COST-EFFECTIVENESS OF SCREENING FOR LUNG CANCER IN A HIGH RISK COHORT USING AUTOMATED SPUTUM CYTOMETRY

By

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES
(Department of Experimental Medicine, Faculty of Medicine)

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

December 2003

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Name of Author *(please print)* — Date

Title of Thesis: Cost-effectiveness of Screening for Lung Cancer in a High Risk Cohort Using Automated Sputum Cytometry

Degree: Master of Science Year: 2003

Abstract

Lung cancer continues to be the leading cause of cancer death in Canada. Thirty percent of cancer deaths in men and one-quarter in women are due to lung cancer alone. Prognosis is better for patients diagnosed with early stage lung cancer (>80% 5 year relative survival) than those with late stage cancer (<10% 5 year relative survival). Screening for early stage lung cancer, before the onset on clinical symptoms, leads to a reduction in risk of invasive cancer. In order for a cancer screening programme to be recommended as a cancer control strategy, certain fundamental criteria must be fulfilled, one of which is the cost-effectiveness of the proposed screening test.

To facilitate funding allocations of scarce resources across health care programs, economic evaluation models are used to compare the cost-effectiveness of different health interventions. In this model, the cost-utility of using automated sputum cytometry (ASC) versus spiral CT alone as a first step in screening for early stage lung cancer is determined.

ASC consists of a high-resolution quantitative microscopy system that analyzes the concentration and distribution of DNA and chromatin structures within the cell nucleus of sputum cells. This will determine the likelihood of lung cancer presence in the particular patient. ASC followed by computed tomography (CT) scanning is hypothesized to be less costly with improved prognosis from early detection of disease.

Using a computer-simulated model, a hypothetical cohort of patients at high risk for lung cancer was screened using ASC as a first step in the screening algorithm. The incremental cost-utility was determined for 5-year annual screening using ASC and CT compared to CT screening alone and no screening.

Results show ASC is moderately cost-effective with an incremental cost-utility (compared with no screening) of $54,923/QALY (2002 CDN$). Using the most favourable assumptions for the model, the cost-effectiveness improved to $34,388/QALY. Comparatively, screening with CT alone was a weakly dominated strategy. Sensitivity analyses showed the most influential parameters to be specificity of the ASC test and prevalence of disease.

Despite certain limitations with the study, a very conservative approach to treatment and costs was adopted in the model and ASC shows promise as a cost-effective lung cancer screening tool.

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Abbreviations

ASC	Automated Sputum Cytometry
B.C.	British Columbia
BCCA	British Columbia Cancer Agency
CAIS	Cancer Agency Information System
CBA	Cost-benefit Analysis
CEA	Cost-effectiveness Analysis
CMA	Cost-minimization Analysis
CT	Computed Tomography (scan)
CTUMS	Canadian Tobacco Use Monitoring Survey
CUA	Cost-utility analysis
DATA	Decision Analysis by TreeAge Software
ICER	Incremental Cost-effectiveness Ratio
NSCLC	Non-small Cell Lung Cancer
PMI	Perceptronix Medical Inc.
QALY	Quality-adjusted Life Year
SCLC	Small Cell Lung Cancer
SEER	Surveillance, Epidemiology, and End Results Database, US

Acknowledgements

Firstly, I would like to express my deepest gratitude to Dr. Stephen Lam and Dr. Branko Palcic for their ongoing support throughout this project. Without their knowledge, guidance and encouragement this project would not have been possible. It was a privilege to work with such distinguished scientists in the field of lung cancer research.

I also with to thank Dr. Aslam Anis for his valuable assistance and suggestions in the design of the decision analysis model. His expertise and patience were very much appreciated. Huiying Sun also provided guidance and direction in the design of the markov model.

In addition, I would like to thank those individuals working on the Lung Health Study at the British Columbia Cancer Agency. In particular, I thank Sukhinder Khattra for her patience and endless guidance while working with the database system.

I would also like to express my appreciation to the faculty and staff in the Department of Health Care and Epidemiology at The University of British Columbia. The courses and direction I received were instrumental in providing a foundation upon which to conduct this health economic research.

Finally, I am indebted to my family, who have shown nothing but continual support and understanding for me as I strive to meet my academic goals. Thank you.

Chapter 1. Introduction

The rising demand for health services coupled with static or decreasing resources with which to pay for them has resulted in increasing interest in the economic analysis of medical interventions. Economic appraisal is concerned with assessing the efficiency of the way in which scarce resources are used. These economic evaluation techniques are a way of organizing, thinking about and carrying out measurement of the consequences identified with alternative courses of action. It is argued by health economists that such evaluations should go hand-in-hand with resource allocation decisions in order to accrue maximum benefits from limited resources. Research into the economic aspects of health care interventions is now carried out and supported by health care professionals, government, the insurance industry and the pharmaceutical industry. Each of these groups brings to the field their own particular biases and vested interests, and the interpretation of studies needs to be carried out with recognition of this fact in mind.

One of the important developments of medical science during the past twenty-five years has been the emergence of screening programmes to detect various cancers at an early stage. Successful population-based programmes include both breast and colorectal cancer screening (Scholefied, 2002; Whynes, 1992; Elixhauser, 1991). In further support of these health interventions, economic evaluation techniques have shown these screening tools to be cost-effective approaches (Whynes, 1992; Sonnenberg, 2002; Gyrd-Hansen, 1991) to wide-spread disease with high mortality. Lung cancer, the most common cause of cancer death in North America, should be a good candidate for screening because of high mortality, differential survival by stage of disease, the current low rate of early detection because of lack of symptoms early in disease, the availability of effective intervention for very early disease and the high costs associated with treatments for later stages of the disease (Marshall, 2001). Currently, there are no medical organizations in North America that recommend lung cancer screening for the general population, particularly as it still remains to be clinically proven that screening reduces lung

cancer mortality. Nevertheless, the topic is at the centre of debate among health professionals with previous screening studies being critically reviewed (Reintgen, 1996; Chamberlain, 1996; Kramer, 1999). In this regard, there are a number of serious limitations to several National Cancer Institute Cooperative Trials and new studies underway show that lung cancer screening does improve survival. Furthermore, there have been dramatic advances in diagnostic imaging and the molecular detection of lung cancer such as computerized tomography (CT scans) and sputum cytology that will likely play a significant role in future lung cancer screening.

Economic evaluations of lung cancer screening tools to date have been limited and there are few published scientific studies that are based on real time clinical data. On account of the high prevalence and mortality of lung cancer as well as its suitability for a population based screening strategy, the cost-effectiveness of such a programme is one that cannot be ignored. One approach being studied at the BCCA is using computer assisted sputum cytology (ASC) as a non-invasive technique to screen patients at high risk for developing lung cancer. A costing model has been designed for this economic evaluation to assess the costs and outcomes of ASC screening compared to no screening and screening using CT scans.

Whenever possible, the statistics reported in this paper are reflective of the Canadian population and in many instances, the province of British Columbia is used specifically as a source for lung cancer information. This is reflective of the location of the study and aids in supporting the implementation of such a population based screening programme specifically in the province of British Columbia.

The objectives of this thesis are as follows:

1. To review various aspects of lung cancer such as burden of disease, etiology and its suitability as a disease for screening, as well as to provide a brief description of ASC and justify reasons for its use in lung cancer screening.

2. To describe the process of economic evaluation as it relates to the topic of lung cancer screening, including definitions, strategies and review of previous scientific studies related to the cost-effectiveness of such screening methods.
3. To evaluate the effectiveness of ASC using real clinical data from the Lung Health Study at the BCCA to be used subsequently in the decision model.
4. To design an economic decision model that tests the effectiveness of using ASC prior to CT scanning in comparison to both no screening and screening with CT scan using the decision analysis software TreeAge™ and to test the robustness of the model with sensitivity analyses.

Chapter 2. Lung Cancer Screening

To proceed with the proposed study of the cost associated with screening for lung cancer in a high risk cohort it is essential to have a detailed understanding of lung cancer. This chapter provides an overall review of lung cancer and its suitability as a disease for screening as well as description of ASC.

For clinical purposes, lung cancer is classified as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC: squamous cell carcinoma, adenocarcinoma, large cell carcinoma) due to the different biological behaviour of these entities. SCLC represents approximately 20% of all lung cancers and is characterized by rapid growth and usually early hematogenous metastases (Diederich, 2003). The different types of NSCLC represent approximately 80% of lung cancer cases and typically exhibit slower growth and later, usually lymphatic metastases. In NSCLC, surgery is believed to represent the most effective therapy and is performed whenever possible (i.e. in localized tumours, which can be completely resected). More advanced, non-resectable tumours are treated with neoadjuvant radiotherapy/chemotherapy and patients with late stage NSCLC can only be offered palliative chemotherapy in most instances. SCLC, on the contrary is regarded as a systemic disease in most cases and treated with chemotherapy with or without radiotherapy. Surgical resection is rarely performed.

2.1 Burden of Disease

At the beginning of this century, lung cancer was a rare disease. The present global epidemic, with over two million deaths estimated in the year 2000, is the direct result of governmentally sanctioned production and aggressive marketing of addictive tobacco products, primarily cigarettes. Lung cancer is the most common cause of cancer death in North America. More people die from lung cancer than breast cancer, colorectal cancer and prostrate cancer

combined (National Cancer Institute of Canada, 2002). The primary reason for such a dismal cure rate is that nearly all lung cancers are found at a very late stage, making curative treating impossible. A presence of symptoms usually indicates advanced disease. A potentially more effective way to improve outcomes is to detect the cancer when curative treatment, such as surgery, can be applied (Morrison, 1992).

According to the Canadian Cancer Society, lung cancer will continue as the leading cause of cancer death among Canadians in 2002. Thirty percent of cancer deaths in men and twenty-five percent in women are due to lung cancer alone (National Cancer Institute of Canada, 2002). Table 2.1 shows the estimated new cases and deaths for the 4 major cancer sites in Canada in 2002. Of the 12,000 new cases among men in Canada, 1,350 cases occur in the province of British Columbia while females in the province account for 1,250 new cases of lung cancer. Table 2.2 provides details of the age-standardized incidence and mortality rates for lung cancer in Canada and in B.C. specifically. Although the incidence of lung cancer for males in B.C. is significantly less than that of the national average, (59 per 100,000 compared to 74 per 100,000), the rate for women in B.C. is comparable to the rate across Canada (46 per 100,000 to 47 per 100,000). Mortality rates among women are actually worse in B.C. compared to national figures which are reflective of the rapid increase in lung cancer mortality in women over the past 3 decades. It is therefore imperative that a lung cancer screening programme in B.C. adopt special efforts to target women who have a predisposition to lung cancer. Lung cancer will remain the leading cause of cancer death among both men and women (Table 2.3) with a total of 18,400 deaths in Canada (more than breast, prostrate and colorectal combined) with 2,300 of those deaths estimated to occur in B.C. in 2002. The unfortunate statistics highlighted above are reflective of a disease with very low 5-year survival rates. Table 2.4 indicates that only 14% of males and 17% of females will survive longer than 5 years from the time of diagnosis.

Table 2.1 Estimated New Cases and Deaths for Cancer Sites by Gender, Canada, 2002

	New Cases 2002 Estimates			Deaths 2002 Estimates			Deaths/Cases Ratio 2002 Estimates		
	Total	M	F	Total	M	F	Total	M	F
All Cancers	**136,900**	**69,800**	**67,200**	**66,200**	**35,100**	**31,100**	**0.48**	**0.50**	**0.46**
Lung (Canada)	20,800	12,000	8,800	18,400	10,700	7,700	0.88	0.89	0.87
Lung (B.C.)	2,600	1,350	1,250	2,300	1,200	1,100	0.88	0.89	0.88
Breast	20,700	140	20,500	5,400	40	5,400	0.26	0.30	0.26
Prostrate	18,200	18,200	---	4,300	4,300	---	0.24	0.24	---
Colorectal	17,600	9,500	8,100	6,600	3,500	3,000	0.37	0.37	0.37

--- Not Applicable
Source: Surveillance and Risk Assessment Division, CCDPC, Health Canada

Table 2.2 Estimated Age-standardized Incidence and Mortality Rates for Major Cancer Sites by Gender, Canada, 2002

	Incidence Rate (per 100,000)		Mortality Rate (per 100,00)	
	Canada	British Columbia	Canada	British Columbia
MALES				
All Cancers	442	456	224	195
Prostrate	120	121	29	24
Lung	**74**	**59**	**67**	**54**
Colorectal	59	54	22	16
FEMALES				
All Cancers	347	323	151	140
Breast	106	102	26	23
Lung	**47**	**46**	**38**	**39**
Colorectal	39	35	14	10

Source: Surveillance and Risk Assessment Division, CCDPC, Health Canada

Table 2.3 Distribution of Lung Cancer by Age Group and Gender, Canada, 2002

Age Group	Total	Males	Females
New Cases			
20-29	20	15	10
30-39	180	80	100
40-49	1000	450	560
50-59	3200	1650	1550
60-69	6000	3600	2400
70-79	7000	4300	2700
80+	3400	1900	1450
Ages 20+	**20800**	**12000**	**8800**
Deaths			
20-29	5	-	-
30-39	110	40	65
40-49	740	310	430
50-59	2400	1250	1100
60-69	4900	3000	1950
70-79	6500	4000	2600
80+	3700	2200	1600
Ages 20+	**18400**	**10700**	**7700**

- Fewer than 3 cases or deaths
Source: Surveillance and Risk Assessment Division, CCDPC, Health Canada

Table 2.4 Age-standardized Five-year Relative Survival Rates, Canada, 1992

	Prostrate		**Colorectal**		**Lung**	
MALES	Relative Survival Rate (%)	95% CI	Relative Survival Rate (%)	95% CI	Relative Survival Rate (%)	95% CI
Canada	87	85,88	56	54,58	**14**	13,15
British Columbia	91	88,93	59	54,63	**12**	10,15

	Breast		**Colorectal**		**Lung**	
FEMALES	Relative Survival Rate (%)	95% CI	Relative Survival Rate (%)	95% CI	Relative Survival Rate (%)	95% CI
Canada	82	81,83	59	58,61	**17**	16,18
British Columbia	85	83,87	61	56,65	**15**	12,18

Source: National Cancer Institute of Canada, Canadian Cancer Statistics, 2002

Survival rates in B.C. are slightly lower than the rate across Canada at 12% and 15% for males and females respectively. A large proportion of lung cancer is detected in patients when the disease has already progressed to a late stage (Stage III or IV) when curative options such as surgery are no longer viable (Lam, 2001). Figure 2.1 shows the likelihood of survival with lung cancer dependent on the stage at diagnosis. It is for this reason that early detection becomes crucial to increasing the life expectancy of lung cancer patients and, in the longer term, reducing mortality.

For any early detection strategy to be effective in reducing the impact of a disease it is necessary that the disease of interest have a detectable, preclinical phase, before widespread symptoms appear (the onset of symptoms usually means late stage disease with respect to lung cancer) (Bach, 2003). Lung cancer has a case fatality rate of some 90% when left to be diagnosed on the prompting of symptoms (or an abnormal finding in chest imaging) (Strauss, 1999). Most clinical experience indicates that the smaller a primary tumour is at the time of detection, the more favourable is the clinical outcome (Martini, 1999). Only about 10% of primary lung tumours that are less than a centimetre in diameter have been found to develop into metastatic tumours (Martini, 1999). The preclinical phase begins when the process of malignant transformation occurs and ends when signs or symptoms of disease permit the clinical diagnosis of cancer (Strauss, 1999).

2.2 Smoking as a Risk Factor for Lung Cancer

The use of tobacco products is the single most important cause of preventable, premature cancer deaths. Other risk factors for lung cancer include exposure to asbestos, radioactive radon, nickel, chromium, and arsenic (Diederich, 2003). Current estimates indicate

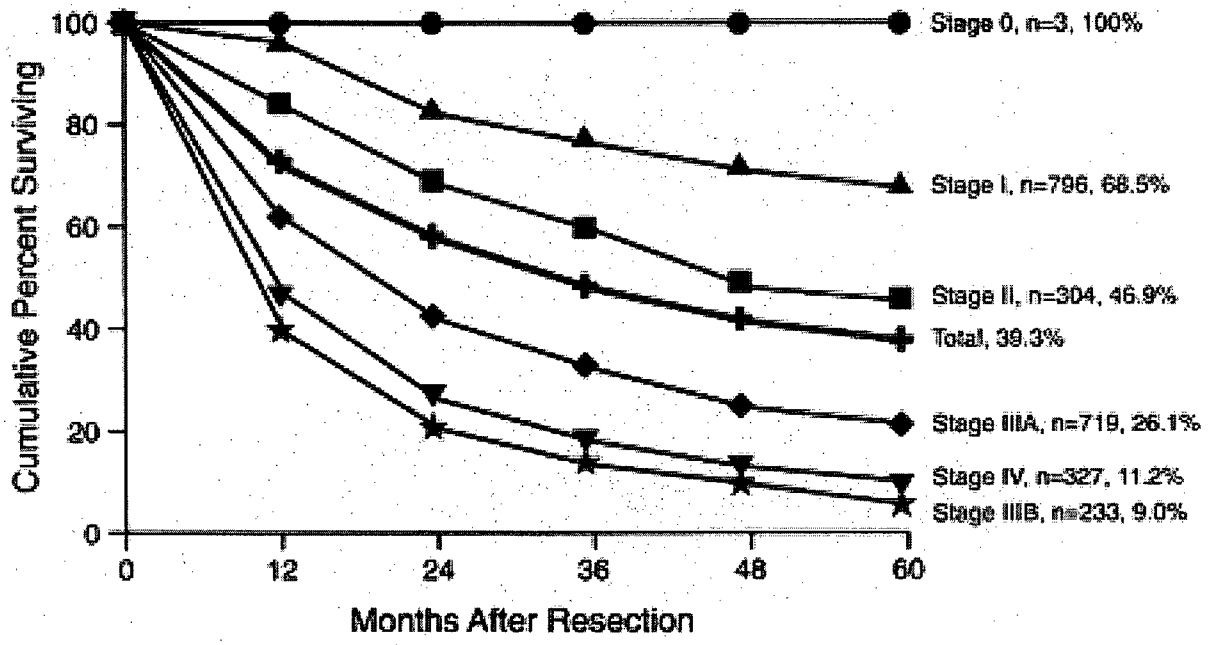

Figure 2.1 Likelihood of survival from lung cancer depending on stage at diagnosis.

that 87% of all cases of lung cancer are directly attributable to cigarette smoking, including 90% of lung cancers in men and 79% of cases in women.[11] In addition, many deaths from other diseases also occur because of smoking. Among men, smoking is responsible for almost one-third of potential years of life lost due to all cancers and among women the number drops to one-fifth of potential years of life lost due to all cancers (American Cancer Society, 1992). Lung cancer relative risk among long-term cigarette smokers is increased 10-30 fold compared to the lifetime non-smoker. Unfortunately, although smoking cessation is an effective lung cancer prevention strategy, many years of smoking abstinence are required for lung cancer risk to be reduced significantly among long-term smokers. Moreover, even after decades of complete smoking abstinence, the risk of lung cancer in former smokers fails to reach the level of the lifelong non-smoker. Because of the relationship between cigarette smoking and carcinogenesis, a population at high risk for lung cancer is readily definable.

