flow chart that outlines the various steps involved in decision analysis modeling (Figure 3). Generally, there are five steps involved and they include: (1) identify and bound the problem, (2) structure the problem in a decision tree, (3) collect the data required to fill the decision tree, (4) analyze the decision tree, and (5) carry out a sensitivity analysis (89).

![Flow chart for developing a decision-analytical model](Adapted from Sun and Faunce, 2007) (90)

Identifying and bounding the problem involves breaking the problem into its component parts, identifying alternative courses of action or options being
considered, identifying subsequent events and alternatives, and identifying outcomes. In this stage it is also important to clearly state the perspective of the model, as well as the length of follow-up or time horizon that is being considered (90). In defining the boundaries of the model, it is important to consider how far a model should go to cover all the possible implications of an intervention or program. These decisions will be driven in part by the availability of data and complexity of the modeling task, but ultimately it will be the extent to which extending the boundaries is considered likely to have an important impact on the effectiveness of the options under investigation that will determine the boundaries of the model (86).

Deciding on the structure of the decision model is a key step in the modeling process. This involves making decisions regarding how the input parameters in the model are to be related and how to characterize the clinical events of interest. Decision models used in economic evaluation are often modeled schematically, and most are creating using decision trees. In these trees, decision nodes are represented by squares, chance nodes by circles and outcomes by triangles. The sequence is traditionally drawn from left to right, representing the progression of events in chronological order. In constructing the model, it is important to ensure that the pathways (branches) be exhaustive (a patient must follow one of the pathways) and mutually exclusive (a patient can only follow one the pathways). The likelihood of a patient acquiring a specific outcome or progressing to an intermediate state is represented by a probability emanating from each chance node, or branch in the model.
Collecting data to fill the model involves identifying probabilities, benefits, and costs and inserting them into the model. Based on the principles of evidence based medicine, all information used to populate the model should be gathered systematically and not selectively. Probabilities are based on previous knowledge and experience, but in some cases the likelihood of particular events may not be available from the medical literature and estimates from relevant experts may need to be obtained. This use of expert opinion may be considered a weakness, but decisions about the use of healthcare interventions still need to be made regardless of the strength of evidence that is available. In the absence of formal evidence, the decision will have to be made on the basis of assumptions and judgments and decision analysis provides an analytical framework within which this can be done explicitly (86).

Outcomes of decision analysis are terminal events of the model and these may include life, death, morbidity, or any other state of health or disease. For example, the goal of therapy will not always be to prolong life, but may be to improve the quality of life of the patient; and in this case, simply measuring life or death is not sufficient. Decision analysis has also incorporated the concept of utilities, or patient preference for certain states. This takes into account that most people would rather be alive and in perfect health instead of alive and undergoing chemotherapy or recovering from a surgical complication, or just simply not well. To adjust for the absolute gain or loss in life, quality adjusted life years (QALY) incorporates utilities to reflect morbidities caused by disease or other interventions, such as screening. It should be noted that outcomes may
also incorporate monetary gains or losses, allowing not only the benefits of competing strategies to be compared, but their associated costs as well (86, 91). This provides the basis for cost-effectiveness analysis.

Once the problem has been structured, values for each outcome must be assigned and after this, probability values associated with each of the chance nodes leading up to these outcomes must then be identified and incorporated into the model. Recall that outcomes of the tree are the terminal events of the model (life, death, or other health state). Once these tasks have been complete, it is time to perform the analysis. This is accomplished though ‘folding back’ and ‘averaging’, a procedure that weights each possible alternative choice pathway outcome by the probability of attaining that outcome. In this process, the value of each health outcome is multiplied by the probability of achieving the outcome and these weighted values are then summed at the chance node that led to the outcomes. This process is repeated from right to left for every outcome until finally, at the proximal chance node, a single value is presented which represents each strategy modeled in the tree (Figure 4) (85, 86). In Figure 4, screening using colonoscopy is modeled to attain the greatest number of life years. Software such as TreeAge is available to aid modeling and calculation of results.
Which screening strategy provides the greatest life expectancy?

Figure 4. Decision tree to compare strategies of screening to decrease mortality from colorectal cancer. This example assumes a baseline lifetime risk of colorectal cancer of 6% without screening (No screening), 1% with screening colonoscopy, 2% with screening by using the faecal occult blood test and flexible sigmoidoscopy (FOBT + FS), 3% with screening by using barium enema (BE), and 4% with screening by using the faecal occult blood test alone (FOBT). Additional assumption includes 50% survival after diagnosis of cancer. The decision tree is analysed by averaging and folding back. Starting from the right side of the tree, the value of each outcome (additional life years expected) is multiplied by the probability of achieving that outcome, then summed with other weighted outcomes at the chance node leading to those outcomes. These values are again multiplied by the probability of attaining that limb of the tree and summed with other weighted outcomes at the next more proximal (to the left in the tree) chance node. At the most proximal chance nodes, there will be a single value representing each modelled strategy that may be used to compare competing strategies at the decision node. In this case, screening using colonoscopy yields the greatest number of life years.

(Adapted from Inadomi, 2004)
Sensitivity analysis is the final step in decision analytic modeling and its purpose is to examine the robustness of results. By varying the values of the probabilities and/or outcomes in the model, investigators are interested in finding out whether the model is sensitive to any specific variable(s); that is, if small changes in a particular variable cause the conclusion of the analysis to change. Sensitivity analysis can be performed by varying one or more parameters using the range of reasonable values for each variable determined either from the literature, or from consultation with experts. If a model is sensitive to any specific variable, then it is encouraged that research be performed to more precisely define the value associated with this variable in effort to more firmly establish the certainty of the conclusions of the analysis (90, 91).

Although very useful, a major limitation to standard sensitivity analysis is that it is only practical to vary a small number of parameters simultaneously, and considering that most models include multiple variables all measured with some element of uncertainty; this analysis becomes very tedious and fails to provide a complete picture of joint parameter uncertainty. Another limitation of standard sensitivity analysis is that it provides no summary measure of the implications of uncertainty (86). An alternative method of sensitivity analysis that is increasingly being used to handle parameter uncertainty is probabilistic sensitivity analysis; and in particular, Monte Carlo simulation modeling (92). In this type of analysis, all parameters in the model can be varied simultaneously. The process involves values for each variable being selected at random from its associated probability distribution, and the model is run multiple times. The use of distributions results in
certain values being weighted more heavily, or being selected more often than other values for a particular variable. Ultimately, the mean and standard deviation of the expected utility for each strategy is recorded, and the frequency with which each strategy is optimal is also provided (92).
CHAPTER III – METHODLOGY

Decision Analysis Modeling

The primary aim of this study was to evaluate whether screening for lung cancer using (1) AFB and/or (2) low dose CT can improve screening performance as measured by reduced lung cancer specific mortality. To address this study question, decision analysis models were prepared using TreeAge Pro 2008 software with the outcome being 5-year lung cancer survival and the alternative screening options: (1) no screening, (2) CT screening, (3) AFB screening, and (4) joint screening with CT and AFB. Figure 5 illustrates the decision analysis model prepared to answer the study question. Because of the large size of the model, it is spread over four pages, with each alternative pathway shown in detail on one page. The model includes alternative decision pathways leading to the terminal node payoffs, with intermediate chance nodes, and variables assigning probabilities to chance nodes and factors that modify probabilities.

Each of the screening options leads to chance nodes separating those with lung cancer from those without lung cancer. In the model screening pathways, individuals with no lung cancer can be true-negative or false-positive by the screening modality and the probability of these events is determined by the screening modalities’ specificity. Individuals who have lung cancer can screen negative (false-negative) or positive (true-positive) and the probability of these events is determined by the screening modalities’ sensitivities.

Lung cancers can be categorized into the following general histologic types: adenocarcinoma (AdCA), squamous cell carcinomas (SqCCA), other non-
small cell lung cancer (ONSCLC), and small cell lung cancer (SCLC). Cancers that were not detected by screening were assumed to have histologic distributions that are similar to those observed in the general population. CT screen detected histologic distributions tend to be over-represented by cancers that are usually peripheral in location, specifically the adenocarcinoma and other non-small cell lung cancers, and are under-represented by histologic types that are usually centrally located, that is, squamous cell carcinoma and small cell lung cancers. Autofluorescence bronchoscopy performs in the opposite manner – AFB detects lung cancers that are centrally located, the SqCCA and the SCLCs and AFB misses the peripheral AdCA and ONSCLCs. In modeling the histologic distributions of CT or AFB screen detected lung cancers, the population histologic distribution was multiplied by a factor (FindFactor) or the inverse of the factor (1/FindFactor) to increase or decrease the proportion of a histologic type to adjust for increases or decreases in histologic proportions caused by screening. The variable FindFactor was set at 1.20 (sensitivity ranges 1.10 to 1.40) for decision analysis. This number was based on the observed distributions of histologic types in screening studies (44, 83, 93-105). It was assumed that lung cancers that were detected by combined CT-AFB screening would be detected in approximately the same proportions as are observed in the unscreened population at large because all major histotypes would be detected with roughly similar increased sensitivity, so would stay in roughly similar ratios to each other.

For the purposes of this study, the outcome or payoff is 5-year lung cancer specific survival. Mortality associated with screening and work-up is also
considered in assessment of the outcome. Five-year lung cancer survival is specific to the histotype and stage, or anatomic extent of disease.

The distribution of stage is expected to differ depending on whether the cancers were screen-detected versus detected as per usual in the general population, that is clinically detected in symptomatic individuals. Screening programs target individuals who are generally free of lung cancer symptoms, and because of the later fact, any lung cancers that are detected by screening are on average at an early stage. Effective screening is expected to lead to a decrease in the proportion of advanced cancers and increase in proportion of early stage cancers, which are believed to be more treatable with curative intent, when compared to lung cancers detected in the unscreened general population. This phenomenon is called stage shift and in the decision analysis model was assigned a value of 70 percent for regional and distant adenocarcinoma, squamous cell carcinoma and other NSCLC. For sensitivity analysis, the range was 45 to 100 percent. In other words, in the baseline analysis 70 percent of regional and distant AdCA, SqCCA and ONSCLC were shifted into the early (localized) stage if they had been screen detected. These stage shift values were taken from the mean and range of published values (44, 83, 93-106). Small cell lung cancers often become “systemic” or metastasize when remaining small, and for this reason it was expected that relatively few SCLC would be affected by stage shift, and the stage shift assigned to screen-detected SCLC was 10 percent, with a range for sensitivity analysis of 5 to 15 percent.
A systematic search of the literature did not identify any past decision analyses or cost-effectiveness analyses of combined screening with CT and AFB for lung cancer, although such multiple analyses have been presented for lung cancer screening using CT or chest radiography alone. To capture the unique complimentary aspects of CT and AFB, the current study does have some important features not presented in previous studies. In particular, the current study evaluates major histologic groups separately, whereas past studies have grouped them altogether or evaluated the lung cancers in two groups: non-small cell lung cancer versus small cell lung cancer. The study evaluates 5-year lung cancer specific survival by histology in three stage groups, localized, regional and distant. Many past studies have used two stage groups, early versus advanced. In addition, few studies have included screening-associated 5-year mortality due to complications related to screening and follow-up of false positive screens in their analyses as is done in the current study.
Figure 5.a. Decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – No screening pathway

<table>
<thead>
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<tr>
<td>AFB alone</td>
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<tr>
<td>CT &amp; AFB applied to all</td>
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What is the most effective approach to multiplex lung cancer screening of high risk (2% LCA) individuals with CT and AFB?

<table>
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--- Global Values ---
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| AdCALocal | 0.1 |
| AdCAreregion | 0.1 |
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| AFBRegional | 0.1 |
| AFBLocal | 0.1 |
| AFBRegion | 0.1 |
| AFBDistant | 0.1 |
| CT | 0.94 |
| CTRegional | 0.1 |
| CTLocal | 0.1 |
| CTRegion | 0.1 |
| CTDistant | 0.1 |
| AFB | 0.98 |
| AFBRegional | 0.1 |
| AFBLocal | 0.1 |
| AFBRegion | 0.1 |
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| CT | 0.94 |
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| CTRegion | 0.1 |
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| AFB | 0.98 |
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| AFBLocal | 0.1 |
| AFBRegion | 0.1 |
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| CT | 0.94 |
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--- Model Parameters ---
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</tr>
<tr>
<td>sSqCCAregion</td>
<td>0.45</td>
</tr>
<tr>
<td>sSqCCAdistant</td>
<td>0.644</td>
</tr>
<tr>
<td>sONSLCregion</td>
<td>0.583</td>
</tr>
<tr>
<td>sONSLCAdistant</td>
<td>0.522</td>
</tr>
<tr>
<td>etLCAwith2p0</td>
<td>[+]</td>
</tr>
</tbody>
</table>

48
Figure 5.b. Decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – CT only pathway
Figure 5.c. Decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – AFB only pathway
Figure 5.d. Decision analysis model of lung cancers screening using computed tomography and autofluorescence bronchoscopy – CT & AFB combined pathway

What is the most effective approach to resource lung cancer screening of high-risk (2% LCAJ) individuals with CT and AFB?

CT & AFB applied to all.

Lung cancer

CT alone

AFB alone

CT & AFB Combined pathway

Figure 5.d. Decision analysis model of lung cancers screening using computed tomography and autofluorescence bronchoscopy – CT & AFB combined pathway

What is the most effective approach to resource lung cancer screening of high-risk (2% LCAJ) individuals with CT and AFB?
Populating the Model with Estimates

Populating the model refers to the process of obtaining final model estimates for the decision analysis model probabilities. These are included as variables in the model and must be assigned values; and for sensitivity analysis by extreme possible values. For Monte Carlo simulation sensitivity analysis, we needed to obtain the estimated values and distributions (e.g., normal distribution) along with distribution parameters (e.g., standard deviations) for each variable. For the most part, the current study estimates and ranges were derived from review and summarization of the literature and by summarizing data obtained from experts in the field. Published data that were used to derive estimates are cited and described later in this section. In addition, the probability estimates and sensitivity analysis ranges are summarized in Table 2.

A list of experts that were approached and asked to provide their "best guess" regarding mortality associated with screening and follow-up of false positive screenings due to CT, AFB, and combined CT and AFB screenings is provided below. Each individual's specialty, affiliation and contact information is also provided.

- Dr. Matthew Freedman; radiologist; research member of the PLCO and NLST; professor at Georgetown University, Washington, DC.
  **e-mail:** freedmmt@georgetown.edu
- Dr. Bill Hocking; oncologist specializing in lung cancer; research member of the PLCO and NLST; Marshfield Clinic, Wisconsin.
  **e-mail:** hocking.william@marshfieldclinic.org
• Dr. Paul Kvale; pulmonologist specializing in lung cancer; research member of the PLCO and NLST; Henry Ford Health System, Detroit, MI.
  
  e-mail: pkvale1@hfhs.org

• Dr. Stephen Lam; pulmonologist/respirologist; expert in AFB and lung cancer; British Columbia Cancer Agency and University of British Columbia, Vancouver, BC.
  
  e-mail: slam2@bccancer.bc.ca

• Dr. Marty Oken; oncologist specializing in lung cancer research; member of the PLCO and NLST; Chair of the PLCO Lung Committee; Duke University School of Medicine, Durham, NC.
  
  e-mail: martin.oken@northmemorial.com

• Dr. Mary Reid; epidemiologist specializing in lung cancer and AFB; Roswell Park Cancer Institute, Buffalo, NY.
  
  e-mail: Mary.Reid@roswellpark.org

In addition, Dr. S. Lam provided access to unpublished data on combined CT and AFB screening results in the British Columbia Cancer Agency (described later) and Dr. Tammemagi (Thesis supervisor) had access to the datasets of the U.S. NCI Prostate Lung Colorectal Ovarian Cancer Screening Trial and U.S. NCI Lung Screening Study.
Table 2. Probability estimates and sensitivity analysis ranges used to populate model