A recent study done by the Canadian Tobacco Use Monitoring Survey (CTUMS) reveals that 5.4 million Canadians or 22% of the population, aged 15 years and older, were smokers in the year 2001 (Health Canada Tobacco Control Program, 2001). The province of B.C. again reported the lowest prevalence for current smokers 15 years and older at 17%. Table 2.5 outlines smoking statistics in Canada and BC specifically. Approximately 24% of men are smokers, slightly higher than the proportion of women (20%) (CTUMS, 2001). Cigarette consumption also varies across the country ranging from a low of 14.6 cigarettes/day in BC to a high of 17.6 cigarettes/day in New Brunswick; the national Canadian average is 16.2 cigarettes/day (CTUMS, 2001).

For several years now there have been more former smokers than current smokers in the Canadian population and statistics show this will remain the case for at least another 50 years due, in part, to the fact that CTUMS found young adults in Canada aged 20-24 still have the

Table 2.5 Percentage of Smokers in Canada and British Columbia by Age Group and Sex, 2001

	All Age Groups	12-14	15-19	20-34	35-44	44-65	65+
Canada							
Both Sexes[1]	21.7	3.0	18.3	26.1	27.1	24.9	10.4
Males	23.5	2.2[E]	17.7	29.5	29.2	27.3	11.7
Females	19.4	3.8	18.9	22.7	24.9	22.6	9.5
British Columbia							
Both Sexes	16.7	F	10.4	20.7	20.4	18.8	7.9
Males	17.9	F	10.1	22.5	21.9	22.2	9.0
Females	14.7	F	10.6	18.9	19.0	15.5	7.1

[1]Those reporting smoking daily.
Source: CTUMS, 2001 – Health Canada Tobacco Control Program

highest smoking rate of any age group at 32% (CTUMS, 2001). Even if this entire cohort quit smoking today they would remain at risk for lung cancer for many years. It is for these reasons that an already high and increasing proportion of newly diagnosed lung cancer cases will continue to be diagnosed among those who have quit smoking. Table 2.6 reveals the distribution of smokers according to smoking status, by age group and sex. There are indeed more former smokers in Canada in 2001 than current smokers.

Amid some of the discouraging statistics on smoking in Canada there is some good news. Overall, Canadians are moving towards a smoke-free society, albeit slowly. According to the Report on Smoking Prevalence in Canada, 1985-1999 (Gilmore, 2000), there have been statistically significant declines in current smoking prevalence of Canadian adults aged 15 and older between 1985 and 1999. The prevalence rate for smoking dropped from 35.1% in 1985 to 30.8% in 1991. From there, rates fell to 27.2% in 1996 and even further to 24.8% in 1999 (Gilmore, 2000). Unfortunately, the only age group in Canada to show a steady increase in smoking prevalence over the past 15 years are those aged 15-19.

Due to the high correlation of smoking and lung cancer (Burns, 2000) it follows that in order for a population based screening program to be cost-effective it is necessary to target a select group of people to screen for the disease. This model will target people who are current or former smokers and will use pack years as one of the qualifying criteria for screening. Pack years are a quantitative measure that combines the length of time and average number of cigarettes smoked by an individual over their lifetime. For example, if an individual smoked 1 pack of cigarettes/day (assuming 20 cigarettes in a pack) for 30 years they are considered to have a 30 pack year history. If another individual smoked ¾ pack/day for 20 years they are considered to have a 15 pack year history. Pack years are used routinely in screening studies when selecting a target population to screen, a population that would be at higher risk for developing lung cancer and therefore more likely to benefit from screening. Recent published literature on

Table 2.6 Smoking Status and Average Number of Cigarettes Smoked Per Day, by Age Group and Sex, Age 15+, Canada 2001

	Sex or age group	Population estimate ('000s)	Current smokers (%)	Former smokers (%)	Never smokers (%)	Average cigarettes smoked per day[1]
Canada	Total	24,916	21.7	23.8	54.4	16.2
	15-19	2,073	22.5	4.9	72.6	12.9
	20-24	2,097	32.1	9.3	58.5	13.9
	25-44	9,666	25.0	21.4	53.6	16.3
	45+	11,080	16.8	32.2	51.0	17.4
	Male (15+)	12,270	23.9	27.3	48.8	17.1
	15-24	2,132	28.2	6.8	64.9	14.5
	25+	10,138	22.9	31.6	45.5	17.7
	Female (15+)	12,646	19.6	20.5	59.9	15.0
	15-24	2,038	26.3	7.5	66.2	12.4
	25+	10,607	18.3	23.0	58.7	15.6
British Columbia	Total	3,342	16.7	22.8	60.6	14.6
	15-19	273	16.8	5.4*	77.8	11.4
	20-24	273	27.0	9.7*	63.3	10.6
	25-44	1,274	18.9	22.1	59.0	15.3
	45+	1,522	12.9	28.8	58.3	15.6
	Males (15+)	1,647	17.1	26.3	56.6	15.5
	15-24	278	23.8	8.2*	68.0	11.8
	25+	1,368	15.8	29.9	54.3	16.5
	Females (15+)	1,696	16.2	19.4	64.4	13.8
	15-24	268	19.9	6.9*	73.2	9.5
	25+	1,428	15.5	21.7	62.7	14.5

[1] Daily smokers only.
* Moderate sampling variability, interpret with caution.
Estimates may not sum to 100 percent due to rounding.
Source: CTUMS Annual Results, 2001 – Health Canada Tobacco Control Program

cohorts for lung cancer screening having targeted people with a 20 to 45 pack year history (Henschke, 2001). In this model, former or current smokers are required to have a minimum 20> pack years in order to be eligible for screening.

2.3 Screening for Lung Cancer

Screening for cancer is based on the premise that earlier diagnosis of the disease, either in the precancerous state or at an earlier stage than clinical symptoms would otherwise present, leads to a reduction in risk of mortality or development of invasive cancer. Morrison (1992) defines screening as "the examination of asymptomatic people in order to classify them as likely or unlikely to have the disease that is the object of screening." People who appear likely to have the disease are investigated further to arrive at a final diagnosis. The goal of mass screening or population screening is to reduce morbidity or mortality from the disease among people screened.

In order for a cancer screening program to be recommended as a cancer control strategy, 6 fundamental criteria must be fulfilled (Table 2.7). First, the disease should be an important health problem and sufficiently prevalent to warrant mass screening. Second, there should be a period when the disease is detectable in an asymptomatic individual (i.e., there should be a detectable preclinical phase). Arguments made earlier in this chapter support the notion that lung cancer has a detectable preclinical phase, although scientists continue to develop methods to improve this area. Third, the accuracy of the screening test should have acceptable sensitivity, specificity and predictive values. Sensitivity is defined as the proportion of truly diseased persons in the screened population who are identified as diseased by the screening test and is also known as the true positive rate (Last, 2000). It is a

Table 2.7 Criteria for the Evaluation of Screening

Criteria	Characteristic of Disease or Test?
1. Burden of disease	Disease
2. Detectable preclinical phase	Disease and screening test
3. Accuracy	Screening test
4. Acceptability	Screening test
5. Effectiveness	Disease and screening test
6. Cost effectiveness	Disease and screening test

Source: Drummond et al., 1997.

measure of the probability of correctly diagnosing a case. Specificity is defined as the proportion of truly non-diseased persons who are identified by the screening test. Specificity is a measure of the probability of correctly identifying a non-diseased person with a screening test. The predictive value of a screening test refers to the probability that a person with a positive test is a true positive (positive predictive value, PPV), while the negative predictive value (NPV) of a test is the probability that a person with a negative test does not have the disease. Both sensitivity and specificity, together with the prevalence of the disease in question, determine predictive value. These three variables are critically important to the economic analysis of a screening test as any false-positives or false-negatives incur unnecessary costs (at times excessive) to the overall programme.

Fourth, the test must be acceptable to patients and physicians. Physicians usually offer the first access point to screening tests used by the population. Although accuracy is important, the consequences of false-positive or false-negative test results and the acceptability of these consequences to providers and the public can influence the acceptability of a screening programme and thus its potential to contribute to cancer control efforts (Chamberlain, 1996).

Fifth, screening must be effective. The treatment of disease during the asymptomatic preclinical phase should be superior to treatment of symptomatic disease. Table 2.8 outlines survival rates for the varying stages of lung cancer diagnosis. The prognosis of lung cancer patients is strongly related to tumour stage at diagnosis particularly in NSCLC. When the tumour is diagnosed at Stage IA (tumour >3cm, surrounded by lung, no lymphatic or hematogenous metastases) prognosis is favourable with a 5-year survival of >80%. However, when diagnosed at more advanced stages 5-year survival drops markedly with almost no cure at Stage IV (distant metastases) (Mountain, 2000). Unfortunately, if diagnosed because of symptoms only 20-25% of NSCLC patients present at Stages I or II which are regard as respectable, whereas approximately

50% of patients present at Stage IV (Greenlee, 2000). This suggests that diagnosis of lung cancer at early stages may improve overall survival from this disease.

Whether or not lung cancer screening improves long-term survival in patients is at the centre of current debate and the focus of a large number of clinical studies. Regardless of the screening technique used in a number of trials worldwide, published results are mixed as to the effectiveness lung cancer screening has on reducing mortality (Miettinen, 2000). Many of the population-based randomized trials using CT and sputum cytology have been criticized for flawed study designs (Miettinen, 2000; Strauss, 1999) and scientists continue work to prove screening does benefit patients at high risk for lung cancer.

Alongside this quest is the economic efficiency of proposed screening programmes and this is the final measure that needs to be addressed. The cost and cost-effectiveness of screening should be acceptable and should not substantially exceed the cost for other preventive measures already in use. This criterion is the basis for the research carried out and presented in Chapter 6 of this paper.

2.4 Computer-Assisted Sputum Cytometry

Economic evaluations are often used to assess whether or not a new procedure, medical device or therapy is more beneficial and less costly than those currently being used. Although there are a number of screening tools being investigated to detect early stage lung cancer, there is no one technique or screening programme that is advocated within the health community (Bach, 2003). In practice, patients suspected of having lung cancer (due to past medical history and/or current symptoms) are followed up with chest x-rays and CT scans that may or may not lead to further testing. Spiral (or helical) CT scans are a more advanced X-ray imaging procedure in which multiple detectors are arrayed in parallel (referred to as multi-slice), enabling an image of

the entire thoracic cavity to be acquired in less than 20 seconds (Mulshine, 2003). The three-dimensional images obtained by spiral CT analysis offer several advantages over two-dimensional X-rays (Mulshine, 2003) and are used as a part of the sequentially screening process in this economic model. X-rays and CT scans subject patients to radiation levels that, although small, may be harmful. They are therefore considered to be invasive procedures. The only non-invasive screening technique used currently for the detection of early stage lung cancer involves sputum cytology (referred to as ASC in this paper).

The lung is a uniquely accessible organ for obtaining diagnostic samples. Not only do the airways provide a conduit for introducing a variety of endoscopic instruments, but the lung itself also produces secretions which, coughed up as phlegm (or sputum), can be collected for analysis. Sputum yields information about the lungs and airways and is distinguished from saliva, which consists of secretions in the mouth and gives information about the oral cavity. Conventional sputum cytology requires highly trained cytopathologists to interpret prepared sputum slides under a microscope. The problem with this method of sputum cytology has been the lack or obviousness of diagnostic cells in the sample as well as having subjective results that may be interpreted differently depending on the individual scientist. The method has been criticized for a variety of reasons and the literature contains mixed results about the efficacy of using it as a primary method for detecting lung cancer (Palcic, 2002 and Strauss, 1999).

The department of Cancer Imaging at the BCCA, in collaboration with a local Vancouver company (Oncometrics Imaging Corp.), have developed a semi-automated, high resolution quantitative microscopy system (CytoSavant) to enable detailed measurements of sputum derived DNA in cell nuclei. With a series of mathematical equations, the concentration and distribution of DNA and chromatin structures with the cell nucleus is characterized to determine if it is suspicious for early lung cancer. This system enables one to not only measure DNA amounts in cells but the size, shape, and texture of the DNA in the cell nuclei. The semi-

automated image cytometer includes a robotic effector, high resolution CCD video camera, software for feature analysis and an interface to computer software for calculating and expressing results of nuclear analysis in a cell gallery, bar graph, and DNA and chromatin distribution charts. Figure 2.2 shows a picture of the image cytometer. Currently, there is a clinical trial underway led by Perceptronix Medical Inc., Vancouver, B.C., to determine the clinical effectiveness of using the ASC method to screen for early stage lung cancer. In this trial, patients with a DNA index score of 1.2 or higher in 5 or more cells (out of 3000) are considered to have sputum that is atypical and further diagnostic testing is recommended.

In addressing the criteria outlined in Table 2.7 for the evaluation of a screening programme, ASC looks to be a promising tool for early lung cancer detection. It is considered a non-intrusive procedure that can be done quickly and with little discomfort to the patient. With respect to the accuracy of the ASC test, scientists at the BCCA have been working to increase the sensitivity of the test while maintaining a high level of specificity. To date they have been able to achieve 65% sensitivity at 90% specificity for early stage (Stage 0 and I) lung cancer (Palcic, 2002). This compares to only 14% sensitivity (at 99% specificity) using conventional sputum cytology. Improved collection and specimen preparation are being studied to further increase the accuracy of ASC.

Another area of potential promise in detecting early stage lung cancer is malignancy associated changes (MAC) which are defined as subtle morphological and physiologic changes that are found in normal cells of patients harbouring late stage malignant disease (Sun, 2002). Although the concept was not generally accepted in the past due to its subjective nature, recent advancements in image cytometry have refuelled the interest in MAC. Researchers postulate that these subtle changes can be observed more precisely with high resolution image cytometry (Ikeda, 1998) and preliminary data show a sensitivity of approximately 90%. Efficacy parameters associated with MAC are also analyzed in this economic evaluation.

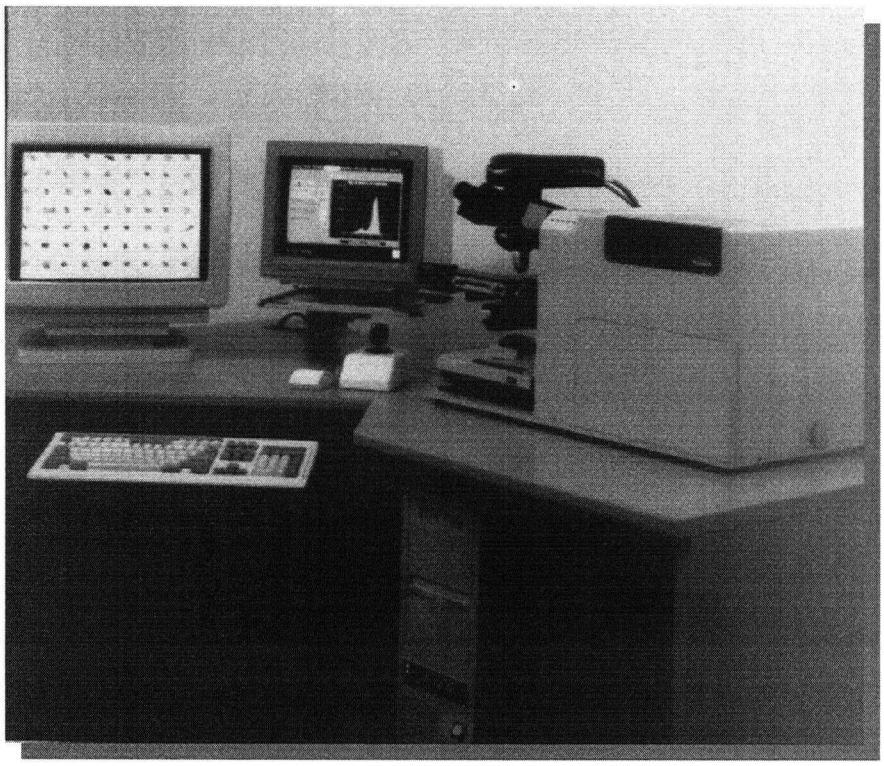

Figure 2.2 Computer-assisted image cytometer at the British Columbia Cancer Agency

Chapter 3. Health Economics

Health economics is a logical and explicit framework to aid health care workers, decision makers, governments, or society, in making decisions regarding the best use of resources. Limits on health care resources mandate that resource allocation decisions be guided by considerations of cost in relation to expected benefits. To facilitate critical allocation decisions, the best current information on both the efficacy of medical practices and their costs must be made available to decision makers in a systematic fashion that will allow them to make valid comparisons among alternatives. This chapter provides a brief overview of economic evaluations in health care and outlines key variables needed for a complete cost analysis of new a medical screening device for lung cancer.

3.1 Economic Evaluations

Modern health economics began its relatively young life in the 1950s and 1960s. In the 1950s famous American economists, such as Kenneth Arrow and Milton Friedman, started analysing the application of classic economic theory to health care and, in particular, to two possible uses: as an aid to decisions on how to allocate resources and as a vehicle for social reform (Jefferson, 2000). A decade later, the increasing pace of technological development and an ageing population, amongst other factors, necessitated the review of resource use with increasing frequency. Economists began publishing descriptive "cost-of-illness" studies dedicated to calculating the burden to society of particular health problems. It wasn't until the mid to late 1970s that economists began trying to adapt evaluative techniques of classic economics such as cost-benefit analysis to health care. The creation in the late 1970s of a single measure of outcome combining quantity and quality of life, which reflected people's preferences for health states, allowed health economists to go further in valuing outcomes of new

interventions. By the 1990s published studies that focused on economic evaluation had increased 8 fold (Jefferson, 2000) with more studies directed to new pharmaceutical products and the relationship between efficiency (achieving the maximal increment in health benefit) and effectiveness of medical interventions. It is likely that economic assessments will increasingly guide policy decisions in the future and this encourages those interested in population-based disease screening to supplement clinical research with economic evaluation.