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>Variable Name</th>
<th>Low Value</th>
<th>High Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROBABILITY OF LUNG CANCER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer prevalence at 2.0%</td>
<td>LCAprev20R19to21</td>
<td>0.020</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>SCREENING INTERVENTION SENSITIVITIES &amp; SPECIFICITIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT sensitivity</td>
<td>CTsensitivity</td>
<td>0.768</td>
<td>0.92</td>
</tr>
<tr>
<td>CT specificity</td>
<td>CTspecificity</td>
<td>0.920</td>
<td>0.95</td>
</tr>
<tr>
<td>AFB sensitivity</td>
<td>AFBsensitivity</td>
<td>0.380</td>
<td>0.45</td>
</tr>
<tr>
<td>AFB specificity</td>
<td>AFBspecificity</td>
<td>0.940</td>
<td>0.98</td>
</tr>
<tr>
<td>Sensitivity of CT &amp; AFB*</td>
<td>CT_AFBsensitivity</td>
<td>0.970</td>
<td>0.98</td>
</tr>
<tr>
<td>Specificity of CT &amp; AFB*</td>
<td>CT_AFBspecificity</td>
<td>0.900</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>PROBABILITY OF HISTOLOGIC TYPES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability AdCA</td>
<td>pAdCA</td>
<td>0.3615</td>
<td>0.46</td>
</tr>
<tr>
<td>Probability SCLC</td>
<td>pSCLC</td>
<td>0.1635</td>
<td>0.18</td>
</tr>
<tr>
<td>Probability SqCCA</td>
<td>pSqCCA</td>
<td>0.3038</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>PROBABILITY THAT A HISTOLOGIC TYPE IS LOCAL, REGIONAL OR DISTANT STAGE CANCER</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability AdCA is local stage</td>
<td>pAdCALocal</td>
<td>0.1710</td>
<td>0.21</td>
</tr>
<tr>
<td>Probability AdCA is regional stage</td>
<td>pAdCARegional</td>
<td>0.3780</td>
<td>0.42</td>
</tr>
<tr>
<td>Probability AdCA is distant stage</td>
<td>pAdCADistant</td>
<td>0.4510</td>
<td>0.49</td>
</tr>
<tr>
<td>Probability SqCCA is local stage</td>
<td>pSqCCALocal</td>
<td>0.2240</td>
<td>0.26</td>
</tr>
<tr>
<td>Probability SqCCA is regional stage</td>
<td>pSqCCARegional</td>
<td>0.4650</td>
<td>0.51</td>
</tr>
<tr>
<td>Probability SqCCA is distant stage</td>
<td>pSqCCADistant</td>
<td>0.3110</td>
<td>0.35</td>
</tr>
<tr>
<td>Probability Other NSCLC is local stage</td>
<td>pONSCLCLocal</td>
<td>0.1290</td>
<td>0.17</td>
</tr>
<tr>
<td>Probability Other NSCLC is regional stage</td>
<td>pONSCLCRegional</td>
<td>0.3780</td>
<td>0.42</td>
</tr>
<tr>
<td>Probability Other NSCLC is distant stage</td>
<td>pONSCLCDistant</td>
<td>0.4930</td>
<td>0.53</td>
</tr>
<tr>
<td>Probability SCLC is local stage</td>
<td>pSCLCLocal</td>
<td>0.0664</td>
<td>0.10</td>
</tr>
<tr>
<td>Probability SCLC is regional stage</td>
<td>pSCLCRegion</td>
<td>0.3373</td>
<td>0.38</td>
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<tr>
<td>Probability SCLC is distant stage</td>
<td>pSCLCDistant</td>
<td>0.5962</td>
<td>0.65</td>
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Table 2 continued.

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>Variable Name</th>
<th>Value</th>
<th>Low Value</th>
<th>High Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-YEAR SURVIVAL PROPORTION BY HISTOLOGY AND STAGE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AdCA local 5-year survival</td>
<td>sAdCAlocal</td>
<td>0.5351</td>
<td>0.52</td>
<td>0.55</td>
</tr>
<tr>
<td>AdCA regional 5-year survival</td>
<td>sAdCAregion</td>
<td>0.1632</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>AdCA distant 5-year survival</td>
<td>sAdCADistant</td>
<td>0.0308</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>SqCCA local 5-year survival</td>
<td>sSqCCAlocal</td>
<td>0.4583</td>
<td>0.45</td>
<td>0.47</td>
</tr>
<tr>
<td>SqCCA regional 5-year survival</td>
<td>sSqCCAreregion</td>
<td>0.1522</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>SqCCA distant 5-year survival</td>
<td>sSqCADistant</td>
<td>0.0440</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Other NSCLC 5-year survival</td>
<td>sONSCLClocal</td>
<td>0.3920</td>
<td>0.37</td>
<td>0.42</td>
</tr>
<tr>
<td>Other NSCLC regional 5-year survival</td>
<td>sONSCLCregion</td>
<td>0.1200</td>
<td>0.11</td>
<td>0.13</td>
</tr>
<tr>
<td>Other NSCLC distant 5-year survival</td>
<td>sONSCLCdistant</td>
<td>0.0252</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>SCLC local 5-year survival</td>
<td>sSCLClocal</td>
<td>0.1741</td>
<td>0.15</td>
<td>0.19</td>
</tr>
<tr>
<td>SCLC regional 5-year survival</td>
<td>sSCLCregion</td>
<td>0.0909</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>SCLC distant 5-year survival</td>
<td>sSCLCdistant</td>
<td>0.0180</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>HISTOLOGY SHIFT DUE TO SCREENING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor for histotype by screening method</td>
<td>FindFactor1p4</td>
<td>1.20</td>
<td>1.10</td>
<td>1.40</td>
</tr>
<tr>
<td><strong>STAGE SHIFT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage shift from advanced to early is 10%</td>
<td>StageShift10percent</td>
<td>0.10</td>
<td>0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>Stage shift from advanced to early is 70%</td>
<td>StageShift70percent</td>
<td>0.70</td>
<td>0.45</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, computed tomography; AFB, autofluorescence bronchoscopy; AdCA, adenocarcinoma; SqCCA, squamous cell carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer

* CT & AFB is applied in combination to all individuals
For Monte Carlo simulation sensitivity analysis, many of the distributions and distribution parameters were unknown, so a method of triangulation distribution was used. In triangulation, the highest probability is assigned to the expected value. Expected value here refers to the parameter estimate believed to be most accurate for each parameter in the model. This is the same value used in baseline decision analysis. The probabilities decrease linearly until they approach zero at the low and high values of the range provided. The formula for the triangulation distribution is provided below:

**Triangular distribution**

Formula:

\[
\begin{align*}
f(x) &= \begin{cases} 
0 & x < \text{Low}X \text{ or } x > \text{High}X \\
2 \times (\text{Hi}ghX - \text{Low}X) \times \frac{x - \text{Low}X}{\text{Mode} - \text{Low}X} & \text{Low}X \leq x \leq \text{Mode} \\
2 \times (\text{Hi}ghX - \text{Low}X) \times \left(1 - \frac{x - \text{Mode}}{\text{Hi}ghX - \text{Mode}}\right) & \text{Mode} < x \leq \text{Hi}ghX
\end{cases}
\end{align*}
\]

Domain: \( \text{Low}X \leq x \leq \text{Hi}ghX \)

Parameters: High X, Mode (likeliest), Low X
A sense of the triangulation distribution in contrast to other commonly used distributions is provided graphically below:

The triangulation distribution is a useful versatile method that approximates other normal-like distributions or skewed normal-like distributions when distribution patterns and parameters are unknown, but expected and extreme values are known.
Probability of lung cancer

The probability of lung cancer reflects the point prevalence of lung cancer in the screened population. For the purposes of this study the risk of lung cancer in the screened population was set at 2.0 percent, reflecting a high risk population. The range of risk for sensitivity analysis was 0.005 to 0.035. These values represent the range of values observed in past screening studies (106). Additionally, the study population is assumed to be 60 or more years of age and consisting of both genders and of a racially mixed population including Whites, Blacks, Hispanics, Pacific Islanders, and North American Natives that reflects the U.S. population circa 2000.

Sensitivity & Specificity of Screening Modalities – Computed Tomography

Data required to calculate pooled estimates for sensitivity and specificity for CT screening were available from five studies (95, 96, 99, 101, 102) (Table 3).

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref#</th>
<th>Sensitivity Numerator</th>
<th>Sensitivity Denominator</th>
<th>Specificity Numerator</th>
<th>Specificity Denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELCAP 2001</td>
<td>(97)</td>
<td>27</td>
<td>33</td>
<td>763</td>
<td>969</td>
</tr>
<tr>
<td>Diederich 2004</td>
<td>(99)</td>
<td>20</td>
<td>22</td>
<td>2111</td>
<td>2530</td>
</tr>
<tr>
<td>Sone 2001</td>
<td>(95)</td>
<td>22</td>
<td>40</td>
<td>5186</td>
<td>5443</td>
</tr>
<tr>
<td>Pastorinio 2003</td>
<td>(101)</td>
<td>11</td>
<td>17</td>
<td>968</td>
<td>1018</td>
</tr>
<tr>
<td>Nawa 2002</td>
<td>(102)</td>
<td>36</td>
<td>39</td>
<td>7412</td>
<td>7917</td>
</tr>
<tr>
<td>Sums:</td>
<td></td>
<td>116</td>
<td>151</td>
<td>16440</td>
<td>17877</td>
</tr>
<tr>
<td>Crude Averages:</td>
<td></td>
<td>0.77</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-sensitivity</td>
<td></td>
<td>0.768</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-specificity</td>
<td></td>
<td>0.920</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-prevalence</td>
<td></td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Based on pooled re-analysis of the five studies described in Table 3, the CT sensitivity was estimated to be 76.8 percent (range of study estimates 55.0% to 92.3%, which was used for sensitivity analysis) and specificity was estimated to be 92.0% (range of study estimates 78.7% to 95.3%). These estimates are similar to those used in recent review studies. For example, Chien and Chen (69) in a Markov chain modeling study of the natural history of lung cancer (sojourn time) estimated CT sensitivity to be 0.85 (Range 0.80 to 0.90) and specificity to be 0.94 (range 0.79 to 0.97). Our estimates are more conservative and our wider ranges for sensitivity analysis allow a broader evaluation of the impact of inaccurate estimates on study conclusions.

**Sensitivity and Specificity of Screening Modalities – AFB Alone and Combined CT & AFB**

The sensitivity and specificities used in the decision analysis models for AFB screening were 38.0 percent (range 15.0% to 45.0%) and 94.0 percent (range 84.0% to 98.0%) (83), and for combined CT and AFB screening were 97.0 percent (range 75.0% to 98.0%) and 90.0 percent (range 70.0% to 98.0%), respectively (83, 95, 96, 99, 101, 102).

The sensitivity and specificity estimates used in the decision analysis model were derived from two studies in which individuals at high risk for lung cancer were screened with both CT and AFB. The first study, carried out in Roswell Park Cancer Institute in Buffalo, New York, screened and followed up 169 individuals (83). A total of 13 lung cancers were detected, three (23.1%) of
which were discovered by AFB alone. The second study screened and followed 2416 individuals in the British Columbia Cancer Agency (Dr. Stephen Lam, BCCA, personal communication 2007, 2008). Fifty-six lung cancers were discovered, of which 11 (19.6%) were discovered by AFB alone. Analysis of data pooled from these two studies estimate sensitivity and specificity for AFB screening to be 38.0 percent and 94.0 percent. The pooled data indicate that in combined CT and AFB screening, one in five (20.3%) lung cancers are detected by AFB and are missed by CT. Adding the 20% additional sensitivity to the pooled sensitivity estimated for CT alone (77%) yields a sensitivity estimate for combined CT and AFB of 97.0 percent. The specificity of combined CT and AFB was estimated to be 90.0%. Accurate data were not available to estimate ranges for these parameters, so the ranges were intentionally broadened for both sensitivity and specificity of combined CT and AFB screening (Table 2). To be considered positive with lung cancer by combined CT and AFB screening, an individual needed to screen positive by either CT or AFB or both.

AFB readily detects dysplasias and carcinoma in situ (intra-epithelial neoplasia, sometimes referred to as Stage 0 lung cancer), which are thought to be precursors to invasive bronchogenic carcinoma. Most dysplastic lesions and some CIS do not progress to cancer and some are thought to regress back to normal looking tissue (22, 47-49, 107). To reduce over-diagnosis bias, this study has included data only for invasive cancers (not including CIS), that is, lung cancers that have invaded through the lamina propria. The likelihood of these invasive cancers remaining dormant or regressing is thought to be low, as recent
studies have found that untreated early stage cancer is associated with high lung cancer mortality (44).

*Probabilities of Histologic Subtypes, that a Histologic Type is Local, Regional, or Distant Stage of Cancer, & 5-year Lung Cancer Specific Survival by Histology and Stage*

These data were derived from the latest 2007 Surveillance, Epidemiology and End Results dataset (Incidence - SEER 17 Regs Limited-Use, Nov 2006 Sub (1973-2004 varying)) using lung and bronchus cancers that were invasive, microscopically confirmed, actively followed, and with no other primary cancer. All data were extracted using SEER*Stat 6.3.6 and according to SEER Historic Stage A classification system. These data are summarized in Table 4.
<table>
<thead>
<tr>
<th>Histology</th>
<th>Cancer Stage</th>
<th>Survival</th>
<th>N</th>
<th>Cause-Specific Survival</th>
<th>Standard Error of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Localized</td>
<td>12 mo</td>
<td>7,325</td>
<td>85.62%</td>
<td>0.42%</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>24 mo</td>
<td></td>
<td>72.92%</td>
<td>0.54%</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>36 mo</td>
<td></td>
<td>64.19%</td>
<td>0.61%</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>48 mo</td>
<td></td>
<td>58.44%</td>
<td>0.66%</td>
</tr>
<tr>
<td></td>
<td>Localized 60 mo</td>
<td>16,171</td>
<td></td>
<td>53.51%</td>
<td>0.71%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>12 mo</td>
<td></td>
<td>51.97%</td>
<td>0.40%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>24 mo</td>
<td></td>
<td>32.32%</td>
<td>0.39%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>36 mo</td>
<td></td>
<td>23.59%</td>
<td>0.37%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>48 mo</td>
<td></td>
<td>19.26%</td>
<td>0.36%</td>
</tr>
<tr>
<td></td>
<td>Regional 60 mo</td>
<td>19,290</td>
<td></td>
<td>16.32%</td>
<td>0.36%</td>
</tr>
<tr>
<td></td>
<td>Distant</td>
<td>12 mo</td>
<td></td>
<td>23.55%</td>
<td>0.32%</td>
</tr>
<tr>
<td></td>
<td>Distant</td>
<td>24 mo</td>
<td></td>
<td>9.67%</td>
<td>0.24%</td>
</tr>
<tr>
<td></td>
<td>Distant</td>
<td>36 mo</td>
<td></td>
<td>5.40%</td>
<td>0.20%</td>
</tr>
<tr>
<td></td>
<td>Distant</td>
<td>48 mo</td>
<td></td>
<td>3.83%</td>
<td>0.18%</td>
</tr>
<tr>
<td></td>
<td>Distant 60 mo</td>
<td></td>
<td></td>
<td>3.08%</td>
<td>0.17%</td>
</tr>
<tr>
<td>Squamous Cell</td>
<td>Localized</td>
<td>12 mo</td>
<td>7,839</td>
<td>79.06%</td>
<td>0.47%</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>24 mo</td>
<td></td>
<td>64.38%</td>
<td>0.57%</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>36 mo</td>
<td></td>
<td>54.54%</td>
<td>0.62%</td>
</tr>
<tr>
<td></td>
<td>Localized</td>
<td>48 mo</td>
<td></td>
<td>49.16%</td>
<td>0.65%</td>
</tr>
<tr>
<td></td>
<td>Localized 60 mo</td>
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<td>45.83%</td>
<td>0.68%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>12 mo</td>
<td>16,245</td>
<td>51.15%</td>
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<tr>
<td></td>
<td>Regional</td>
<td>24 mo</td>
<td></td>
<td>29.42%</td>
<td>0.38%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>36 mo</td>
<td></td>
<td>21.12%</td>
<td>0.36%</td>
</tr>
<tr>
<td></td>
<td>Regional</td>
<td>48 mo</td>
<td></td>
<td>17.40%</td>
<td>0.35%</td>
</tr>
<tr>
<td></td>
<td>Regional 60 mo</td>
<td></td>
<td></td>
<td>15.22%</td>
<td>0.35%</td>
</tr>
<tr>
<td></td>
<td>Distant</td>
<td>12 mo</td>
<td>10,859</td>
<td>24.08%</td>
<td>0.43%</td>
</tr>
<tr>
<td></td>
<td>Distant</td>
<td>24 mo</td>
<td></td>
<td>10.51%</td>
<td>0.32%</td>
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<tr>
<td></td>
<td>Distant</td>
<td>36 mo</td>
<td></td>
<td>6.76%</td>
<td>0.28%</td>
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<tr>
<td></td>
<td>Distant</td>
<td>48 mo</td>
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<td>5.27%</td>
<td>0.26%</td>
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<tr>
<td></td>
<td>Distant 60 mo</td>
<td></td>
<td></td>
<td>4.40%</td>
<td>0.26%</td>
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<tr>
<td>Other NSCLC</td>
<td>Localized</td>
<td>12 mo</td>
<td>2,470</td>
<td>73.87%</td>
<td>0.90%</td>
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<tr>
<td></td>
<td>Localized</td>
<td>24 mo</td>
<td></td>
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<td>1.07%</td>
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<tr>
<td></td>
<td>Localized</td>
<td>36 mo</td>
<td></td>
<td>47.16%</td>
<td>1.13%</td>
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<tr>
<td></td>
<td>Localized</td>
<td>48 mo</td>
<td></td>
<td>41.55%</td>
<td>1.21%</td>
</tr>
<tr>
<td></td>
<td>Localized 60 mo</td>
<td></td>
<td></td>
<td>39.20%</td>
<td>1.26%</td>
</tr>
<tr>
<td></td>
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<td>7,236</td>
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</tr>
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<td>0.55%</td>
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<tr>
<td></td>
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<td>36 mo</td>
<td></td>
<td>17.25%</td>
<td>0.53%</td>
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<tr>
<td></td>
<td>Regional</td>
<td>48 mo</td>
<td></td>
<td>14.04%</td>
<td>0.53%</td>
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<td>Regional 60 mo</td>
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<td>12.00%</td>
<td>0.54%</td>
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<tr>
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<td>Distant</td>
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<tr>
<td></td>
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<td>Distant 60 mo</td>
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<td>2.52%</td>
<td>0.28%</td>
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<tr>
<td>Small cell</td>
<td>Localized</td>
<td>12 mo</td>
<td>1,622</td>
<td>65.50%</td>
<td>1.20%</td>
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<td></td>
<td>Localized</td>
<td>24 mo</td>
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<td>33.84%</td>
<td>1.25%</td>
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<td></td>
<td>Localized</td>
<td>36 mo</td>
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<td>24.53%</td>
<td>1.18%</td>
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<td></td>
<td>Localized</td>
<td>48 mo</td>
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<td>19.91%</td>
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<td></td>
<td>Localized 60 mo</td>
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<td>17.41%</td>
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<td>Regional</td>
<td>12 mo</td>
<td>8,245</td>
<td>48.81%</td>
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<td></td>
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<td>13.28%</td>
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<td>2.96%</td>
<td>0.17%</td>
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<td>Distant</td>
<td>48 mo</td>
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<td>2.31%</td>
<td>0.16%</td>
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<tr>
<td></td>
<td>Distant 60 mo</td>
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<td>1.80%</td>
<td>0.15%</td>
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*Abbreviations: mo, month; N, number; SEER, Surveillance, Epidemiology and End Results; NSCLC, non-small cell lung cancer*
CHAPTER IV – RESULTS