Economic analysis seeks to identify and make explicit one set of criteria which may be useful in deciding among different uses for limited resources. Without systematic analysis it is difficult to clearly identify the relevant alternatives. For example, should a health care institution introduce a haemodialysis programme or an anti-hypertension therapy programme to prevent stroke? An economic analysis of the two choices would help decision makers determine which is more efficient in terms of cost and outcomes or which produces the most health benefits for the least amount of money. Drummond et al. (1997) define economic evaluation as:

> "the comparative analysis of alternative courses of action in terms of both their costs and consequences. Therefore, the basic tasks of any economic evaluation are to identify, measure, value and compare the costs and consequences of the alternatives being considered."

They emphasize that two central features are: (i) that evaluations deal with both inputs (costs) and outputs (consequences or outcomes) and (ii) that economic analysis concerns itself with choices between one or more alternatives. The main role of economic evaluation is to show the relative value of alternative interventions for improving health. Analyses provide information that can help decision makers in a wide variety of settings weigh alternatives and decide which best serve their needs in a particular health setting (Goodwin, 1998). Jefferson et al. (2000) have outlined important steps that should be taken in conducting economic evaluations.

Research steps for an economic evaluation:
Adopted from Jefferson et al., 2000.

- Specification of the question, and baseline comparison group
- Specification of the viewpoint, type and coverage of economic study
- Specification of the key outcome and estimation of effectiveness
- Specification of method for valuation of health outcomes
- Definition of costs to be estimated
- Estimation of differences in quantities of resource use
- Estimation of unit costs of elements of resource use
- Specification of analytic model
- Discounting of both costs and outcomes
- Taking account of time preference
- Summarize economic results
- Sensitivity analysis

The perspective or viewpoint of an economic evaluation is extremely important. The viewpoint for an analysis may be that of a specific provider or providing institution, the patient or groups of patients, a third-party payer (public or private) or society (Laaser, 1990). It is argued that a societal perspective, in which all costs and benefits associated with the introduction of a new program are considered, is the most appropriate (Laupacis, 1992). The ranking of cost-effectiveness ratios calculated from society's point of view should be neutral to value or distributional decisions. Cleary, it is difficult for the analyst to consider every single cost and consequence of a health care programme to all members of society. It is however important to recognize that in considering the use of community resources, the viewpoint of the providing institution may often be too restrictive and a broader viewpoint should be considered. For this particular lung cancer screening model it is most suitable to conduct the economic analysis from a societal view point since the programme is to be widely offered in and accepted by, society.

Evaluation of a screening programme involves the consideration of two issues. First, whether the proposed program is feasible, and second, whether it is effective. The total costs of a potential screening programme must be considered as well as the costs per detected per detected case of the disease (Kramer, 1999). Greater cost-effectiveness in screening programmes could be

achieved if the a specific population could be targeted, on the basis of risk factors, from which most incident cases would likely derive. If this were possible, those who are not at risk for a particular cancer would not undergo routine screening.

3.2 Methods of Economic Evaluations

All methods of economic evaluation have one principle in common: they examine one (or more) possible interventions and compare inputs or resources necessary to carry out such interventions with their consequences or effects. The various methods of economic evaluation differ in the way they itemise and value inputs and consequences. These differences reflect different aims and viewpoints of the decision-making problems. In order to make comparisons between available options it is necessary to find a common unit of value for each of the inputs of the health intervention. If it is relevant to the type of evaluation being conducted, the health consequences are also valued in terms of common units. The four major types of economic evaluation methods are described below.

Cost-minimisation analysis (CMA) – when consequences of the intervention are the same, then only inputs are taken into consideration. The aim is to decide the cheapest way of achieving the same outcome.

Cost-effectiveness analysis (CEA) – when the consequences of different interventions may vary but can be measured in the same units, then inputs are costed. Competing interventions are compared in terms of cost per unit of consequence.

Cost-utility analysis (CUA) – when interventions that are compared produce different consequences in terms of both quantity and quality of life, they are expressed in utilities. These are measures which comprise both length of life and subjective levels of well being. The best known utility measure is the quality-adjusted-life-years or QALYs. In this case, competing interventions are compared in terms of cost per utility or cost per QALY.

Cost-benefit analysis (CBA) – when both the inputs and the consequences of different interventions are expressed in monetary units so that they compare directly across programmes even outside health care.

The main consideration regarding the various methods of economic evaluation is the difference in the way the outcomes are measured, whether in actual number of life years gained, utilities, or monetary terms. CBA is the most detailed of the four methods but also requires significant effort in the design and analysis stages since health must be assigned a dollar value. For the evaluation of this lung cancer screening programme the approach used is that of cost-utility analysis.

In designing economic models that allow costs and outcomes to be valued many researchers use what is called a decision tree approach to comparing the various alternatives for a particular health problem. Decision trees have gained considerable popularity as a vehicle for undertaking economic evaluations as they can describe complex sequences of clinical alternatives. A decision tree flows from left to right beginning with the initial clinical choice or decision for a defined cohort of patients. As a result of the decisions made there will be outcomes of known probabilities that channel patients through the screening process and into the disease state if necessary.

3.3 Costs and Outcomes

Valuing inputs and outcomes (consequences) is the most difficult aspect of conducting economic evaluations. The values of resources are assigned by defining costs. These are considered by economists to be the benefits of opportunities foregone or the best possible alternative use of the same resources (opportunity costs). The opportunity cost of a treatment or intervention is the value of those resources if employed elsewhere (Sloan, 1996). Market prices are available for many of the resources used in health care (CT scans, bronchoscopy, and lung cancer treatment). The theoretical price for a resource is it's opportunity cost however, the pragmatic approach to costing is to take existing market prices unless there is some particular reason to do otherwise, for example if prices of some resources are subsidized by a third party.

3.3.1 Direct and Indirect Costs

Direct costs are those borne by the health care system, community and patients' families in addressing the illness. In this lung cancer screening model these direct costs include such things as the cost of the ACS test, CT scans, bronchoscopy, and treatment costs for the various stages of lung cancer. In a broader sense, direct costs also include the cost of operation of health facilities, land values, paid health professionals, and consumable supplies. Quite often, when new technologies are introduced there are a number of upfront direct costs such as purchasing equipment. It is necessary to determine the opportunity cost of this investment capital plus the depreciation of the equipment over an extended period of time. Annuitization of the depreciation and opportunity costs of capital is applied in such situations and often the cost of equipment is amortized over several years. With respect to the proposed model in this paper, it is assumed that facilities and equipment are currently in place for such diagnostic procedures to be carried out. While it is acknowledged that these are significant assumptions to be making in an

economic model, any extensive research to validate these assumptions is beyond the scope of this paper.

Indirect costs are mainly productivity losses caused by the problem or diseases, borne by the individual, family, society, or employer. Examples include loss of life, lost work time by patients and care-givers, lost leisure time, pain/suffering, bereavement, travel/incidental costs and environment costs. Indirect costs are much harder to measure and there are a variety of methods used by health economists to place a value on these items as they can still have significant effects of the total cost of new interventions. Measurement techniques include the willingness-to-pay approach and contingent valuation (O'Brien, 1994) but they are not the focus of this paper and the costs addressed in this model include only limited indirect costs.

3.3.2 Discounting

Inputs and consequences of a health intervention accrue at different times, especially for chronic diseases and the population based programmes addressing them. In this case, we cannot directly compare the inputs of a programme today with its consequences which may accrue in 5 or 10 years time. Economists 'bring forward' the value of such consequences by using a technique called discounting. This allows the calculation of the present value of inputs and benefits which would accrue in the future. Discounting is based mainly on a time preference which assumes that individuals prefer to forego a part of the benefits if they can accrue them now, rather than accruing them fully in the uncertain future (Jefferson, 2000). The strength of this preference is expressed by the discount rate which is applied in economic evaluations. The choice of a discount rate and the choice of which items it should be applied to are a matter of debate among economists. Recent published studies assessing the cost-effectiveness of lung cancer screening using helical CT scans employed discounts rates of 3% to 5% for costs and life years (Marshall, 2001; Mahadevia, 2002; Henschke, 2000). These are reflective of values most

commonly used in medical literature (Goodwin, 1998; Krahn, 1993). In the model constructed for this project, a 10 year follow-up time line for costs and a 50 year follow-up time for benefits are applied since screening for lung cancer has benefits that accrue in the future. A discount rate of 3% is used of for both costs and QALYs in this model which reflects the guidelines put forth by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA, 1997).

3.3.3. Outcome Measures

The goal of a new medical intervention is to improve the health status of a target population. In this cost-utility analysis the clinical outcome used to measure the health benefit is the number of quality-adjusted life years gained. It is hypothesized that the earlier lung cancer is detected in an individual, the greater the chance for long term survival and accrual of maximal life years. Due to time constraints, most randomized controlled trials are not able to follow patients for their entire lifetime and so outcomes are measured over a shorter predetermined time frame. When using a decision model to simulate the inputs and outcomes of a hypothetical cohort, time can be easily adjusted to allow for longer follow-up. More complete results are achieved in terms of life years gained by using ASC as an initial screening tool for lung cancer. Cost-utility will be reported in terms of cost per QALY gained. The incremental cost-utility ratio between screening strategies will be presented to summarize results.

There is considerable argument in economic evaluations that evaluate screening programmes to use cost-utility or cost-benefit analysis. Both types of evaluation reflect the fact that there is a difference in the quality of life for patients living with early stage lung cancer compared to those patients living with end stage disease. Quality of life measures describe the subjective level of well-being among patients and the use of the QALY is the most common method for incorporating such criteria. Within the field of health economics there is extensive debate over the validity of methods used to measure quality of life. Utility analysis is viewed as a

useful technique because it allows for quality of life assignments to a given set of treatment outcomes, while simultaneously providing a generic outcome measure for comparison of costs and outcomes in different programmes. The QALY is arrived at by adjusting the length of time affected with the health outcome by the utility value on a scale of 0 to 1 where 0 indicates death and 1 indicates perfect health. The adjusted time in each health state is summed to calculate the number of quality-adjusted life years over an entire lifetime (or as long as patients are followed). The QALY measure can capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) and integrate them into a single measure. Figure 3.1 provides a visual representation of how QALYs are used and how they affect the health benefits of a programme.

3.4 Statistical Variables and Probabilities

The decision model for evaluating the cost-effectiveness of 3 different approaches to lung cancer screening incorporates many statistical variables into the algorithms. When creating such a model it is necessary to make assumptions about a large proportion of parameters that affect the results and it is often argued that validity of cost-effectiveness results are only as good as the assumptions they are based on.

3.4.1 Probability Inputs

Disease prevalence is especially important in the beginning phase of a lung cancer screening model. This value will determine how many lung cancer cases actually arise in the hypothetical cohort and how many cases exist for detection with screening. Estimates of probabilities used in a decision model should come from previous randomized, controlled studies

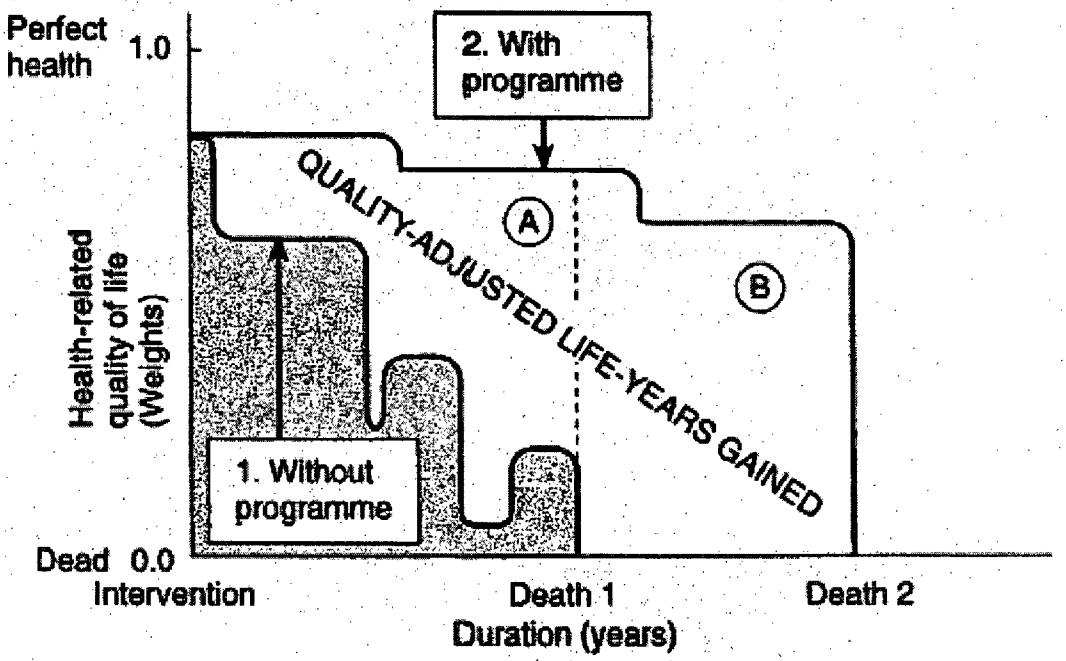

Figure 3.1 QALYs gained from an intervention

Without the health intervention the individual's health related quality of life would deteriorate according to the lower curve and the individual would die at time Death 1. With the health intervention the individual would deteriorate more slowly, live longer, and die at time Death 2. The area between the two curves is the number of QALYs gained by the intervention. Part A is the amount of QALY gained due to quality improvements and Part B is the amount of QALY gained due to quantity improvements (Adapted from Drummond et al., 2002).

published in peer-reviewed literature to reduce the level of uncertainty surrounding the assumptions. In this economic model, clinical data from the Lung Health Study (refer to Chapter 5), conducted at the BCCA, will aid in determining a prevalence detection rate of lung cancer in a high risk cohort screened using the proposed technique of ASC.

As discussed in Chapter 2, the sensitivity and specificity of the screening tests also play a significant role in the results of an economic analysis. The decision tree incorporates 3 sequential techniques used to screen for lung cancer including ACS, CT scan and bronchoscopy. Each of these procedures has its own sensitivity and specificity. Again, these values are taken from published results of previous lung cancer screening studies and can be varied in a sensitivity analysis described in the next section.

Lastly, there are transition probabilities associated with the various stages of lung cancer in the decision tree. Patients in the model will not necessarily stay in the same state for the entire follow-up period but rather move from one state to another. For example, the probability of moving from early stage lung cancer to late stage lung cancer is different that the probability of moving from late stage cancer back to a healthy state. Similarly, the chances of a patients moving to a death state and no longer accruing life years, varies depending on the stage of the disease. Transition probabilities for disease survival and remission as well as natural mortality (life tables) are used in this model.

3.4.2 Sensitivity Analysis

Models are an attempt to capture and summarise reality. However, the effects of health care are often uncertain and our models tend to be based on real data (epidemiological, clinical, or resource data) which are sometimes incomplete, of uncertain quality, or simply not available. Epidemiology, for instance, provides us with an estimate of probabilities (of developing lung cancer, moving from one disease stage to another or dying from lung cancer).

Where data are absent or of questionable certainty, the gap may be filled using assumptions. To deal with uncertainty in models of this type, economic evaluations use a technique called sensitivity analysis which repeats the comparison between inputs and consequences while varying the assumptions within a likely range. In other words, sensitivity analyses test the robustness of conclusions by varying the probabilities that have uncertainty around them. (Jefferson et al, 2000). Variables can be altered on an individual basis or in combination with one or more additional variables in a multi-way sensitivity analysis. Since this model incorporates a large number of variables, each with a distinct range of plausible values, sensitivity analyses compare a base case analysis to using the most favourable and least favourable set of input variables. Depending on the outcome of one way sensitivity analyses, those variables found to have the greatest effect on cost-utility outcomes can be varied simultaneously in a two or three way sensitivity analysis.

Chapter 4. Literature Review

4.1 Introduction

With increasing interest in the way that health care dollars are spent, there is greater focus on cost-effectiveness in medical research. Since the early 1990s the number of cost-effectiveness analyses (CEA) published has nearly tripled (Figure 4.1). The popularity of cost-effectiveness analysis over cost-benefit analysis (CBA) is due to methodological difficulties with the latter that require all inputs and consequences to be valued in dollars. New benefit measurement techniques such as willingness-to-pay and conjoint analysis may rekindle CBA over time (Jefferson, 2000).

It is important to point out the use of terms in medical literature that refer to the various methods of economic evaluations. North American economists often use the term CEA to include both cost-minimization analysis (CMA) and cost-utility analysis (CUA). The titles of published economic evaluations are not always accurate indicators of the type of economic evaluation actually conducted and it is up to the reader to assess how inputs and consequences are measured. Table 4.1 outlines the criteria for various types of economic evaluation. For a complete analysis, the cost and consequences must be examined for each alternative and then those alternatives must be compared to one another.

To evaluate the data from economic studies on lung cancer screening it is worth discussing the cost-effectiveness of other screening programmes currently in place in the health care community. In addition, it is useful to have some insight into the costs of treating lung cancer and the disease's financial burden on society. For these reasons, this chapter includes information from published literature that should offer some added perspective on the results of economic studies in lung cancer screening.