Baseline Analysis

The final decision analysis model with rolled-back probabilities inserted in place of the variable name is presented in Figure 6. When values believed to be most accurate for each parameter were inserted into the model, we found that combined CT and AFB screening yielded the highest 5-year overall expected lung cancer survival (0.9863). After this, individual screening using CT or AFB followed, with expected survival estimates of 0.9859 and 0.9842, respectively. The worst expected survival resulted from no screening (0.9829). These survival estimates are based on screening a population considered at high risk for lung cancer. While some will develop lung cancer (2%), the majority will not (98%). For sensitivity analysis, lung cancer prevalence was varied from 0.5 percent to 3.5 percent.

For individuals who develop lung cancer, expected survival is understandably much worse. Expected survival for those with lung cancer is best for those screened with combined CT and AFB. For this screening option, the expected survival is 0.3256 for individuals with lung cancer. This expected survival is much better than would be expected for individuals with lung cancer and that are diagnosed without screening. For the no screen branch, expected survival for patients with lung cancer was estimated to be 0.1445. Expected survival for lung cancer patients detected by CT alone was much better than for patients screened with AFB alone, 0.2966 versus 0.2124 respectively.
In our model, the impact of screening associated mortality resulting from false-positive diagnosis was estimated to be 0.001 percent for CT alone, 0.001 percent for AFB alone, and 0.002 percent for CT and AFB combined. For the combined CT and AFB screening alternative, the 5-year expected survival for individuals that do not develop lung cancer was calculated to be 0.9998. Expected survival for patients falling into the false-negative category (lung cancer missed by screening) was assumed to be the same as would be expected had these individuals not been screened, which was significantly less than for any of the screening branches. In the CT alone and AFB alone screening branches, the probability of a screen being a false-negative was substantial: 0.23 and 0.62, respectively. In the combined CT and AFB screening branch, the probability of a false-negative screen was relatively low (0.03). These differences reflect the complimentary nature of the two screening modalities.
Figure 6.a. Rolled back decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – No screening pathway

What is the most effect approach to multiplex lung cancer screening of high risk (2% LCA) individuals with CT and AFB?

CT & AFB applied to all: 0.9863

CT alone: [+] 0.9869

AFB alone: [+] 0.9842

CT & AFB applied to all: [+] 0.9863, P = 1.000
Figure 6.b. Rolled back decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – CT only pathway

What is the most effect approach to multiplex lung cancer screening of high risk (2% LCA) individuals with CT and AFB?

CT alone

No screening

CT & AFB applied to all

No lung cancer

No screening

False Negative

CT & AFB applied to all

CT, AFB alone

CT & AFB applied to all

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Figure 6.c. Rolled back decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – AFB only pathway.

[Diagram showing decision analysis model with nodes and branches indicating decision points, outcomes, and probabilities.]

What is the most effective approach to multiplex lung cancer screening of high-risk (2% LCA) individuals with CT and AFB? CT & AFB applied to all 0.9863 CT alone 0.9859 AFB alone 0.9842 True negative 0.9996 True positive 0.0004 False positive 0.0005 No lung cancer 0.983 No screening 1.0000 Lung cancer 0.0174
Figure 6.d. Rolled back decision analysis model of lung cancer screening using computed tomography and autofluorescence bronchoscopy – CT & AFB combined pathway

What is the most effect approach to multiplex lung cancer screening of high risk (2% LCA) individuals with CT and AFB?

CT & AFB applied to all

No lung cancer

CT alone

AFB alone

Lung cancer

CT & AFB applied to all

True negative

False negative

True positive

No screening

[+ 0.9829]

[+ 0.9859]

[+ 0.9842]

[0.9863]

[0.3256]

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Sensitivity Analyses

Sensitivity analyses allow us to investigate the robustness of the results. The sensitivity analyses that are presented focus on model parameters that were not obtained from SEER database. These include: prevalence of lung cancer (in our high risk population under study), sensitivity and specificity of CT, AFB and combined CT and AFB, histology shift due to screening, and stage shift due to screening (non-small-cell lung cancers). Sensitivity analyses on estimates obtained from SEER database were carried out and found to have negligible impact on our conclusions. One way sensitivity analysis on stage shift for small-cell lung cancer also had no important impact on our conclusions (results not presented). It is important to appreciate that the word sensitivity has two different meanings. Sensitivity in one context refers to the type of analysis being performed; i.e., sensitivity analysis (evaluating the impact of varying study estimates on conclusions), and in the context of screening, it refers to the probability that a patient who truly has a disease will screen positive.

When we varied prevalence of lung cancer in our study population, screening using CT and AFB applied in combination produced the highest expected survival over the entire range of values (Figure 7). This is followed by screening using individual CT, AFB, and no screening. As lung cancer risk increased in the population, the overall 5-year expected survival decreased.
Figure 7. One way sensitivity analysis on lung cancer prevalence in high risk populations

For each of the three screening option arms under study, we performed one way sensitivity analyses by varying sensitivity and specificity for each alternative individually. We also performed two way sensitivity analyses, varying both parameters simultaneously for each of the three alternatives.

For screening using CT alone, one way sensitivity analysis revealed that the results are sensitive to this parameter. Screening using CT alone becomes more favourable than CT and AFB combined when the sensitivity of CT exceeds 0.8841, indicated by a higher expected survival (Figure 8a). When specificity of CT was varied (0.787-0.953), the results were robust across the entire range, whereby combined CT and AFB retained the highest expected survival (Figure 8b). Two way sensitivity analysis of CT screening sensitivity and specificity reveals that when both parameters are varied simultaneously, the results are no
longer robust (Figure 8c). However, we still found that CT and AFB screening combined is superior to CT screening alone for most sensitivity/specificity combinations.

One- and two-way sensitivity analyses of AFB screening sensitivity and screening revealed that over all realistic ranges of AFB sensitivity and specificity, combined CT and AFB is the superior screening strategy (Figure 9a-c).