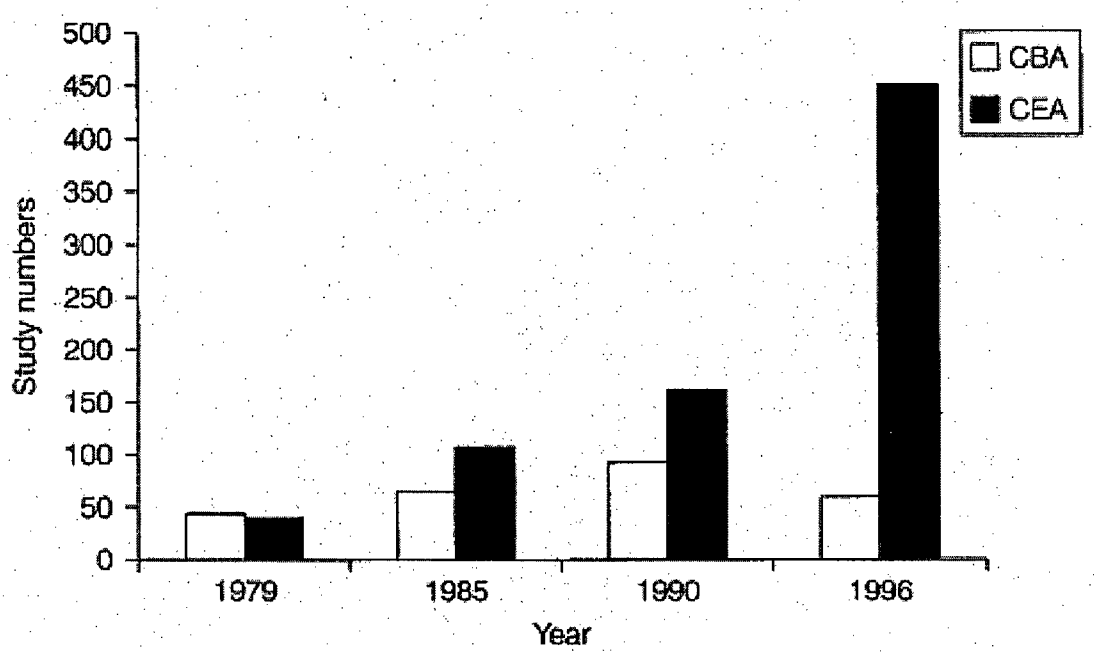

Figure 4.1 Trends in the number of published cost-effectiveness studies
CBA-Cost benefit analysis, CEA-Cost effectiveness analysis
(Adopted from Elixhauser, 1998).

Table 4.1 Distinguishing Characteristics of Published Economic Health Care Evaluations

Is there comparison of two or more alternatives?	Are both costs (inputs) and consequences (outcomes) of the alternatives examined?		
	NO		**YES**
NO	Examines only consequences	Examines only costs	
	PARTIAL EVALUATION		PARTIAL EVALUATION
	Outcome description	Cost description	Cost-outcome description
YES	PARTIAL EVALUATION		FULL EVALUATION
	Efficacy or effectiveness study	Cost analysis	Cost-minimization analysis Cost-effectiveness analysis Cost-utility analysis Cost-benefit analysis

4.2 Data Sources and Methods

For this literature review, the focus was on studies in which a cost-effectiveness or cost-utility analysis was the central aim of the research. Several computerized, bibliographic databases were searched including PUBMED, EMBASE, HealthSTAR, OVID, and CancerLit. A combination of search terms was used to narrow the search to economic studies rather than studies relating to the clinical effectiveness of screening for lung cancer. "Lung cancer screening and cost" as well as "lung cancer screening and cost-effectiveness" were the search terms used most frequently. In addition, "lung cancer and economics" and "lung cancer and cost", were terms used to capture a broader spectrum of the cost of this illness in the health care setting.

Selection criteria for these scientific articles limited the studies to those published in English between January 1990 and January 2003. Due to limited data on the economics of lung cancer screening programmes, editorials, commentaries, and results presented in government publications (in Canada only) were considered and reviewed for relevant information. Letters, unpublished studies, and summaries of presentations given at medical conferences or brief transcripts of meetings were excluded. Only data provided in the reports were considered with the exception of 1 study by Chirikos et al. (2002), in which a technical report, providing further detail on the economic model, was obtained from the authors.

The articles selected for inclusion in this review were categorized into 3 groups. Group A contained articles whose central focus was a CEA or CUA of lung cancer screening. Group B contained articles with an incomplete economic analysis or with data relating to the cost of treating/managing lung cancer. Lastly, articles relating to other cancer screening programmes or the cost-effectiveness of other medical interventions were placed in Group C. It should be noted that studies falling into Group C were selected from articles published between 1990 and 2002 found using search terms that incorporated other cancers (breast, colorectal, prostrate, cervical),

screening and cost-effectiveness. Only studies that had a complete economic analysis of screening were considered for inclusion in Group C.

The scientific quality of the selected articles was assessed according to criteria developed by Drummond et al. (1997) for the critical appraisal of a published article in health economics. A critique of each study in Group A is also presented in the discussion (Section 4.4).

4.3 Results

Upon searching several bibliographic databases revealed a variety of studies relating to the economics of lung cancer were found. However, only a small number of articles were directly related to the economics of lung cancer screening and more specifically there were only 7 eligible published studies that contained a complete economic evaluation of a lung cancer screening strategy. Table 4.2 outlines the number of eligible and ineligible citations identified through the different databases. There was overlap between different databases and the number of studies unique to any one database is given in brackets in Table 4.2. Many of the studies on cost-effectiveness focused on staging and/or treatment options for lung cancer and were therefore eliminated. An equal number of papers examined the clinical effectiveness of screening or treating lung cancer and were also classifieds as ineligible for review. Despite the fact that such articles on clinical efficacy of lung cancer screening were not reviewed in this chapter, data from these studies was used in the modeling section of this paper. It should be noted that 2 of the studies written in Japanese (Baba et al., 1998 and Iinuma et al., 1988), although eliminated, had abstracts showing the article contained cost-effective analyses related to lung cancer screening. Table 4.3 summarizes the number of eligible articles in each of Group A, B and C.

Table 4.2 Number of Citations and Details on Ineligible Studies Identified Through Different Databases.

	PUBMED (dates)	**EMBASE**	**HealthSTAR**	**CancerLit**	**OVID**	TOTAL (# in brackets)
Total Number of Citations	118(118)*	71(24)	85(25)	108(17)	77(9)	193
Total Eligible Citations	19(19)	12(3)	14(5)	19(4)	14(1)	32
Group A Studies	7(7)	4(0)	5(0)	2(0)	1(0)	7
Group B Studies	12(12)	8(3)	9(5)	17(4)	13(1)	25
Total Ineligible Citations	99(99)	59(21)	71(20)	89(13)	63(8)	161
1. Studies focused on C/E of staging or treatment of LC	32(32)	17(3)	16(4)	24(5)	22(1)	45
2. Studies on clinical effectiveness of screening/treatments for LC	31(31)	11(1)	26(7)	21(2)	18(4)	45
3. Studies focused on other cancers	10(10)	15(8)	11(5)	19(0)	14(3)	26
4. Studies not in English	11(11)	3(0)	5(0)	13(1)	0	12
5. Studies focus on decision analysis design strategies	1(1)	3(2)	7(2)	4(0)	2(0)	5
6. Studies published prior to 1990	14(14)	10(7)	6(2)	18(5)	7(0)	28

*# in brackets ( ) indicates those articles unique to that particular database

Group A Studies

Most cost-effectiveness studies in lung cancer screening have focused on chest x-ray or CT scans as the methods of early detection for lung cancer. There are no published studies that assess the cost-effectiveness of using ASC an initial screening test for lung cancer. Table 4.4 presents a summary of the 7 published cost-effectiveness analyses. All results have been inflated to 2002 US dollars to facilitate comparisons across studies. Of the 7 studies in this grouping, 5 of them were conducted in the United States and 2 in Japan. All of the studies compare one or more screening alternatives to no screening. There is a wide range of costs per life year gained reported in these studies due to differences in model assumptions and parameters used in the studies. A 1-time prevalence screening program may cost as little as $6,414 per life year saved (Marshall et al., 2001) and as much as $94,047 per life year saved (Chirikos et al., 2002) with an annual 5-year screening programme. The only study to incorporate QALYs in cost-utility ratios was the most recent one conducted by Mahadevia et al. (2003) out of Johns Hopkins Medical Centre in Baltimore. This is the most complete economic evaluation from the perspective of health economists, many of whom believe that quality of life plays an important role in cost-effectiveness. The base-case analysis from this study, which models screening in current smokers annually for 20 years, resulted in a cost-utility ratio of $118,139 per QALY. A critical assessment of these 7 studies was carried out according **to** the criterion set out by Drummond et al. (1997) in evaluating economic evaluations (Table 4.5). Results show a varying degree of thoroughness among the economic decision models. It was unclear as to the perspective of the economic analysis in the papers published by Caro et al. (2000) and by Okamoto (2000). In a number of the studies, important costs were omitted (Marshall et al., 2001 and Caro et al., 2000) and although all costs and consequences were measured in appropriate

Table 4.3 Summary of Articles Selected for Inclusion in Literature Review

	Focus of Study	Number of Eligible Articles
Group A	Complete economic analysis of a lung cancer screening strategy	7
Group B	Incomplete economic analysis of a lung cancer screening strategy, economic data on cost of treatment/management of lung cancer, economic burden of disease studies	21
Group C	Cost-effectiveness of other cancer screening strategies and other medical interventions, acceptable cost-effectiveness ratios in the health community	11

Table 4.4 Detailed Review of 7 Group A Studies – Full Economic Evaluations

Authors Date/Location Dollar Values	**Type of Economic Evaluation**	**Target Population Frequency of Screening**	**Lung Cancer Screening Technique(s) Used**	**Parameters**	**Cost-Effectiveness or Cost-Utility**	**C/E Adjusted for Inflation to 2002 US$**
Mahadevia et al. 2003/Baltimore 2001 US$$	Cost-utility (QALYs gained)	60 yrs old, (55% male) 100 000 hypothetical cohort 20> Pack Years Annual screen for 20 yrs Follow-up for 40 yrs	Helical CT scan	50% stage shift LC Incidence 0.43 Lngth/Overdiag.bias: 200% Current Smokers	$116,300 per QALY	$118,139 per QALY
					$42,500 per QALY (favourable estimate)	$43,172 per QALY
Chirikos et al. 2002/Florida 2000 US$$	Cost-effectiveness (life yrs gained)	45-74 yrs old Annual screen for 5 yrs Follow-up for 15 yrs	Low-Dose Helical CT (no contrast – 1st screen) (with contrast – diagnostic)	100% participation 50% localized LC w/screen Life yrs not discounted	$33,884 per life yr	$35,400 per life yr
				30% localized LC w/screen Least favourable assumpt.	$90,022 per life yr	$94,047 per life yr
Marshall et al. 2001/California 1999 US$$	Cost-effectiveness (life yrs gained)	60-74 yrs old (45% male) 100 000 hypothetical cohort 45 Pack Years (median) 1 time prevalence screen Follow-up for 5 years	Low-Dose Helical CT	LC prevalence 2.7%	$5,940 per life yr	$6,414 per life yr
				LC prevalence 0.7%	$23,100 per life yr	$24,944 per life yr
				1-year lead time bias	$58,183 per life yr	$62,828 per life yr
Marshall et. al. 2001/Hamilton 1999 US$$	Cost-utility (life yrs gained)	60-74 yrs old 100 000 hypothetical cohort Annual screen for 5 years	Low-Dose Helical CT	LC prevalence 2.7%	$18,968 per life yr $19,522/QALY	$21,080/QALY
				1-year lead time bias	$61,723 per life yr $50,473/QALY	$54,502/QALY

Table 4.4 cont'd.

Authors Date/Location Dollar Values	**Type of Economic Evaluation**	**Target Population Frequency of Screening**	**Lung Cancer Screening Technique(s) Used**	**Parameters**	**Cost-Effectiveness or Cost-Utility**	**C/E Adjusted for Inflation to 2002 US$**
Raab et al. 1997/Iowa City 1995 US$$	Cost-effectiveness (life yrs gained)	1 male patient with suspected LC (peripheral vs central lesion) 1 time screen	Sputa (S) 3 day pooled FNA (F) Thoracoscopy (T) Bronchoscopy (B) Expectant management (E)	Sputum Sensitivity (Central) 0.4 (Peripheral) 0.2	Central Lesions: Sputa as initial test dominated[+]	Dominated (less costly, more effective)
				Sputum Specificity (Central) 0.95 (Peripheral) 0.95	Peripheral Lesions: $27,600 per life yr for SFBE vs FBE	$32,580 per life yr
				Pretest probability of local NSCLC 0.3	Sputa prior to F, FBT, T dominated[+]	Dominated (less cost, more effective)
Okamoto, N. 2000/Japan	Cost-effectiveness (life yrs gained)	Mass Screening (1983) Mass Screening (1993) CT Screening (1993) Males 55+, females 65+	Chest X-ray Chest X-Ray/sputum cytol. CT scan	5 yr survival 60% with CT (50% stage shift)	1983 and 1993 yen converted to 2002 US dollars	$59,000 per life yr (1983 mass screen) $35,800 per life yr (1993 mass screen) $29,500 per life yr (1993 CT screen)
Caro et al. 2000/Massachusetts 1998 US$$	Cost-effectiveness (life yrs gained)	45-80 yr old males only 100 000 hypoth. cohort Heavy smokers Annual screen	Chest X-ray	Mortality reduction 18% 100% participation	$19,874 per life yr	$21,935 per life yr
					$35,772 per life yr (10% mortal. reduct)	$39,481 per life yr
					$23,526 per life yr (50% participation)	$25,965 per life yr
Baba et al. 1998/Japan	Cost-effectiveness (life saved)	40-80 yr old General population 1 time screen	Chest X-ray	Clinical data used LC prevalence 0.09%	$93,000 per life saved (50+ yrs old)	$102,646 per life saved
					$51,400 per life saved (70+ yrs old)	$56,730 per life saved

Table 4.5 Critical Evaluation of Group A Studies – Full Economic Analyses

Criterion for Evaluation of an Economic Analysis	Mahadevia et al.	Chirikos et al.	Marshall et al. (1x prev. scrn.)	Marshall et al. (5x annual scn)	Caro et al.	Okamoto, N.	Raab et al.	Baba et al.
1. Was a well defined question posed in answerable form?	Y	Y	Y	Y	P	P	Y	P
2. Was a comprehensive description of the alternatives given?	Y	Y	Y	Y	N	P	Y	Y
3. Was the effectiveness of the programmes or services established?	P*	P	P	P	P	P	P	P
4. Were all the important and relevant costs and consequences for each alternative identified?**	Y	N	N	Y	N	P	Y	P
5. Were costs and consequences measured accurately in appropriate physical units?	Y	Y	Y	Y	Y	Y	Y	P
6. Were costs and consequences valued credibly?	Y	Y	Y	Y	Y	Y	Y	Y
7. Were costs and consequences adjusted for differential timing (discounting)?	Y	only costs	Y	Y	only costs	N	Y	N
8. Was an incremental analysis of costs and consequences of alternatives performed?	Y	Y	Y	Y	N	Y	Y	N
9. Was allowance made for uncertainty in the estimates of costs and consequences?	Y (extensive)	Y (minimal)	Y	Y (extensive)	Y (minimal)	Y (minimal)	Y (minimal)	N
10. Did the presentation and discussion of study results include all issues of concern to users?	Y	Y	Y	Y	N	N	P	N

* = Partially done (i.e. the clinical effectiveness of lung cancer screening is still being debated in the medical literature)
** = Only the study conducted by Mahadevia et al. incorporated some opportunity costs into the economic model

units, two models did not discount life-years gained, Chirikos et al. (2003) and Caro et al. (2000). All studies incorporated some degree of sensitivity analysis for input variables in the models, although there was some question regarding the range and choice of variable tested. Due to controversial medical data currently surrounding the clinical effectiveness of various lung cancer screening strategies (i.e. whether screening actually reduce mortality), each of these 7 studies only partially fulfilled the requirement that programmes be screening efficacy be clinically established.

Group B Studies

There were a number of instances when cost-effectiveness results were presented alongside studies assessing the clinical effectiveness of lung cancer screening strategies. In all cases, these were not complete economic analyses but rather crude estimates of the costs related to one particular method of screening. For example, in a study conducted by Sone et al. (2001) in Japan that evaluated a mass screening programme for lung cancer using CT scans, the cost per life year gained from screening was estimated to be $21,296 (2000 US$) for women aged 55 to 59 and $8,148 for men aged 55 to 59. Incorporating a higher detection rate of lung cancer using CT scans, the authors reduced the costs to approximately $2,290 for women and $728 for men to save a life year in the 55 to 59 year-old patients.

In a proposed screening model designed by Maccabbee (1994), chest x-ray was used to screen smokers between the age of 50-75 with a >20 pack year smoking history with a 1-time prevalence screen. Estimates of cost-effectiveness reported were $7,140 per life year gained. Assumptions in this crude model include a 10% decrease in mortality from chest x-ray screening and 100% participation by 13 million Americans. More recently, Nakhosteen (2000) outlined the costs associated with a proposed feasibility study on the detection of early lung carcinoma in Germany. Techniques used to screen 5000 high risk smokers (>30 pack years), aged 50-74 and

1000 industrially exposed smokers, included the use of the CytoSavant for sputum cytometry, the same device put forth in this research, as well as the LIFE-LUNG bronchoscope also used as a third line diagnostic tool in this research. Crude costing for such a programme was estimated at 1,715,282 Euros (2,620,905 CDN$) for screening and 737,500 Euros (1,126,869 CDN$) for treatment of screened patients. The author concluded that such a feasibility study would exceed the cost of present day diagnosis and therapy by approximately 1.1 million Euros (1,680,770 CDN$).

With respect to diagnostic costs, only a study by Goldberg-Kahn et al. (1997) used a decision analytic model to compare four strategies (fine-needle aspirate (FNA), sputum cytology, bronchoscopy, and open biopsy) for the workup of a solitary radiographic lung lesion (a 2.8cm lesion in a 51.4 year-old patient who smokes 15 cigarettes per day). Outcomes were expressed in terms of cost per correct diagnosis. Results showed open biopsy to be the best initial procedure with a cost per correct diagnosis of $12,888 (1996 US$). Sputum examination had the highest cost at $63,424 per correct diagnosis with FNA and bronchoscopy in between at $21,543 and $16,615 respectively. Sputum cytology was the preferred strategy only when the patient was not a surgical candidate, the lesion size was large (>4.7cm) and only if sputum sensitivity was greater than 45%. It should be emphasized that this study focused only on costs and not health outcomes.

Finally, the Health Analysis and Modeling Group at Statistics Canada have produced a number of reports on the costs associated with lung cancer diagnosis and treatment in Canada. A micro simulation model called POHEM (Population Health Model), designed by this group, provides a framework for integrating diverse data and analytical results in the health discipline (Will, 2001). POHEM creates synthetic populations at birth and provides them with demographic and labour force characteristics. It incorporates and reconciles data on risk factors, disease onset and progression, health care resources utilization, direct medical care costs and health outcomes

(Wolfson, 1992; Houle, 1997). POHEM currently models lung cancer, breast cancer, coronary disease, arthritis and dementia and soon to be completed colorectal cancer (Will, 2001).

Although POHEM primarily assess the cost-effectiveness of diagnostic and therapeutic options for lung cancer, an evaluation of lung cancer screening using POHEM was presented by Berthelot et al. at the 14th Annual Meeting of the International Society of Technology Assessment in Health Care (Ottawa, 1998). Results from this decision model evaluating sputum cytology testing as a screening tool in a 50 year-old cohort, where chemoprevention is assumed to be 45% effective at reducing lung cancer, showed the cost per life year saved to be between $42,000 (1998 CAN$) and $58,000 depending on frequency of screening. These same parameters applied to a 65 year-old cohort reduced the cost per life year saved to between $39,000 and $25,000. Both scenarios applied sensitivity and specificity values of 0.82 and 0.65 respectively for sputum cytology. No discounting was performed and no quality of life measures were built into this particular model.

Group C Studies

For comparison, cost-effectiveness and cost-utility results for other cancer screening strategies as well as other medical interventions are reported in Table 4.6. These studies were not selected in a random fashion, but rather to provide focused comparisons with interventions or target populations that many agree are cost-effective and have costs per life year gained in the same range as lung cancer screening estimates. Although there is no clearly stated cut-off for the acceptance of interventions as being cost-effective, interventions that have cost-effectiveness equal to or less than $50,000 (U.S.) per life year gained are considered to be acceptable (Goodwin, 1998). Canadian authors Laupacis et al. (1992) evaluated cut-off limits based on

Table 4.6 League Table of Various Health Care Inventions Including Other Cancer Screening Strategies

Other Screening Interventions	Cost per life year/Cost per QALY (2000 US dollars)	Reference
Nicotine gum (vs no gum) and smoking advice for persons 35-69 yrs old	$13,100 per life yr	Strauss
Annual cervical screening for women >60 yrs old	$15,600 per life yr	Strauss
Annual mammography and breast examination (vs just examination) for females 40-64 yrs old	$24,100 per life yr	Strauss
Mammography screening vs no population based screening for women 45-69 yrs old	$18,000 per QALY	Earle
Colorectal cancer screening for persons >40 yrs old	$6,400 per life yr	Strauss
Colonoscopy for colorectal cancer screening for persons >40 yrs old	$127,700 per life yr	Strauss
Hypertension screening in asymptomatic persons 60 yrs old	$19,900 per life yr	Tengs
Hypertension screening every 5 yrs for men 55-64 yrs old	$41,900 per life yr	Tengs
Screen blood donors for HIV	$19,900 per life yr	Tengs
Bone mass screening for perimenopausal women 50 yrs old (plus treat if <1.0 g/cm^2)	$25,500 per life yr	Tengs
Smoking cessation advice for men 50-54 yrs old	$1,340 per life yr	Tengs
Smoking cessation advice for women 50-54 yrs old	2,300 per life yr	Tengs
Nicotine gum (vs. no gum) and cessation advice for men 35-69 yrs old	$10,150 per life yr	Tengs

grades of recommendation for the adoption and appropriate use of new technologies. The group concluded that technologies that cost less than $25,500/QALY (2002 CDN$ adjusted for inflation) are almost universally accepted as being appropriate ways of using society's and the health care system's resources. Many technologies costing between $25,500/QALY and $128,000/QALY are provided routinely, but the availability of some is significantly limited.

Tengs et al. (1995) have published a comprehensive list of life saving interventions and their associated cost-effectiveness (N=587). Included in the review were studies on environmental, health care, toxin control, transportation and occupational interventions. As the data in Table 4.6 shows, other cancer screening strategies such as breast, cervical and some colorectal cancers are considered cost-effective. The literature review study found the median cost per life year saved in the health care sector (N=310) to be $23,550/life year (adjusted to 2002 dollars) (Tengs et al, 1995). No lung cancer screening strategies were included in the analysis.

4.4 Discussion

After examining the literature for published studies on the cost-effectiveness of lung cancer screening it is clear that there is considerable debate on the success of such programmes. Much of the research being conducted relates to the clinical effectiveness of screening devices in this field since there is no gold standard advocated in lung cancer screening as of yet. These types of studies were not reviewed in this paper.

All of the papers reviewed were written in English and a large proportion (5 out of 7) of the Group A studies (containing full economic evaluations) were carried out in the United States which could lead to publication bias. With respect to difference among countries where these studies were conducted, the United States and Canada are known to have similar demographics

and disease incidence for lung cancer, but do have different clinical practice patterns and health care system incentives. As well, all Group A studies were based on decision analysis models that were constructed based on clinical assumptions and results from other medical literature.

There can be a challenge in making comparisons across studies because of varying results from clinical trials evaluating the efficacy and effectiveness of lung cancer screening. Researchers are able to choose input variables for decision models on lung cancer screening from a large number of clinical studies and therefore results may be biased in favour of reducing cost-effectiveness/utility ratios. Mahadevia et al. (2003) used weighted averages of some variables such as lung cancer prevalence, false positives and test sensitivity and specificity. Until screening for early stage lung cancer is proven to be clinically effective, (i.e. reduces mortality), no wide spread, population based screening programme will be advocated. This does not mean however, that such economic analyses are irrelevant since physicians and oncologist in this field are currently using many of these detection strategies regularly.

Only one economic model included quality of life among lung cancer patients (Chirikos et al., 2002) and as such incorporates the widest scope of input variables into the decision model. This study does not however discount quality of life years but does discount costs and therefore the resulting cost-utility ratios are underestimated. Without a doubt, there are methodological differences in each of these studies and all the results should be interpreted with some caution. The recommended target population for lung cancer screening is an older cohort of current or former smokers. It is rare that cancer screening programmes are offered to the general population but Chirikos et al. (2003) evaluated a model for lung cancer screening without targeting a high risk population thereby generating very conservative results.

Group B studies were chosen for review because the results can be of assistance to other researchers in this field and to this project. The Goldberg-Kahn study (1997) conducted in Nebraska, U.S., focused only on the difference in cost per correct diagnosis for a variety of

diagnostic procedures in lung cancer including conventional sputum cytology. Results such as these can be of use in future economic decision analysis models and should guide further research into which input variables are most influential in such evaluations.

Canadian statistics offer a more accurate picture of the burden on lung cancer in this country and the micro simulation model constructed by Health Canada aids in creating a clearer picture of diagnosis and treatment costs for this disease. POHEM has only analyzed a rudimentary model for lung cancer screening at this point in time and inclusion of many pertinent variables still need to be added to the model (i.e. discounting, quality of life, and sensitivity analysis for costs).

Using $50,000 US per life year gained as an acceptable cut-off for health interventions means that many of these decision models show lung cancer screening to be moderately cost-effective, provided certain clinical findings are validated with randomized-controlled trials. The origins of the $50,000 figure are murky but might be traced to 1973 when the United States congress decided that government would pay for haemodialysis for patients with end-stage renal disease. As a result, the cost-effectiveness of this, $50,000 per life year has become standard. There is some evidence that the relative prices of medications and surgical procedures tend to be higher in the United States than in other countries (Drummond, 1992, 1994).

It is useful to compare the cost-effectiveness associated with other cancer screening programmes already in place. Earle et al. (2000) have published an extensive league table of cost-effectiveness ratios for various medical interventions. The results are presented in terms of cost per QALY in 1998 US dollars. Table 4.6 includes some examples. The first widely accepted breast cancer screening programme in Canada was designed and evaluated at the BCCA in British Columbia and the methodology behind this successful programme can help guide the province's lung cancer screening model.

From a health economist's point of view, the best time to conduct cost-effective analyses is alongside randomized-controlled trials. There were no studies that addressed the cost-utility of using ASC as a first screening tool as is proposed this paper. In addition, as the role of health economics in medical interventions continues to strengthen, more studies are expected to be published in this area.

Chapter 5. The Lung Health Study at the British Columbia Cancer Agency

As part of this research, the effectiveness of using computer ASC in a clinical setting is evaluated and the results form the basis for further assumptions that are built into the economic model constructed in Chapter 6.

5.1 Introduction

Since there is little research on the use of ASC in detecting early stage lung cancer it is helpful to incorporate results from current field studies into the economic model. This will prevent having to use disease prevalence, staging shifts and other data on lung cancer that was obtained using different screening algorithms than the one proposed in this paper.

The Lung Health Study is a clinical arm of the Cancer Imaging Department at the BC Cancer Research Centre. The main focus of the Lung Health Study is chemoprevention and screening trials. Individuals at high risk for lung dysplasias are screened using the CytoSavant micro-imager and the LIFE bronchoscopy system, both of which were developed by the Cancer Imaging Department. Alongside this study, research is also being conducted to assess the use of thoracic spiral CT scans alongside sputum analysis as a potentially effective algorithm for lung cancer screening.

Criteria for entry into the study requires that patients are between the ages of 45 and 74, be current or former smokers with a >30 pack year history, who are not currently undergoing chemotherapy or radiation therapy and a resident of British Columbia. All patients receive sputum analysis. Specimens are collected using an oscillating vest worn by the patient that helps to loosen secretions in the lung. In a combined effort with the Vancouver General Hospital Radiology Department patients also receive a spiral CT scan as part of a parallel study being conducting by the BCCA. Those individuals with positive sputum are offered a bronchoscopy at

the BCCA. Despite the fact that no lung cancer screening strategy is advocated, bronchoscopy is considered to be the gold standard in the diagnosis of lung cancer. The study is currently on-going at the BCCA with a focus on early detection of lung cancer.

5.2 Data Sources and Methods

The Lung Health Study data is maintained in a database at the BC Cancer Research Centre. Information collected from the initial questionnaire, including smoking and disease history as well as sputum, CT and bronchoscopy results are managed by a data manager for the project. Since information previous to 1995 was considered to be incomplete (i.e. not all results were entered into the database) results for this analysis were conducted using information from patients who had entered the study between January 1, 1995 up to and including December 31, 2001. It should be noted that in addition to Lung Health Study patients, this database contains information on any patient seen at the Respiratory Clinic at the BCCA. In order for results to be as complete as possible the entire database was searched for patients who were born after January 1, 1956, who also had a smoking history of >20 pack years as calculated by study researchers. This change in selection criteria from >30 pack years to >20 pack years was applied in order for results from the economic analysis to be considered conservative with respect to other published data on lung cancer and smoking history (Mahadevia et al., 2003).

Patients who met the initial eligibility criteria were further reviewed for any reasons that would make them ineligible for final inclusion. If any of the following applied to a patient they were deemed ineligible for inclusion in further statistical calculations:

- non-smoker
- previous lung cancer
- previous head and neck cancer
- any previous cancer within last 5 years (excluding non-melanoma skin)
- clinic patient or referral patient (i.e. already suspected of having lung cancer)

- follow-up patients seen for repeat bronchoscopy
- consult patient (presented with lung mass)
- ABI study patients (from previous study where lung cancer is suspected)
- missing information (i.e. not enough known about patient history to make an informed decision on eligibility)

From the perspective of any cancer screening programme, the goal is to detect the cancer at an early stage before clinical symptoms appear. All eligible patients in this cohort, although smokers, has no clinical indications of lung cancer and were otherwise 'healthy' at the time of sputum screening.

The provincial cancer registry in the province of British Columbia was then used as a source for current diagnostic status among eligible patients. Using a provincial health number, date of birth, first and last name, patients from the Lung Health Study were linked to the cancer registry database to determine which patients had a diagnosis of lung cancer. The B.C. cancer registry is considered to be the most complete source of information for disease status among patients in the province. Although most prevalent cases of lung cancer were found through the Lung Health study, this linkage allowed those patients who had developed lung cancer subsequent to our initial testing to be identified. Additional information was also collected on patients using this linkage including any other cancer diagnosis, patient status (alive or dead), and death date.

Data obtained through linkage with the B.C. Cancer Registry was collected in two separate linkages. The first linkage included patients in our database that had an Agency ID (N=1833) number and could therefore be easily linked to a registry data field. The second linkage for patients with no Agency ID in our database (N=1360) required that a selection of other identification fields be used. These fields included patient surname, patient first name, date of birth, and PHN. All four of these fields from the Lung Health Study database had to match exactly with cancer registry data in order for a patient record to be considered eligible. It should

be emphasized that the registry was only used to assess what patients in the Lung Health Study had develop cancer (particularly without our knowledge) and that all other statistical analyses was carried out on data from our own study database.

Sputum results from all patients were classified as normal or atypical depending on results from ASC. In order for a patients sputum cytometry results to be classifieds as atypical the DNA index scores for each patient were examined. If the number of cells with a DNA index of 1.2 was equal to or greater than 5 (out of approximately 3000 cells), the sputum was classified as atypical. In cases where there were 4 or less cells with a DNA index of 1.2, the sputum sample was considered normal. Patients with previous cancers who also had a positive sputum cytometry test were evaluated as follows. Those with any previous lung cancer were not considered in further calculations, and all others with recent cancers less than 5 years old were excluded. Patients with a previous cancer considered to be in remission for more than 5 years were included in calculations.

An individual chart review was conducted for eligible patients found to have lung cancer, whether through the Lung Health Study or the cancer registry. Patient information was examined for any data that may have been previously missed that may exclude the patient from inclusion in the final statistics. Time between sputum analysis and diagnosis was noted as well as the time lapsed between initial stage at diagnosis and current stage of disease. Bronchoscopy results were used to determine stage at diagnosis and type of lung cancer (NSCLC or SCLC). Patients were further classified according to the number of sequential bronchoscopies carried out.

Cohort characteristics were calculated including age, pack years, sex ratios, smoking history, and average length of follow-up (yrs). The lung cancer prevalence rate in this high risk cohort was also determined and is used in the economic model in the following chapter.

5.3 Results

In order to avoid prematurely excluding any lung cancer patients, both linkages were done prior to applying any exclusion criteria to individual patients. Of the 3193 patients in our database at the B.C. Cancer Research Centre, 1833 had Cancer Agency ID numbers and were included in the first linkage with the registry. The link reported that 364 of these patients had lung cancer and after applying exclusion criteria to this group (in addition to individual record review from the Cancer Agency Information System (CAIS), only 44 patients required detailed chart review for a final eligibility decision. After ensuring all inclusion criteria were met and no exclusion criteria applied to these patients, 31 lung cancer patients were deemed eligible for inclusion in this analysis. Non lung cancer patients were also subject to inclusion/exclusion criteria and as a results the initial 1833 patients were reduced to 554 eligible patients.

The remaining 1360 patients in the B.C. Cancer Research Centre database lacked Cancer Agency ID numbers meaning although they may have sputum analysis they have not proceeded to bronchoscopy for a variety of reason and therefore have no ID number with the BCCA. Results returned from the link with the registry indicated that 24 patients had developed cancer since last contact with the Lung Health Study. Applying inclusion and exclusion criteria to these 24 patients allowed those eligible to be further reduced to 5 and detailed chart reviews found no further reason to exclude any of the 5 patients. Non lung caner patients were also screened with inclusion/exclusion criteria and the original 1360 in this group was reduced to 1331 eligible patients. Combining these results with the first linkage, a total of 36 (31 + 5) patients were found to have lung cancer among 1885 (554 + 1331) eligible study patients.

Next, the 1885 patients in the database that were eligible for inclusion in the study were separated into the following sub-groups for statistical purposes:

A. All Eligible Patients
B. All Eligible Patients with at Least 1 Bronchoscopy
C. Lung Cancer Patients
D. Lung Cancer Patients with at Least 1 Bronchoscopy
E. Lung Cancer Patients with No Bronchoscopy

Statistical characteristics for each of the above 5 sub-groups is presented in Tables 5.1 through 5.5. Calculated data includes the mean, standard deviation, median, minimum and maximum values relating to age, sex, smoking history, and duration of follow-up (i.e. how long patients have been followed from the time they entered the database to December 31, 2002). In addition, forced expiratory volumes (FEV1 and FEV1%) are included to summarize information on patient's lung volume capacity, a factor believed to decrease as a result of smoking. In situations when data was not available for all members of a subgroup, a note was made and the denominator adjusted accordingly.

Comparing the statistics presented in Table's 5.1 and 5.3, the mean age of the screened cohort was 58 while the mean age of lung cancer patients in the screened detected cohort increased to 62. This trend was also seen in pack year data with the mean being 50 pack years for the entire cohort, then increasing to 60 pack years for those 36 patients with lung cancer. Of the 509 patients in the entire cohort who were former smokers, 2.2% developed lung cancer. In comparison, 1.8% (25/1369) of current smokers developed lung cancer. FEV1 % predicted results decreased in lung cancer patients compared to the 1885 cohort with values of 71% and 84% respectively. Figure 5.1 outlines the clinical course taken by the 1885 patients as a result

Table 5.1 All Eligible Patients, Age 45+ and 20+ Pack Years with Sputum Analysis

Total N = 1885	Male	Female
SEX	987 (52.4%)	898 (47.6%)

	Current	Former
SMOKING HISTORY	1369 (72.9%)	509 (27.1%)

	Normal	Atypia*
SPUTUM	674 (38.3%)	1087 (61.7%)

	Mean	Stand. Dev.	Median	Min	Max
AGE	57.94	7.70	57.02	45.00	80.07
PACK YEARS	49.84	19.05	45.26	20.00	196.00
Duration of F/U (Yrs)	3.16	1.71	2.61	0.61	12.43
FEV1**	2.73	0.91			
FEV1 % predicted**	84.11	33.2			

* Atypia defined as: >=5 cells with DNA score >=1.2
** Note – only 1781 of the 1885 (94.4%) patients have FEV1 results.

Table 5.2 All Eligible Patients, Age 45+ and 20+ Pack Years with at Least 1 Bronchoscopy

Total N = 1003	Male	Female
SEX	534 (53.2%)	469 (46.8%)

	Current	Former
SMOKING HISTORY	728 (72.6%)	275 (27.4%)

	Normal**	Atypia*
SPUTUM	283 (29.9%)	720 (70.1%)

	Mean	Stand. Dev.	Median	Min	Max
AGE	58.04	7.68	57.14	45.02	80.07
PACK YEARS	50.81	19.80	45.38	20.00	176.40
Duration of F/U (Yrs)	3.42	1.67	2.73	0.61	12.43
FEV1[§]	2.68	0.91			
FEV1 % predicted[§]	82.31	41.91			

* Atypia defined as: >=5 cells with DNA score >=1.2
** Large proportion of these patients developed ATYPIA after NORMAL baseline sputum
§ Note – only 870 of the 1003 (86.7%) patients have FEV1 results.