Sensitivity analyses of combined CT and AFB screening revealed that when sensitivity dropped below a certain threshold, combined CT and AFB screening becomes dominated by screening using CT alone. At low values for sensitivity (below 0.846), CT alone was associated with the highest expected survival (Figure 10a). When specificity of combined CT and AFB was varied (0.700-0.980), the results were robust across the entire range, whereby combined CT and AFB retained the highest expected survival (Figure 10b). In two way sensitivity analysis, at most low range values for sensitivity and specificity of combined CT and AFB, CT alone was the superior screening option (Figure 10c). Current data indicate that sensitivities above 0.846 are realistically obtainable where modern medical care and facilities are available (106).

In these sensitivity analyses, sensitivity and/or specificity of one screening modality was altered, while others were kept constant. This is unrealistic. For example, if the sensitivity and specificity of combined CT and AFB decline, it is expected that the sensitivity and specificity of CT screening also will decline, as the two methods are correlated. TreeAge did allow evaluation of correlation
between the two variables, but the amount of correlation could not be varied and was perfect. This led to unrealistic results, which are not presented here.
Figure 8. a) One way sensitivity analysis of CT screening sensitivity b) One way sensitivity analysis of CT screening specificity c) Two way sensitivity analysis of CT sensitivity and specificity (Screening corresponding with best expected survival is indicated by shaded area)
Figure 9. a) One way sensitivity analysis of AFB screening sensitivity b) One way sensitivity analysis of AFB specificity c) Two way sensitivity analysis of AFB sensitivity and specificity (Screening regime corresponding with best expected survival is indicated by shaded area)
Figure 10. a) One way sensitivity analysis of combined CT & AFB screening sensitivity b) One way sensitivity analysis of CT & AFB specificity c) Two way sensitivity analysis of CT & AFB sensitivity and specificity (Screening regime corresponding with best expected survival is indicated by shaded area)
By performing one way sensitivity analysis on shift in histology due to screening, we were able to determine that this parameter was not important in changing the results – over the range of values examined for shift in histology due to screening the relative impacts of the four alternatives remained the same: combined CT and AFB had the best survival (Figure 11).

Figure 11. One way sensitivity analysis of shift in histology due to screening

One way sensitivity analysis of shift in stage (advanced to early) produced similar results. Varying this parameter did not change the outcome of the model as determined in the original baseline analysis (combined CT and AFB remains the most effective screening option) (Figure 12); and again we are able to conclude that our results are not sensitive to variation in this parameter. When
we performed two way sensitivity analysis, varying both shift in histology due to screening and shift in stage simultaneously, the results did not change. Screening by combined CT and AFB proved to be the best screening option across the entire range of values for both parameters, and the greater the stage shift, the greater the expected survival and the larger the gap in absolute terms in survival benefit over alternative screening modalities.

**Figure 12.** One way sensitivity analysis on shift in stage (advanced to early: non-small-cell lung cancers)
Figure 13. Two way sensitivity analysis on *shift in histology* and *shift in stage* (advanced to early)

To evaluate which parameters have the greatest impact on expected survival, a tornado diagram was produced (Figure 14). This diagram ranks the parameters in order of their impact on uncertainty associated with expected overall 5-year lung expected survival. Based on our analysis, lung cancer prevalence was the most important model parameter affecting expected overall survival, followed by shift in stage for non-small cell lung cancers (advanced to early), specificity and sensitivity of combined CT and AFB, CT sensitivity, and shift in stage for small cell lung cancer; listed here by rank of importance. The impacts of other parameters presented were much less important.

Notice that for specificity of combined CT and AFB, sensitivity of combined CT and AFB and CT sensitivity, a bold vertical line is present. This line indicates the threshold at which a specific screening strategy becomes *dominated* by
another as either sensitivity or specificity become elevated. For sensitivity of combined CT and AFB screening, CT alone becomes dominated by CT and AFB combined; and for sensitivity of CT screening, combined CT and AFB becomes dominated by CT alone. The term dominated is used to indicate the situation where one screening strategy becomes superior to another; i.e., it takes over as the screening option associated with the highest expected survival.

**Figure 14.** Tornado diagram. Impact of parameter model uncertainty on expected 5-year lung cancer survival
Monte Carlo Simulation Analysis

Table 5 presents the results of the Monte Carlo microsimulation sensitivity analysis of the decision analysis model for lung cancer screening. The microsimulation model allows random variation to occur according to the probability distributions specified for each estimate, which in this study was done using the triangulation distribution. Using this method, the highest probability is assigned at the most likely value anticipated for a given variable and probabilities decline linearly from that point to the anticipated extreme values for each variable.

Table 5: Monte Carlo simulation sensitivity analysis (1000 trials each screening intervention) for 5-year survival in the lung cancer screening model

<table>
<thead>
<tr>
<th></th>
<th>5-year survival in the whole population</th>
<th>5-year survival in those with lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CL</td>
</tr>
<tr>
<td>No Screen</td>
<td>0.9830</td>
<td>(0.9729, 0.9930)</td>
</tr>
<tr>
<td>CT</td>
<td>0.9859</td>
<td>(0.9775, 0.9939)</td>
</tr>
<tr>
<td>AFB</td>
<td>0.9841</td>
<td>(0.9745, 0.9933)</td>
</tr>
<tr>
<td>CT &amp; AFB</td>
<td>0.9861</td>
<td>(0.9780, 0.9941)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CL, credibility limits

This sensitivity analysis evaluating overall 5-year lung cancer survival indicates that lung cancer screening with CT or AFB only, or with combined CT and AFB lead to superior survival. CT alone and combined CT and AFB have similar survivals, which appear to be superior to screening with AFB alone. The
95% credibility limits overlap, so it is difficult to identify a clearly superior screening method from microsimulation Monte Carlo sensitivity analysis of overall 5-year survival.

The Monte Carlo microsimulation for 5-year survival in individuals who have lung cancer is more discriminating. Screening with AFB is superior to no screening (20.2% vs. 14.5% 5-year survival, with non-overlapping 95% credibility limits). Screening with CT alone is superior to AFB screening alone (29.4% vs. 20.2% 5-year survival, with non-overlapping 95% credibility limits, Table 5). Screening with combined CT and AFB appears superior to CT screening alone (31.3% vs. 29.4% 5-year survival), although, the 95% credibility limits overlap substantially. Because the Monte Carlo simulation distribution of expected survival values for combined CT and AFB was non-normal (Figure 16), the nonparametric Wilcoxon rank sum (Mann-Whitney) test was used to evaluate statistical differences between expected survival values between CT and combined CT & AFB screening. The p-value was <0.0001, indicating that screening with combined CT and AFB is significantly better than CT screening alone at improving 5-year lung cancer specific survival in patients with lung cancer.
Figure 15. Monte Carlo simulation sensitivity analysis of *CT screening* in those with lung cancer – distribution of expected 5-year survival proportions

Figure 16. Monte Carlo simulation sensitivity analysis of *combined CT & AFB screening* in those with lung cancer – distribution of expected 5-year survival proportions
CHAPTER V – DISCUSSION AND CONCLUSIONS

The results from this study suggest that screening by combined CT and AFB is moderately better than CT alone at improving lung cancer survival, and both approaches are substantially better than AFB screening alone or no screening. The conditions required for screening by CT and AFB combined to outperform CT alone are described, as are the results from sensitivity and Monte Carlo simulation analyses.

Baseline Analysis

*Lung Cancer Patients Only*

In baseline analysis, the expected 5-year lung cancer-specific survival probability for individuals that do not undergo screening (no screening group) and that develop lung cancer was 0.1445. This estimate is consistent with what is known about lung cancer survival and what is currently being reported in the literature (4). For CT screening, expected survival among lung cancer patients was estimated to be 0.2966. This translates into an expected mortality reduction equal to 15.21% (relative to no screening when evaluated by 5-year survival proportions) and is only moderately higher than what others have recently reported. Mahadevia and colleagues reported a mortality reduction of 13% (20-year follow-up) (52), while Chien and Chen reported a reduction of 15% (10-year follow-up) (64, 69). In contrast, Bach and colleagues (53) did not report any significant advantage of screening using CT (5-year follow-up), whereas Henschke and colleagues (44) estimate a mortality reduction in the range of 80%
Bach and colleagues based their conclusions on modeling, which may explain why they failed to detect any benefit from screening, and lack of a proper control group may explain Henschke's findings.

Among the three screening regimes evaluated in this study, the best expected survival was associated with combined CT and AFB. The expected survival for this group was 0.3256. The probability associated with survival for screening using AFB alone, which was the lowest among all screening regimes evaluated, was 0.2124. Since no other study has investigated the impact of screening using combined CT and AFB or AFB alone on survival, it is not possible to compare these values with any others.