Table 5.3 Lung Cancer Patients, Age 45+ and 20+ Pack Years

Total N = 36	Male	Female
SEX	19 (52.8%)	17 (47.2%)

	Current	Former
SMOKING HISTORY	25 (69.4%)	11 (30.6%)

	Normal	Atypia*
SPUTUM	5 (13.9%)	31 (86.1%)

	Mean	Stand. Dev.	Median	Min	Max
AGE	61.70	8.25	61.95	45.00	78.35
PACK YEARS	59.66	30.58	49.65	31.00	172.00
Duration of F/U (Yrs)	3.93	2.85	3.57	0.63	13.99
FEV1	2.15	0.83			
FEV1 % predicted	70.91	25.07			

* Atypia defined as: >=5 cells with DNA score >=1.2

Table 5.4 Lung Cancer Patients, Age 45+ and 20+ Pack Years with at least 1 Bronchoscopy

Total N = 31	Male	Female
SEX	17 (54.8%)	14 (45.2%)

	Current	Former
SMOKING HISTORY	19 (61.3%)	12 (38.7%)

	Normal	Atypia*
SPUTUM	3 (9.7%)	28 (90.3%)

	Mean	Stand. Dev.	Median	Min	Max
AGE	61.97	8.35	62.31	45.00	78.35
PACK YEARS	43.80	32.69	48.1	31.00	172.00
Duration of F/U (Yrs)	3.84	3.04	2.41	0.63	13.99
FEV1	2.19	0.82			
FEV1 % predicted	71.52	24.70			

* Atypia defined as: >=5 cells with DNA score >=1.2

Table 5.5 Lung Cancer Patients, Age 45+ and 20+ Pack Years with No Bronchoscopy

Total N = 5*	Male	Female
SEX	2 (40%)	3 (60%)

	Current	Former
SMOKING HISTORY	5 (100%)	0

	Normal	Atypia*
SPUTUM	2 (40%)	3 (60%)

	Mean	Stand. Dev.	Median	Min	Max
AGE	60.01	7.41	58.33	49.61	72.49
PACK YEARS	52.69	7.12	51.2	46.00	66.00
Duration of F/U (Yrs)	4.51	1.08	4.27	3.34	6.14
FEV1	2.02	0.86			
FEV1 % predicted	66.20	24.35			

*All 5 of these patients found to have lung cancer on follow-up through the registry.

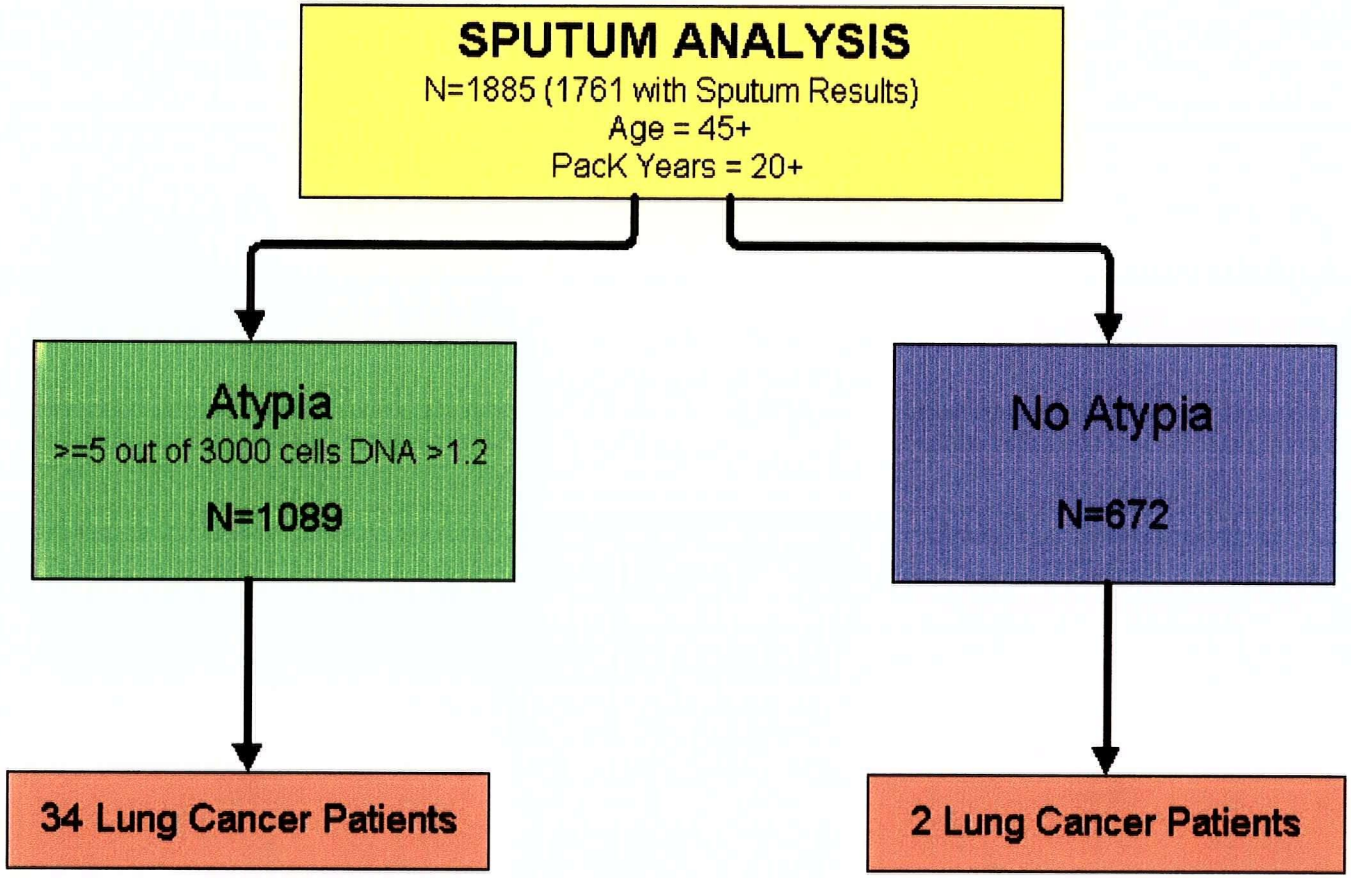

Figure 5.1 Breakdown of Lung Health Study patients by sputum diagnosis and number of bronchoscopies, N=1885 including 36 lung cancer patients

of sputum analysis and bronchoscopy procedures. There were 17 incident cancers detected through baseline bronchoscopy, serial bronchoscopies or sputum only. There were 19 prevalent cancers detected upon initial screening. Only 2 patients with normal sputum analysis developed lung cancer and were identified through the registry link.

Additional information was reported on the 36 patients found to have lung cancer. The mode of diagnosis, cell type and stage distribution further characterize the lung cancer patients (Table 5.6, 5.7 and 5.8) and highlight the result that 12 patients were positively identified as having develop lung cancer through the provincial registry linkage. A large proportion of lung cancer patients were diagnosed with either adenocarcinoma (44%) or squamous cell carcinoma (36%), both NSCLC. From the stage distribution at diagnosis (Table 5.8), a significant portion of lung cancers were found in Stage 0 or Stage I, for which the likelihood of survival increases. Using these results, the prevalence rate for lung cancer in this high risk cohort was determined to be 1.9%.

5.4 Discussion

A significant number of patients in the B.C. Cancer Research Centre database had to be excluded for one or more of the reason stated earlier in the exclusion criteria. Many patients were either referred to the BCCA, were consult patients or were having follow-up diagnostic testing. In all of these situations patients presented with symptoms and therefore had to be excluded as a screening programme aims to detect cancer cases with no clinical symptoms. The linkages done with the provincial registry allowed 12 patients with lung cancer to be identified whose diagnosis would not have otherwise been known to our study group.

Table 5.6 Mode of Diagnosis for 36 Lung Cancer Patients

Mode of Diagnosis	Number of Cases
Prevalence Screen Case	19 (53%)
Incident Follow-up Case	17 (47%)
• Serial Bronchoscopies	5
• BC Cancer Registry	12
➢ Previous Negative Bronchoscopy	8
➢ Previous Negative Sputum	4

Table 5.7 Cell Type Distribution for 36 Lung Cancer Patients

Cell Type*	Number of Cases
Squamous Cell (NSCLC)	13 (36%)
Adenocarcinoma (NSCLC)	16 (44%)
Poorly differentiated NSCLC	2 (6%)
Small Cell Lung Cancer (SCLC)	5 (14%)

*According to patient pathology reports.

Table 5.8 Stage Distribution for 36 Lung Cancer Patients

Cell Type	**Prevalence Screen**	**Follow-up**	**Overall**
NSCLC			
Stage 0	22%	31%	26%
Stage I	45%	8%	29%
Stage II	11%	0	6%
Stage III	22%	38%	29%
Stage IV	0	23%	10%
SCLC			
Limited disease	1	0	1
Extensive disease	0	4	4

Eligibility criteria for this analysis required that patients be 45 years or older with a smoking history of 20 or more pack years. Although researchers in this field agree that a lung cancer screening programme needs to target high risk individuals in order to be effective both from a clinical and economic viewpoint, there is no standard set of criteria for defining such a high risk cohort. Other lung cancer screening studies have involved participants between the ages of 40-70 yrs, (Henschke et al., 1999), 60-75 yrs (Swensen et al., 2002) and 60-74 yrs (Marshall et al., 2001). Pack years is not always used to determine smoking history and some published studies only state that current and former heavy smokers were invited for screening (Swensen, 2002; Sone, 2001; Sobue, 2002). In studies where pack years are calculated values range from minimums of between 20 and 40, with a mean value of 44 pack years (Henschke, 1999). The conservative criteria of 45+ years-old and 20+ pack years could be narrowed further to target a higher risk group since the mean age and pack year history of lung cancer patients was found to be 62 and 60 respectively. Increasing the screening age from 45 to 55 would result in 7 of the 36 lung cancer cases being missed but the detection rate would increase from 1.9% to 2.1%. These clinical results from ASC screening will be used in the economic model in Chapter 6.

Without a doubt the major goal of a lung cancer screening programme is to detect early stage disease when there is improved likelihood of survival. The stage distribution results presented above indicate that 8 of the 36 cancers were detected in Stage 0 and 11 cancers were found at Stage I meaning just over 50% of cases were diagnosed in the early part of disease progression when curative surgery is available. The cell type results are consistent with current data in other lung cancer populations and reflect the increase in the proportion of cancers classified as adenocarcinomas (Than et al., 1997), especially among female smokers. Since adenocarcinoma is a peripheral disease in the lung, there is a common belief that it does not exfoliate cells that remain intact in sputum, rendering sputum analysis of little utility. The proposed method of sputum cytometry analysis however has shown it is effective in detecting

adenocarcinomas in a field study by Palcic et al. (2002) and the results presented here support this.

This analysis is not without limitations. This was a retrospective analysis to some degree and it was therefore impossible to ensure the completeness of data for all 1885 eligible patients. In some instances, pack year information was missing, sputum results were not recorded or past medical histories may not be complete. Patients with missing data were removed from the denominator when calculating sub-group characteristics. A small proportion of sputum analysis was carried out on specimens collected through the 3-day pool method and not the standard vest method used at the BCCA.

The provincial cancer registry provides the most complete source of information on cancer cases in the province of B.C. but it is not without its own limits. Certainly not all lung cancers are accounted for in this registry. Those patients who do not seek treatment may be missed as well as those whose primary cause of death is not lung cancer itself. This lung cancer screening programme is offered through the BCCA in the city of Vancouver, a major metropolitan hub for the province. It is known that smoking prevalence is slightly higher in the interior/rural regions of British Columbia and therefore a higher prevalence of lung cancer may be reported in these areas. Fifty-five percent of those living in the Vancouver/Richmond health region claim to never have smoked, while the number drops to as low as 39% in the Coast Garibaldi health region (Vancouver Coastal Health Authority, 2002). Smokers living in rural areas of the province may be less likely to travel farther distances for lung cancer screening and this highlights the need to ensure a population based screening programme is accessible to those that would benefit most from it. The BCCA clinical trial is ongoing and as more data is collected, clearer assumptions regarding the efficacy of ASC will be supported.

Chapter 6. Economic Decision Analysis Model for the Evaluation of Lung Cancer Screening with Automated Sputum Cytometry

6.1 Introduction

This model is designed to evaluate the cost-utility of using sputum cytometry as a first step screening test in detecting preclinical lung cancer. A societal perspective is adopted for the analysis to support this screening programme being adopted on a large scale population basis in the future. In Canada, a national, government funded health care system is in place. Costs are measured in dollars and reported in 2003 Canadian dollars and benefits are measured in quality adjusted life years.

A full economic evaluation involves the comparison of one or more alternatives to the proposed intervention. Although there is no current mandated lung cancer screening programme anywhere in the world, current clinical practice dictates the use of helical CT scans and bronchoscopy in the detection of cancerous lesions in the lung. Bronchoscopy involves a definitive pathology report on the presence or absence of malignancy. In this model there are three mutually exclusive screening alternatives in the decisions tree. To demonstrate a stage shift (i.e. a greater proportion of patients diagnosed with preclinical lung cancer) as a results of screening, one arm of the study demonstrates disease progression when no screening is implemented. The three decision pathways are summarized below. Diagnostic follow-up implies further CT scans, bronchoscopy, or other definitive clinical diagnostic procedures.

1. Sputum cytometry → CT scan → Diagnostic follow-up → Lung cancer
2. CT scan → Diagnostic follow-up → Lung cancer
3. No screening → Lung cancer

A simplified depiction of the decision analysis tree is shown in Figure 6.1 which condenses the many diagnostic follow-up procedures in each of the screening arms. The detailed clinical

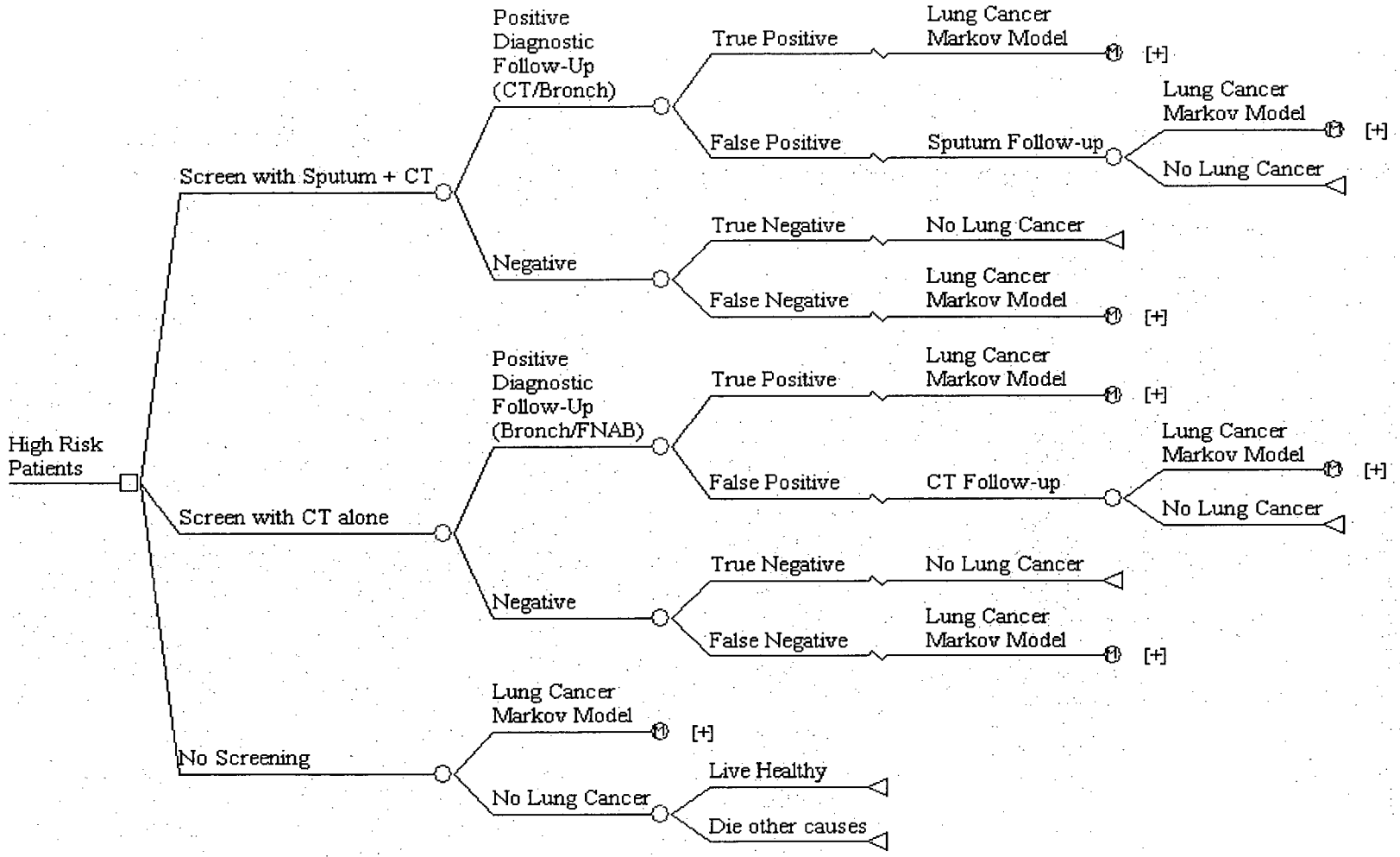

Figure 6.1 Simplified decision analysis tree comparing three screening strategies.

pathways and health states that persons would traverse having received screening are shown for reference only in Figure 6.2 and 6.3. Once an individual is diagnosed with lung cancer, the patient cycles through the various stages of disease by means of a markov model (see Section 6.2). Through sensitivity analyses, model parameters that are influential in determining the cost-utility of screening will be identified.

The research aim was to gain insight into the important factors influencing screening efficacy and economic effectiveness while testing the hypothesis that using sputum cytometry as an initial screening test would be cost-effective compared to no screening and screening with CT scans. Since CT screening is unable to detect preclinical lung cancer, the potential benefits (QALYs) are expected to improve with sputum cytometry compared to CT screening. The higher false positive rate from CT screening is expected to contribute significantly to diagnostic follow-up costs in this arm of the model, while screening with sputum alongside CT scans is hypothesized to reduce over-all costs.

6.2 Data Sources and Model Design

Every effort has been made to use scientifically published, peer-reviewed data upon which to base any quantitative assumptions in this decision analysis. Clear rational for model assumptions is provided in situations where published data was limited. A number of sources have been used to generate costs, probabilities and assumptions for this cost-utility model. Whenever possible, all costing data (both for screening tests and for management of lung cancer) was taken from Canadian studies and reported in Canadian dollars inflated to 2002 values using the Consumer Price Index (CPI) for Health Care from the Bank of Canada (base period 1992 = 100).

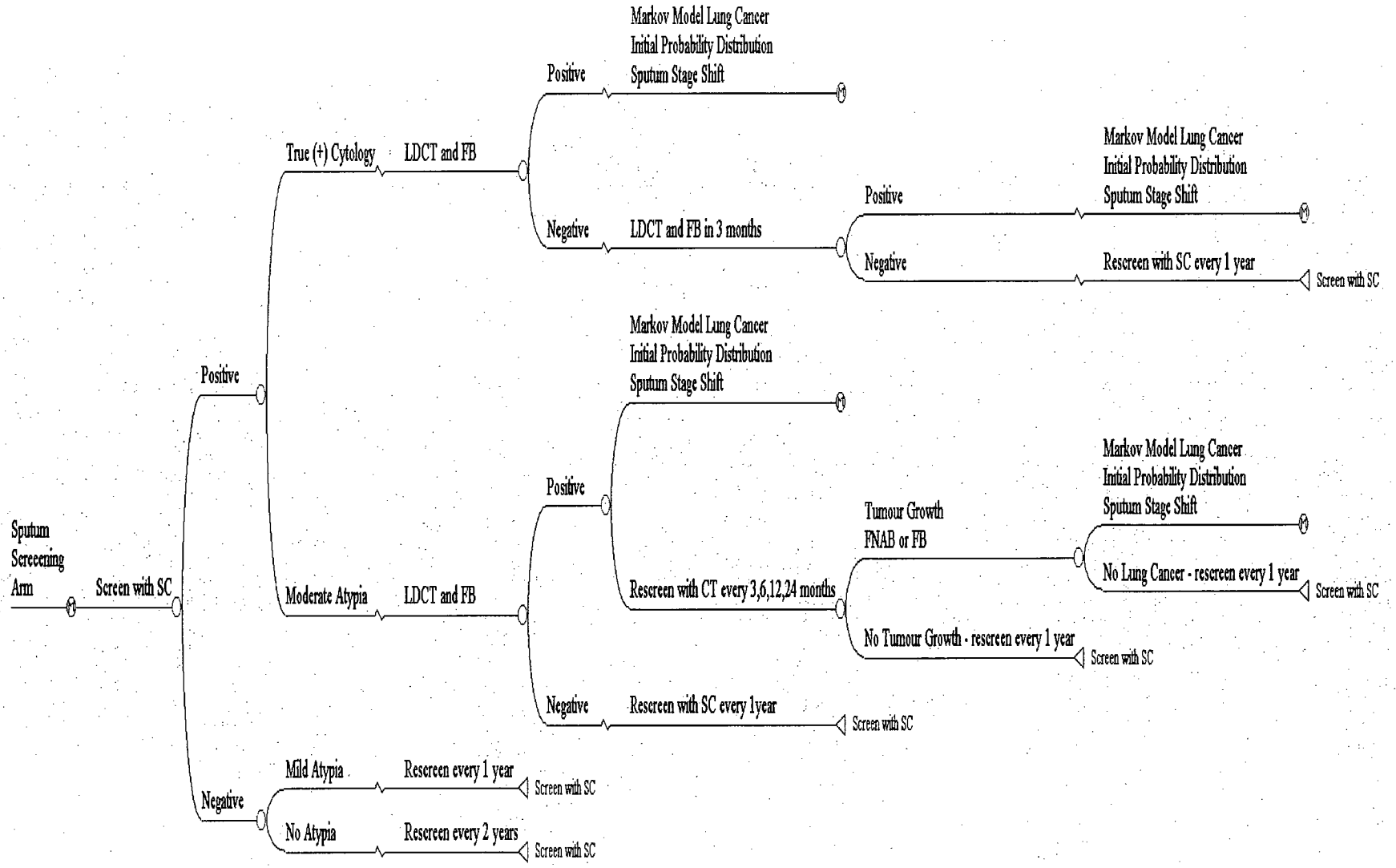

Figure 6.2 Detailed clinical screening pathway for the sputum + CT screening arm.

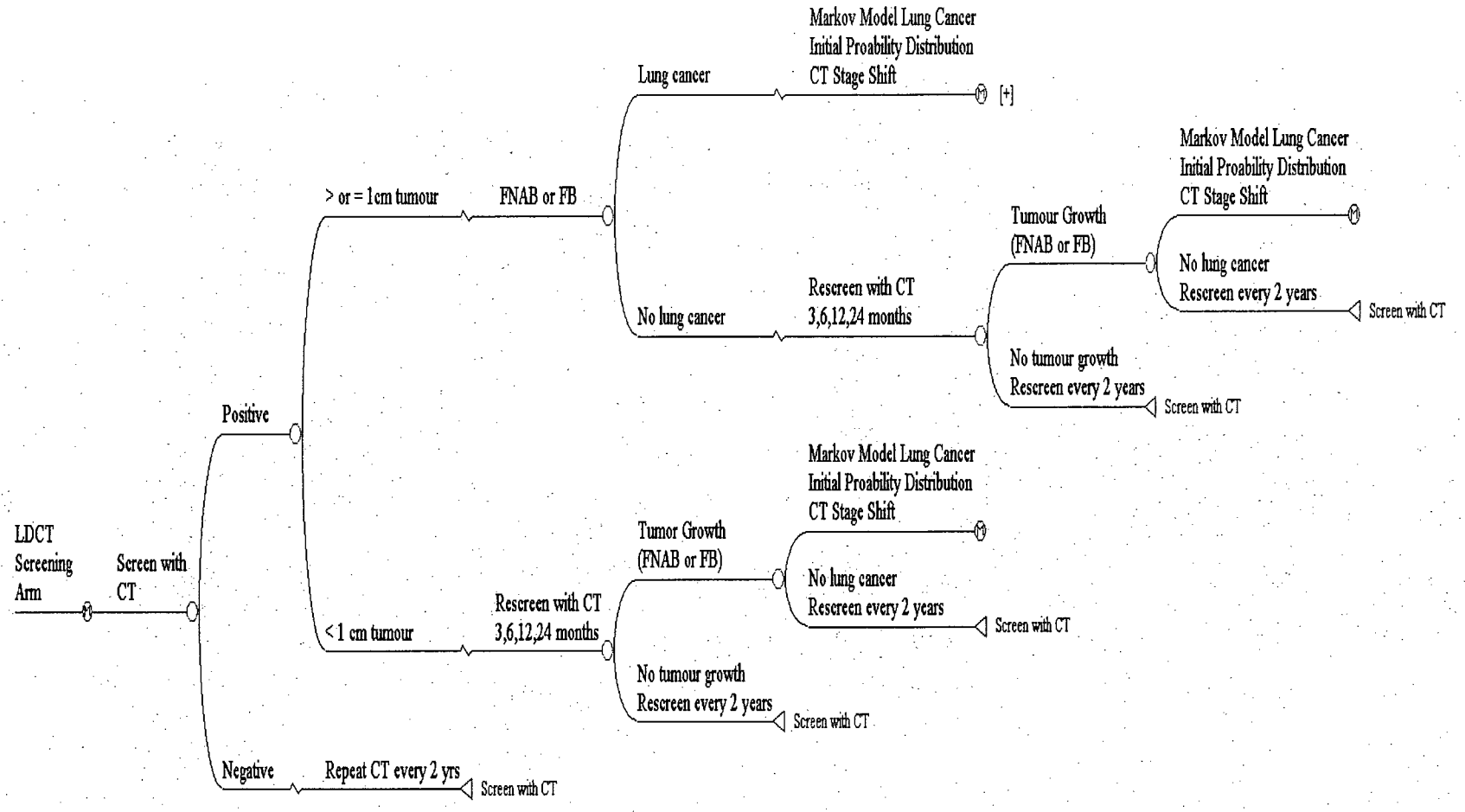

Figure 6.3 Detailed clinical screening pathway for the CT screening arm.

The Health Analysis and Modeling Group at Statistics Canada (Ottawa), provided much of the data on the cost of managing lung cancer in Canada as well as the distribution of disease in the population. The cost of sputum cytometry was obtained from Perceptronix Medical Inc. (PMI), a local research and development company in Vancouver currently conducting a clinical trial on the clinical effectiveness of sputum cytometry. Only direct medical costs were considered in the model as it was assumed that all facilities and equipment were previously established for such a screening programme. All costs were discounted at 3% per year with sensitivity analyses conducted using 0% and 5% discount rates.

The parameters required for evaluating a screening programme include characteristics of the disease (prevalence, incidence, mortality rates, and quality of life) and characteristics of the screening test (sensitivity, specificity, positive/negative predictive values). In instances where Canadian data on lung cancer survival and mortality was incomplete, the Surveillance, Epidemiology, and End Results (SEER) national cancer database in the United States was used to supplement statistical probabilities.

The hypothetical cohort consisted of 100,000 current or former smokers with a minimum 20 pack year smoking history (see Appendix A for calculation of pack years), who were between 45 and 74 years old. Five year annual screening was modeled. Costs associated with diagnosis and treatment were determined for a 10 year follow-up period beginning at the time of initial screening. After 10 years, lung cancer patients were considered cured and entered remission for the remainder of their lifetime, although yearly surveillance costs were still incurred in this group of patients. The 5-year survival rate for patients diagnosed with lung cancer is 14% for males and 17% for females (Health Canada, 2002) and in this respect those few patients that do survive for 10 years would be considered cured. It is necessary to follow the cohort for an extended period of time to capture any changes in QALYs that might occur years after screening. Costs and QALYs were therefore calculated over a 50 year follow-up period at which time 99% of the

cohort died. Those participants in the non-screened group faced yearly transition probabilities of staying alive without apparent lung cancer, developing and dying from lung cancer, or dying from other causes. Survivorship with lung cancer was considered to be the same for those in the screened and non-screened group and was modeled using data from SEER.

Participants in the screening arm of the model were also subject to lung cancer transition probabilities but faced a different clinical stage distribution as a result of the disease being diagnosed through screening. Often referred to as a downward stage shift, many of the cancers detected by screening are presumed to be in the preclinical or local stage rather than at a more advanced stage hence the greater chance of survival in screen detected cases of lung cancer. For example, if the stage distribution for the non-screened group is 80% advanced and 20% localized, then a 50% stage shift would result in a 40% advanced and 60% localized stage distribution for the screened group. A recently published study by Mahadevia et al. (2003) assumed a 50% downward stage shift in their model for CT screening. Preliminary data from CT screening research at the BCCA indicates a stage shift of 59% (unpublished data, McWilliams). Table 6.1 shows the initial stage distribution for each of the 3 pathways in the model. CT screening can only detect radiological tumours as early as Stage I while sputum can cytometry can detect cellular changes at Stage 0.

Approximately 85% of lung cancers are NSCLC with the remaining 15% classified as SCLC (Reis, 2000). To keep the complexity of the model with manageable limits, disease characteristics are based on probabilities for those with NSCLC only. The staging of NSCLC has also changed over the past 40 years. In this analysis, SEER lung cancer survival data for the first 10 years only is derived from the American Joint Committee on Cancer Staging system (which classifies lung cancers into Stage 0 through Stage IV). For the remaining years ($\geq$11) survival data is based on historic SEER summary Stage 1977 database which classifies cancers into early,

Table 6.1 Distribution of Tumours Detected in a Hypothetical Cohort According to the 3 Screening Alternatives

	Without Screening			Helical CT Screening			Sputum Screening (LHS)		
Disease stage	Male (%)	Female (%)	**Total (%)**	Male (%)	Female (%)	**Total (%)**	Male (%)	Female (%)	**Total (%)**
Stage 0	0.0	0.0	**0.0**	0.0	0.0	**0.0**	31.8	7.1	**22.2**
Stage I	18.7	23.5	**20.6**	82.4	88.2	**85.3**	40.9	50.0	**44.4**
Stage II	4.1	4.1	**4.1**	4.3	3.0	**3.7**	13.6	7.1	**11.1**
Stage III	31.0	26.5	**29.2**	13.3	8.8	**11.1**	13.6	35.7	**22.2**
Stage IV	46.2	45.9	**46.1**	0.0	0.0	**0.0**	0.0	0.0	**0.0**

localized, regional and distant stages. This dual system was needed to account for the lack of longitudinal survival data in each staging system. Quality of life was incorporated into the model outcomes using QALYs for the various health states. QALYs combine both life expectancy and quality of life into one measure and are considered necessary for any cost-utility analysis where patients may have a change in quality of life as a result of an intervention. Utility weights were obtained from the literature as reported by Earle et al. (2000) and by Trippoli et al. (2001) who also found a difference in the quality of life among those patients with screen detected lung cancer as opposed to those with no screening. To incorporate these proxy values in this analysis it was assumed that Stage 0 and I disease were local, Stage II and III regional and Stage IV distant. Table 6.2 shows utility weights used to determine effectiveness outcomes. QALYs were discounted at 3% per year.

A base-case analysis was performed using estimates considered to be most accurate for each parameter in the model. The cycle length of the model was one year meaning that one cycle through the model is equivalent to one year of life for each patient.. Incremental cost-utility ratios (ICER) are calculated by comparing the difference in cost and effects for each of the 3 mutually exclusive options. Screening options are ranked in order of ascending costs. To test the robustness of the results, sensitivity analyses were carried out to evaluate the impact on cost-effectiveness of using more extreme estimates for each parameter. The effect of varying the baseline cancer risk, the performance of the diagnostic test, the cost of the test, and the degree of stage shift were varied on an individual basis (one-way sensitivity analysis) and in combination with other variables (multi-way analysis). Table 6.3 shows annual probabilities and costs used in the base case analysis as well as those values used in sensitivity analyses. Where multiple sources were cited for quantitative assumptions, weighted averages were calculated. The model itself was constructed using Decision Analysis by TreeAge™ (DATA) Software, Data Pro 4.0, Healthcare Edition.

Table 6.2 Utility Values for Those Patients Living with Lung Cancer

	Base Case Analysis	Favours Screening	Against Screening	Reference
Stage 0 and I No Screening Arm	0.73	0.69	0.83	Earle
Stage 0 and I Screening Arms	0.83	0.88	0.69	Trippoli
Stage II and III	0.71	0.66	0.81	Earle
Stage IV	0.66	0.30	0.76	Earle

While most decision trees include a simple notion of time (i.e., events to the right of the tree occur after those to the left), there are no shortcuts in a standard tree structure representing events that recur over time. A state transition model, based on a markov model, was designed to efficiently represent recursive events. A markov model describes the movement of members of a population through a set of states. Transition probabilities represent the likelihood that any individual in a certain state will move into a different state. Such a model was used in this decision tree to simulate the movement of patients through various stages of lung cancer, into remission and onto the final death stage. It was essential to implement a semi-markov process in this model since a patient's probability of moving to the next clinical phase of lung cancer changes with increasing age. SEER historical transition probabilities were only available for a period of up to 30 years post lung cancer diagnosis. Since this cohort of patients was followed for 50 years the remaining transition probabilities were estimated by DATA™ using interpolation. This method will return a transition probability value which is calculated by linear interpolation between successive table indexes. Figure 6.4 depicts the first 10 years of the markov model for those patients who develop lung cancer. Surviving lung cancer patients move into the second portion (or remission stage) of the markov model (shown in Figure 6.5) beginning in year 11 and remain there until they die. In actuality DATA combines these two markov trees for analyses but they are depicted separately here for clearer illustration. Table 6.4 shows the transition probabilities for Stage 0 through Stage IV for the initial 10 years. Table 6.5 shows the survival probabilities for years 11 onward for early through distant stage lung cancers. The likelihood of death from lung cancer in each stage is the same for both screened and non-screened patients who develop disease but the initial stage distribution of lung cancer is different, as discussed above. For those patients who do not receive screening the transition probabilities from alive and healthy to dead (as a person ages) are taken from Statistics Canada Life Tables (Table 6.6).

Table 6.3 Annual Probabilities and Costs Used in the Economic Model for Lung Cancer Screening

	Base Case Analysis	Favours Screening	Against Screening	Reference
Lung cancer probabilities				
Prevalence at initial screening	0.019	0.031	0.012	LHS
Incidence in subsequent screenings	0.028	0.028	0.028	Mahadevia
Proportion of non-screen NSCLC that are local stage, %	20	15	17	Maha/Marsh
Proportion of screened NSCLC that are local stage, %	67	82	65	Swensen
Stage Shift from no screening to screening, local stage, %	60	75	30	LHS
Mortality, %**				
Localized stage NSCLC	10	5	10	SEER
Advanced stage NSCLC	49	49	49	SEER
Distant stage NSCLC	63	63	63	SEER
Screening Test Performance				
Sputum Cytometry Sensitivity	0.45	0.80	0.40	PMI
Sputum Cytometry Specificity	0.90	0.95	0.85	PMI
Helical CT Scan Sensitivity	0.93	0.93	0.85	Marshall
Helical CT Scan Specificity	0.81	0.81	0.49	Marshall
False Positive CT Scan rate	0.19	0.19	0.51	ELCAP
Costs, 2002 CDN$				
Screening				
Sputum Cytometry	100	75	150	PMI/BCCA
Helical CT scan	200	150	300	Marsh/Maha
Follow-up CT scan	350	250	500	Marsh/Maha
Fine needle aspirate biopsy	460	460	460	BCMA
Fluorescence Bronchoscopy	749	749	749	BCMA
Cancer Care				
Stage 0, NSCLC, first year	3,130	2,470	6,813	BCCA
Stage 0, NSCLC, ongoing year	1,500	1,000	3,000	BCCA
Stage I, NSCLC, first year	20,738	16,242	35,000	Berthelot
Stage I, NSCLC, ongoing year	1,500	1,000	3,000	Berthelot
Stage II and III, NSCLC, first year	24,870	28,731	51,247	Berthelot
Stage II and III, NSCLC, ongoing year	2,010	1,500	4,000	Berthelot
Stage IV, NSCLC, first year	26,435	56,527	43,168	Berthelot
Stage IV, NSCLC, ongoing year	1,765	1,200	3,500	Berthelot
NSCLC, terminal year	10,540	10,540	10,540	Berthelot

*Detailed transition probabilities listed elsewhere.