*All Screened Individuals*

Lung cancer survival in the entire screened population was much better than for lung cancer patients. This is because only a small percentage of high-risk individuals that are screened actually develop lung cancer (in this study 2%). For our results to be different when comparing lung cancer patients only to the entire screened cohort, the mortality associated with screening (the adverse effects of following up a false-positive) would need to be fairly high and the specificity associated with screening would need to be quite poor.

The conclusions drawn were not different when we examined expected survival for the entire screened population. Screening using combined CT and AFB was still the best option (expected survival = 0.9863). The expected survival of screening using CT alone was 0.9859. Screening by AFB alone was the next
preferred option (expected survival = 0.9842) followed by no screening (expected survival = 0.9829).

**Sensitivity Analysis**

*Conditions when Screening by Combined CT & AFB is Superior to CT Alone*

To determine under what conditions combined CT and AFB is superior to screening by CT alone, we examined one way analyses for all important variables that were included in our model.

Reasonable ranges for sensitivity and specificity (as determined from the literature, expert opinion and unpublished data) for the three screening options (CT alone, AFB alone, and combined CT and AFB) were examined in Figures 8-10. Combined CT and AFB screening was determined to be superior to CT alone under the following conditions: when sensitivity of screening by CT alone is below 0.8841, for all values of specificity of screening by CT alone, for all values of sensitivity and specificity of screening by AFB alone, when sensitivity of screening by combined CT and AFB is greater than 0.8460, and for all values of specificity for combined CT and AFB. Combined CT and AFB was superior to screening by CT alone for all reasonable values of shift in histology (Figure 11), shift in stage (Figure 12) and prevalence of lung cancer in the population (Figure 7).
Sensitivity Analyses Examining CT Alone, AFB Alone, and Combined CT & AFB

Screening Sensitivity and Specificity

The results from this study were found to be sensitive to variation in CT screening sensitivity. Specifically, once sensitivity of CT alone surpassed 0.8841, it became the better screening option, surpassing combined CT and AFB. Although this finding provides us with reason to remain cautious, it should be recognized that if CT sensitivity is moved towards the ideal or perfect performance, combined CT and AFB would also have shifted towards perfect. Due to limitations in the modeling software, we were forced to keep the combined CT and AFB constant in this specific sensitivity analysis. Because of the innate imaging property of CT (it misses central airway cancers); CT could not approach 100% sensitivity. Therefore, the issue being describing here is an abstract situation, which in current reality is the essence of the problem that multiplex (combined) screening is trying to overcome. One way sensitivity analysis of CT specificity revealed that the results are not sensitive to this parameter.

Sensitivity and specificity associated with AFB was analyzed next. When sensitivity and specificity was varied across reasonable values for this technique, the relative survivals associated with the screening options remained the same; and our conclusion regarding them remained the same. Screening by AFB alone was associated with the worst expected survival among the screening options under study and it is therefore highly unlikely that screening using this technique is feasible on its own. These findings do not rule out the possibility that AFB may one day be recommended as an adjunct to CT screening.
In the final one way analyses performed, variation in sensitivity and specificity of combined CT & AFB was studied. While variation in specificity had no important effect, we found that below a threshold value of 0.846 for sensitivity, combined CT and AFB is dominated by CT alone. Again, while this finding provides us with reason to be cautious, it is important to recognize that screening using combined CT and AFB will almost certainly never be less sensitive than CT alone.

By performing two way analyses for each of the three screening regimes under consideration (varying sensitivity and specificity simultaneously), we received a better sense of how dominant each option was; and specifically, we were able to determine the sensitivity/specificity combinations or conditions for which combined CT and AFB was superior to screening by CT alone.

When CT sensitivity/specificity was varied simultaneously, we found that combined CT and AFB is superior across a broader range (i.e., it results in the highest expected survival for the majority of CT sensitivity/specificity combinations), if we assume that parameters associated with combined CT and AFB do not change (Figure 8c). In two way sensitivity analysis of AFB, combined CT and AFB remained the superior screening option across all combinations of sensitivity and specificity (Figure 9c). This result was not consistent in two way sensitivity analysis of combined CT and AFB. In fact, the results were almost the opposite. Across all low range value combinations, CT alone is presented as the better screening option (Figure 10c).
Sensitivity Analyses Examining Lung Cancer Prevalence, Shift in Histology, and Shift in Stage

Lung cancer prevalence was modeled to include values between 0.05 and 3.5 percent. While the results remained robust in one way sensitivity analysis performed on this variable, the variability in expected survival was quite substantial. As prevalence of lung cancer increases, expected survival decreases (Figure 7). Note that this observation only applies to expected survival for the entire screened population. Prevalence of lung cancer does not affect survival for patients that have lung cancer.

To evaluate whether variation in shift in histology or shift in stage across ranges has the potential to impact our results, we performed one- and two-way sensitivity analyses. In all analyses, screening using combined CT and AFB remained the superior screening strategy, indicating that our results are not sensitive to these parameters (Figures 11-13). However, it is worth noting that as was the case for lung cancer prevalence, degree of stage shift had a significant impact on expected survival for the entire screened population. As stage shift becomes larger, expected survival becomes better. Screening by combined CT and AFB, followed by CT alone and AFB alone had the biggest improvement in expected survival associated with shift in stage.

Impact of Parameter Variation on Expected Survival

Lung cancer prevalence was found to be the most important model parameter affecting expected survival in the overall population. While prevalence of disease
has no impact on survival of diseased individuals, this finding still remains important in the context of cost-effectiveness. As disease becomes more prevalent, cost-effectiveness improves, presuming that the intervention is effective.

Other variables that have an important impact on expected survival in the entire screened population include the following: shift in stage, sensitivity and specificity of screening by CT & AFB combined, and sensitivity of screening by CT alone (Figure 14). By identifying which model parameters (parameter uncertainties) have the greatest impact on expected survival, we are able to determine where research is needed most; or which model parameters estimates, if more accurate, would have the greatest impact on our ability to more accurately report the potential benefit (lung cancer survival) associated with lung cancer screening.

**Monte Carlo Simulation Analysis**

Monte Carlo simulation analysis was performed to evaluate whether the results from our original baseline analysis remain consistent when uncertainty surrounding all model parameters is varied simultaneously. Recall that the microsimulation model allowed random variation to occur according to the probability distributions specified for each estimate, which in this study was done using the triangulation distribution method.

The results for 5-year expected survival in the entire screened population were consistent with what we found for patients with lung cancer. In both
populations, CT and AFB applied in combination was found to be the superior screening option, albeit with 95% credibility limits overlapping with limits associated with screening using CT alone. For 5-year expected survival in the entire screened population, screening by CT alone was very similar to screening by CT and AFB combined (0.9859 vs. 0.9861). One explanation for this finding may be that mortality associated with false positive diagnosis using combined CT and AFB is high. We set the mortality rate for this screening combination equal to 0.2 percent (2 per 1000) and it is possible that this value was overestimated.

The nonparametric Wilcoxon rank sum (Mann-Whitney) test revealed that screening with combined CT and AFB is significantly better than CT screening alone at improving 5-year lung cancer specific survival among individuals who have lung cancer (p < 0.0001).

Model Assumptions and Limitations
Considering the nature of this study and the many uncertainties surrounding screening effectiveness, it was expected that we would be forced to make some assumptions and that there would be limitations to discuss. In this section we describe the assumptions and limitations of our analysis.

Model Assumptions
In our analysis we made several assumptions, and they included:

(1) radiation from the scans does not increase risk of lung cancer and reduce lung cancer survival,
(2) That small cell lung cancers (because of their early metastatic nature) undergo less stage shift relative to other histologic types,

(3) That change in stage and histology distribution in the screened cohort results in improved clinical management, treatment and survival,

(4) That shifts in histology for adenocarcinoma and other non-small-cell lung cancers occurred in the same magnitude and were equally offset by an inverse shift in squamous cell and small-cell lung cancer, and

(5) That screening does not reduce individuals lifetime risk of lung cancer through a reduction in smoking due to their greater awareness of lung cancer susceptibility.

Assumptions (1) and (3), if eventually found to be untrue, bias our results in favour of screening, but have no impact on which screening option is superior. In considering assumption (2), note that when stage shift for small cell lung cancer was varied (between 5% and 15%); we found that it had negligible impact on our results. Regarding assumption (4), the sensitivity analysis for this variable suggests that it has very little influence on the ranking of screening. Therefore, it is not expected that altering each histology by slightly different amounts would have a large impact on conclusions drawn. For assumption (5), there is a good possibility that screening increases awareness of lung cancer susceptibility, resulting in a reduction in smoking and a reduction in risk. Therefore, assumption (5) likely biases the results of this investigation towards the null (screening does not improve survival), making our results more conservative.
Limitations

Assessment of Outcome – This study did not evaluate or consider the impact of screening on quality of life, or preference for certain health states over others. We only looked at lung cancer specific survival. Individuals diagnosed with early stage lung cancer may undergo invasive testing, surgery, radiation, chemotherapy and suffer considerable anxiety and discomfort, and therefore it would have been informative to evaluate the impact of screening on quality adjusted life, in addition to survival. In the future, studies should be performed to determine the quality of life in individuals with screen detected early stage lung cancer and the disutility associated with false positive test results.

SEER Registry and Use of Never Smokers Histology and Survival Data – In this study, only high risk smokers were evaluated; however, the use of SEER Registry to obtain histology and survival data did not allow exclusion of never-smokers. Because the histology distribution and survival proportions is known to be different between smokers and never-smokers, some bias was introduced (5). Specifically, SqCCA is more common among smokers than never-smokers, and survival is generally worse for smokers than never-smokers (even for the same stage and histology of lung cancer) (5, 108). In this study, SqCCA was underestimated and survival was likely overestimated for the no-screening arm, and thus the effect of AFB screening and combined screening was likely understated. Taking into account that never-smokers have only a slight survival advantage over smokers (5), and that the overwhelming majority of lung cancers are diagnosed among current or former smokers, it is unlikely that our inability to
distinguish between smokers and never-smokers introduced major bias or had an important impact on our results. In fact, had we been able to exclude never-smokers, it is expected that joint screening using CT and AFB would present as being even more superior to screening by CT alone (because of AFBs improved ability to detect SqCCA).

**Study Strengths**

This study incorporates the most current information available. To our knowledge, this investigation is the first of its kind to incorporate screening using decision analysis to evaluate the lung cancer screening benefit of AFB with or without CT screening. In addition, our method for classifying histology and stage of lung cancer is more detailed than found in previous studies of a similar nature. We were required to discriminate between the major histologic types of lung cancer due to the complimentary nature of the screening modalities under investigation. In our study, AFB was modeled to be better at detecting squamous cell lung cancer and small cell lung cancer, whereas CT was modeled to be better at detecting adenocarcinoma and other non-small cell lung cancer.

In this analysis, cases of carcinoma in situ/intraepithelial neoplasia (stage 0) were excluded. These lesions are not technically "invasive" cancers and it is possible that many of them may be indolent or even revert to normal tissue. Their inclusion in this study would have led to biased estimates of screening success. On the other hand, some of these lesions may turn into invasive cancer and thus detection and removal may improve survival/mortality. The decision to
exclude these cancers from analysis led to more conservative estimates of effectiveness.

**Implications of Findings to Public Health**

Using results from Monte Carlo simulation analysis, we attempt to quantify the impact of screening on survival in lung cancer patients. We also attempt to quantify the potential benefit (difference in effectiveness) of screening by CT and AFB combined compared with screening by CT and AFB individually. Lung cancer statistics were obtained from both the American and Canadian Cancer Societies.

In the United States an estimated 213,380 new lung cancers are diagnosed each year (American Cancer Society, Cancer Facts and Figures, 2007) and in Canada, it is estimated that roughly 23,900 new lung cancers are detected each year (Canadian Cancer Society, Canadian Cancer Statistics, 2008). Of these new cases, it is estimated that approximately 88% occur among individuals with a smoking history (5). This translates into 187,774 new cases in the US and 21,032 new cases in Canada that are associated with smoking each year.

Based on these estimates and on the results from our analysis (using mean values and associated 95% CIs), if combined CT and AFB screening were applied to every individual at high risk for lung cancer then in theory, screening could postpone or prevent an estimated 31,508 American deaths (95% CI = 27,527 to 34,137) and 3,808 Canadian deaths (95% CI = 3,083 to 3,823) each year.
(16.78% mortality reduction; 95% CI = 14.66% to 18.18%). In comparison, screening by CT alone could postpone or prevent approximately 27,978 American deaths (95% CI = 21,575 to 34,118) and 3,133 Canadian deaths (95% CI = 2,416 to 3,821) each year (14.90% mortality reduction; 95% CI = 11.49% to 18.17%); and screening by AFB alone could postpone or prevent about 10,740 American deaths (95% CI = 5,971 to 14,458) and 1,203 Canadian deaths (95% CI = 668 to 1,619) each year (5.72% mortality reduction; 95% CI = 3.18% to 7.70%).

The difference between the number of deaths postponed or prevented by screening (based on reported mean values) using combined CT and AFB compared to AFB alone is greater than the number of additional deaths postponed or prevented combined CT and AFB compared to screening by CT alone (mortality reduction difference of 20,768 in US and 2,605 in Canada vs. 3,530 in US and 675 in Canada).

Mortality reduction as described here refers to mortality as measured before five years. These estimates are an overestimate of true mortality reduction as some individuals will continue to die of lung cancer after five years.

**Future Directions**

For screening to have any chance of becoming adopted into public health practice researchers need to do a better job of identifying those individuals who are at the highest risk for lung cancer. This will maximize benefit from screening, minimize harms associated with false positive screens and improve overall cost-
effectiveness. But even more importantly, further clinical trials and accurate data are needed. We need to determine the extent to which combined CT and AFB is superior to other lung cancer screening modalities and at what cost. If it is eventually determined that screening, either by CT alone or by combined CT & AFB is successful at improving lung cancer specific survival and at a reasonable cost (determined by what society/government is willing to pay), screening will still need to be considered in the context of other healthcare alternatives.

Recently, the Terry Fox Research Institute awarded funding in support of a pan-Canadian lung cancer screening trial (7 screening centres across Canada), which will incorporate screening using CT and AFB and that will provide us with definitive evidence regarding whether screening with combined CT and AFB has higher accuracy than screening by CT alone. The principle investigators of this study are Drs. Stephen Lam (University of British Columbia/British Columbia Cancer Agency) and Ming-Sound Tsao (University of Toronto/Princess Margaret Hospital).

**Speculations**

While the purpose of this study was not to evaluate cost-effectiveness, in order to inform policy makers, cost-effectiveness analysis would have contributed important additional information. The most feasible scenario under which screening could be cost-effective would be if very high-risk individuals are targeted and screening is either highly effective and/or CT and AFB screening costs fall substantially. Note that in order for any intervention to be cost-effective,
it must be effective. In this study, screening by combined CT and AFB was only slightly better than screening by CT alone at improving 5-year lung cancer specific survival. Considering the relatively high cost and invasive nature of AFB, it is unlikely that combination screening will be found cost-effective at this time. The cost associated with saving one additional life will likely be too high based on what society and government is willing to pay.

In this analysis, all lung cancers detected were prevalence cases. By incorporating annual screening, it is expected that the number of abnormal screens (incidence cases) would be much lower and that more lung cancers would be detected at an earlier and more curable stage, compared with baseline prevalence screening. We do not expect that incorporating annual screening into our model would have any impact on the overall conclusions drawn from our study. Complimentary screening by CT and AFB in combination would be expected to remain as the best screening option.

Conclusions
Despite implementation of successful smoking cessation programs, lung cancer remains the leading cause of cancer death in the developed world. While it has not yet been proven, it is thought that through early detection screening may have the potential to improve lung cancer specific survival. CT and chest radiography are currently being investigated, but these modalities are thought to have limitations and it is unclear whether new approaches under development might successfully augment CT screening.
This study examined the potential for screening that combines CT with AFB. Decision analysis revealed that combined screening was slightly better than CT screening alone and substantially better than AFB alone at improving 5-year survival in both the entire screened population and in patients with lung cancer. Results from Monte Carlo simulation analysis indicate that survival in lung cancer patients is significantly better for combined CT and AFB screening, compared with screening by CT alone.

Overall, results from this study suggest that combined CT and AFB is slightly better than CT alone at improving lung cancer survival, and both approaches are substantially better than AFB screening alone or no screening. Further clinical trials are needed to quantify the extent to which combined CT and AFB is superior to other lung cancer screening modalities; and more accurate methods of identifying individuals at highest risk for lung cancer is important before considering whether adoption into public health practice is warranted.
References