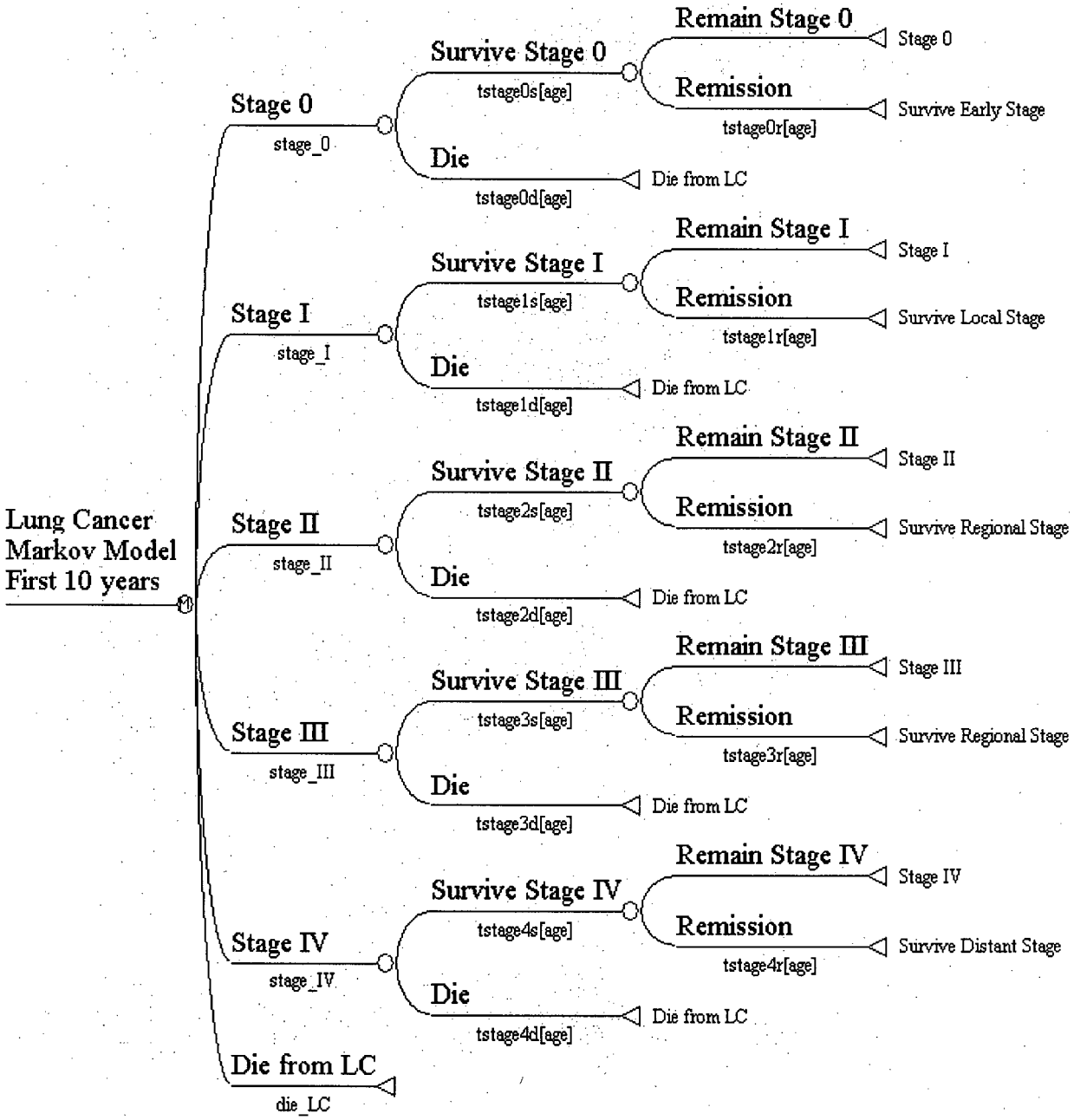

Figure 6.4 Markov model for lung cancer patients for first 10 years post diagnosis.

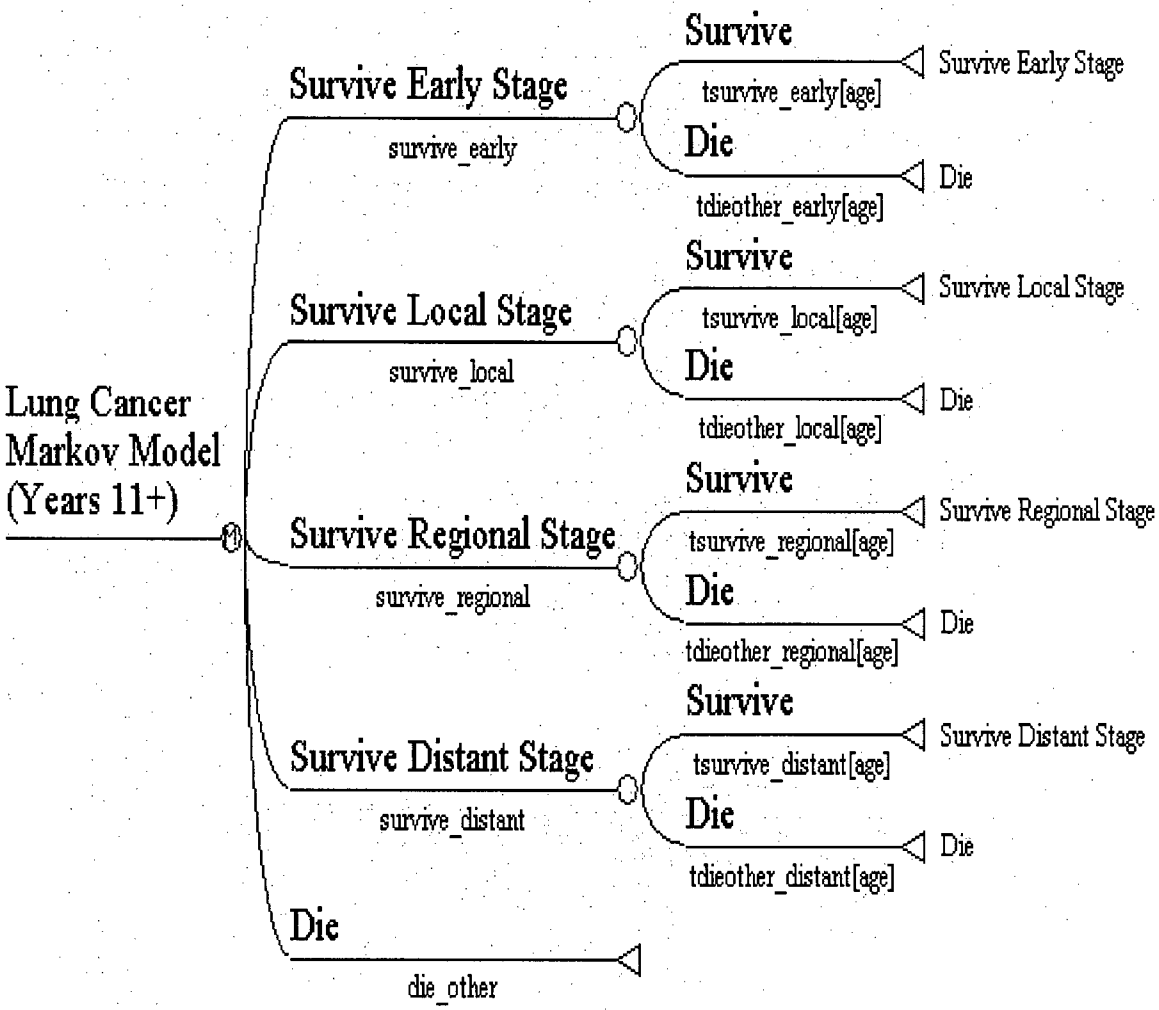

Figure 6.5 Markov model for lung cancer patients for years 11+ after diagnosis.

6.3 Results

The model was analyzed by rolling back the tree to determine the average cost and number of life years gained per patient. Costs were calculated over 5 years for screening and for the 45 year disease follow-up/surveillance period and are reported in 2002 Canadian dollars. Patients who developed lung cancer cycled through the markov model for a period of 10 years after which they were assumed cured and moved into a remission markov model.

For patients in the no screening arm there were 1,042 lung cancer deaths per 100,000 patients compared with 882 lung cancer deaths per 100,000 screened patients in the CT screening arm and 857 deaths per 100,000 patients in the sputum screening arm. This result indicates a relative mortality reduction of 15.3% with CT screening and 17.7% with sputum screening arm. Incremental costs consumed and the incremental effectiveness (QALYs) produced from the three mutually exclusive screening strategies are shown in Table 6.7. Comparing the incremental costs for each strategy, CT screening alone has a greater incremental cost compared to sputum screening ($7,072 vs. $1,088). Interpretation of these incremental costs leads to the conclusion that under these circumstances, CT screening is weakly dominated by sputum screening and should never be implemented as a lung cancer screening strategy. The CT screening option was removed from the analysis as a potential strategy and the ICER recalculated comparing sputum screening to no screening (Table 6.8).

In the base-case analysis the average lifetime cost per patient was $13,061 in the sputum + CT screening arm compared to $5,262 in the no screening arm. There was a net gain of 0.1420 QALYs in the sputum + CT arm and this resulted in an ICER of $54,923/QALY. Table 6.9 provides a summary around the variance in results for each of the three screening strategies. The distribution of costs and effects (QALYs) for the sputum screening arm is shown in Figure 6.6 and 6.7. The bimodal distribution of costs is reflective of those patients that remain free from lung cancer compared to those who develop the disease.

Table 6.4 Markov Transition Probabilities for Lung Cancer Patients for First 10 Years After Diagnosis

	Stage 0		Stage I		Stage II	
Cycle #	Die	Survive	Die	Survive	Die	Survive
0	0.2526	0.7474	0.2076	0.7924	0.2632	0.7368
1	0.2464	0.7536	0.1826	0.8174	0.2829	0.7171
2	0.1312	0.8688	0.1309	0.8691	0.2051	0.7949
3	0.1751	0.8249	0.097	0.903	0.1508	0.8492
4	0.0655	0.9345	0.08	0.92	0.125	0.875
5	0.0467	0.9533	0.0741	0.9259	0.1039	0.8961
6	0.0706	0.9294	0.0635	0.9365	0.087	0.913
7	0.0421	0.9579	0.0635	0.9365	0.0936	0.9064
8	0.0364	0.9636	0.0596	0.9404	0.094	0.906
9	0.0363	0.9637	0.0547	0.9453	0.0633	0.9367
10	0.0458	0.9542	0.0581	0.9419	0.0849	0.9151

	Stage III		Stage IV	
Cycle #	Die	Survive	Die	Survive
0	0.589	0.411	0.8172	0.1828
1	0.5158	0.4842	0.6833	0.3167
2	0.3404	0.6596	0.4667	0.5333
3	0.22	0.78	0.2779	0.7221
4	0.1567	0.8433	0.1973	0.8027
5	0.1174	0.8826	0.1491	0.8509
6	0.1164	0.8836	0.1556	0.8444
7	0.1038	0.8962	0.1151	0.8849
8	0.0939	0.9061	0.1058	0.8942
9	0.0754	0.9246	0.0784	0.9216
10	0.1125	0.8875	0.1477	0.8523

Table 6.5 Transition Probabilities for Lung Cancer Patients in Remission for Years 11 Onward

	Early Stage (Stage 0)		Localized Stage (Stage I)	
Cycle #	Die	Survive	Die	Survive
11	1	0	0.9606	0.0394
12	0.7673	0.2327	0.9648	0.0352
13	1	0	0.9682	0.0318
14	1	0	0.9548	0.0452
15	0.6838	0.3162	0.9396	0.0604
16	1	0	0.9719	0.0281
17	1	0	0.9453	0.0547
18	1	0	0.957	0.043
19	0.8845	0.1155	0.9271	0.0729
20	0.7744	0.2256	0.9647	0.0353
21	n/a	n/a	0.98	0.02
22	n/a	n/a	0.942	0.058
23	n/a	n/a	0.94	0.06
24	n/a	n/a	0.9224	0.0776
25	n/a	n/a	0.9588	0.0412
26	n/a	n/a	0.9615	0.0385
27	n/a	n/a	0.9195	0.0805
	Regional Stage (Stage II and III)		Distant Stage (Stage IV)	
Cycle #	Die	Survive	Die	Survive
11	0.9503	0.0497	0.9644	0.0356
12	0.9354	0.0646	0.8979	0.1021
13	0.9505	0.0495	0.9429	0.0571
14	0.9183	0.0817	0.9897	0.0103
15	0.9279	0.0721	0.9222	0.0778
16	0.9218	0.0782	0.8687	0.1313
17	0.9107	0.0893	1	0
18	0.975	0.025	0.9804	0.0196
19	0.9768	0.0232	0.8722	0.1278
20	0.9246	0.0754	1	0
21	0.9642	0.0358	0.9536	0.0464
22	0.8711	0.1289	0.9278	0.0722
23	0.8419	0.1581	0.8813	0.1187
24	0.9389	0.0611	n/a	n/a
25	0.886	0.114	n/a	n/a
26	0.7326	0.2674	n/a	n/a

Table 6.6 Survival Table for Patients Without Lung Cancer

Age of healthy person	Probability of Surviving 1 additional year
50	0.99597
55	0.99372
60	0.99015
65	0.98390
70	0.97403
75	0.95832
80	0.93191
85	0.88574
90	0.81317
95	0.71725
100	0.59939

*Statistics Canada, Life Table, 1997

Table 6.7 Base-case Results Comparing 3 Screening Strategies, 2002 CDN$*

	Total Average Lifetime Costs, $	Incremental Costs, $	Total Average Quality Adjusted Life Expectancy, y	Incremental Quality Adjusted Life Expectancy, y	Incremental Cost-Utility Ratio
No screening	**$5,262**	**---**	**28.8876**	**--**	**--**
CT screening alone	**$12,334**	**$7,072**	**29.0082**	**0.1206**	**$58,640 (dominated)**
Sputum + CT screening	**$13,061**	**$1,088**	**29.0296**	**0.0214**	**$50,875**

*Costs and QALYs discounted at 3%

Table 6.8 Base-case Results Comparing 2 Screening Strategies, 2002 CDN$*

	Total Average Lifetime Costs[+], $	Incremental Costs, $	Total Average Quality Adjusted Life Expectancy, y	Incremental Quality Adjusted Life Expectancy, y	Incremental Cost-Utility Ratio
No screening	**$5,262**	**---**	**28.8876**	**--**	
Sputum + CT screening	**$13,061**	**$7,799**	**29.0296**	**0.1420**	**$54,923**

* CT Screening removed as a result of being a dominated strategy

[+]Costs and QALYs discounted at 3%

Table 6.9 Summary Statistics for the 3 Screening Strategies, 2002 CDN$

	No Screening		CT Screening		Sputum + CT Screening	
Statistical Summary	**Cost**	**QALYs**	**Cost**	**QALYs**	**Cost**	**QALYs**
Mean	5,262	28.8876	12,334	29.0082	13,061	29.0296
SD	5,036	10.99	7,661	9.652	8,985	10.773
Minimum	200	1.4560	1,525	1.6994	1,229	1.8005
Median	3,911	22.6793	8,269	21.9979	9,549	22.619
Maximum	50,877	45.899	57,020	46.9783	56,364	48.093

6.3.1 Sensitivity Analyses

One way sensitivity analysis was performed by varying individual parameters in the model and observing the changes in cost-utility ratios. In each of the following sensitivity analyses, the ICER is determined by comparing results between sputum + CT screening and no screening. An increase in the sensitivity of sputum cytometry screening and the prevalence of lung cancer in the high risk cohort had the greatest effect on model predictions. With a test sensitivity of 0.9 the ICER dropped to $35,530/QALY. More conservatively, increasing the sensitivity to 0.7 resulted in a ICER of $41,884/QALY (Figure 6.8). If the prevalence of lung cancer in the screened population dropped to 0.8% from 1.9%, the ICER raises dramatically to $100,845/QALY while an increase in disease prevalence to 3% resulted in an ICER of $44,659/QALY (Figure 6.9).

The cost of the sputum test and the degree of stage shift had less impact on cost-effectiveness. Reducing the cost of the test from $100 to $50 improved the ICER by approximately $12,800 from the baseline result (Figure 6.10). Cutting the stage shift in half, from 60% to 30%, resulted in a significant change in the ICER to $76,718/QALY. Improving the stage shift to 70% had less of an effect on the outcome of ICER of $41,716/QALY (Figure 6.11).

Lastly, sensitivity analysis was performed using discounts rates of 0% (no discounting) and 5%. Failure to discount future health related benefits will tend to show more favourable cost-utility ratios compared with discounting. The cost per QALY was affected by the discount rate, however the overall conclusions of the study were not. Applying 0% and 5% discount rates to the 3 screening strategies continued to demonstrate that CT screening is dominated. Cost-utility ratios ranged from $43,806/QALY at a 0% discount rate, to $61,120/QALY with a 5% discount rate.

The decision tree software used to construct and analyze this economic model allows for both one and two way sensitivity analysis to be conducted. Table 6.9 show the effects of combining two variables that were examined in the 1-way sensitivity analyses reported above. Variables with a greater potential for variance, such as the specificity of the test (with improved imaging techniques) the degree of stage shift (detecting a greater proportion of lung cancers in the pre-invasive stage) were varied in combination with one another. Using the most favourable and unfavourable estimates (Table 6.10) for all the parameters in the model, the impact of these simultaneous changes were significant. Results show that using the least favourable estimates of all the input variables generates a significantly high ICER of $94,171/QALY. Conversely, using the most favourable estimates for the same parameters significantly reduces the ICER from $54,923/QALY (baseline analysis) to $34,338/QALY.

As discussed in Chapter 2, malignancy associated changes (MAC) are also being studied as a potential biomarker in pre-invasive neoplastic lesions of the lung. To test the outcome measures against using MAC in sputum samples (as measured by cytometric analysis) the sensitivity of the test was changed to 0.95 while the specificity was decreased to 0.4 (unpublished results from PMI Inc., 2003). Statistically, this would increase the number of true positive cases but also increase the number of false positive cases detecting through sputum screening. This would lead to unnecessary diagnostic follow-up in a significant number of patients and the ICER would be $66,571/QALY.

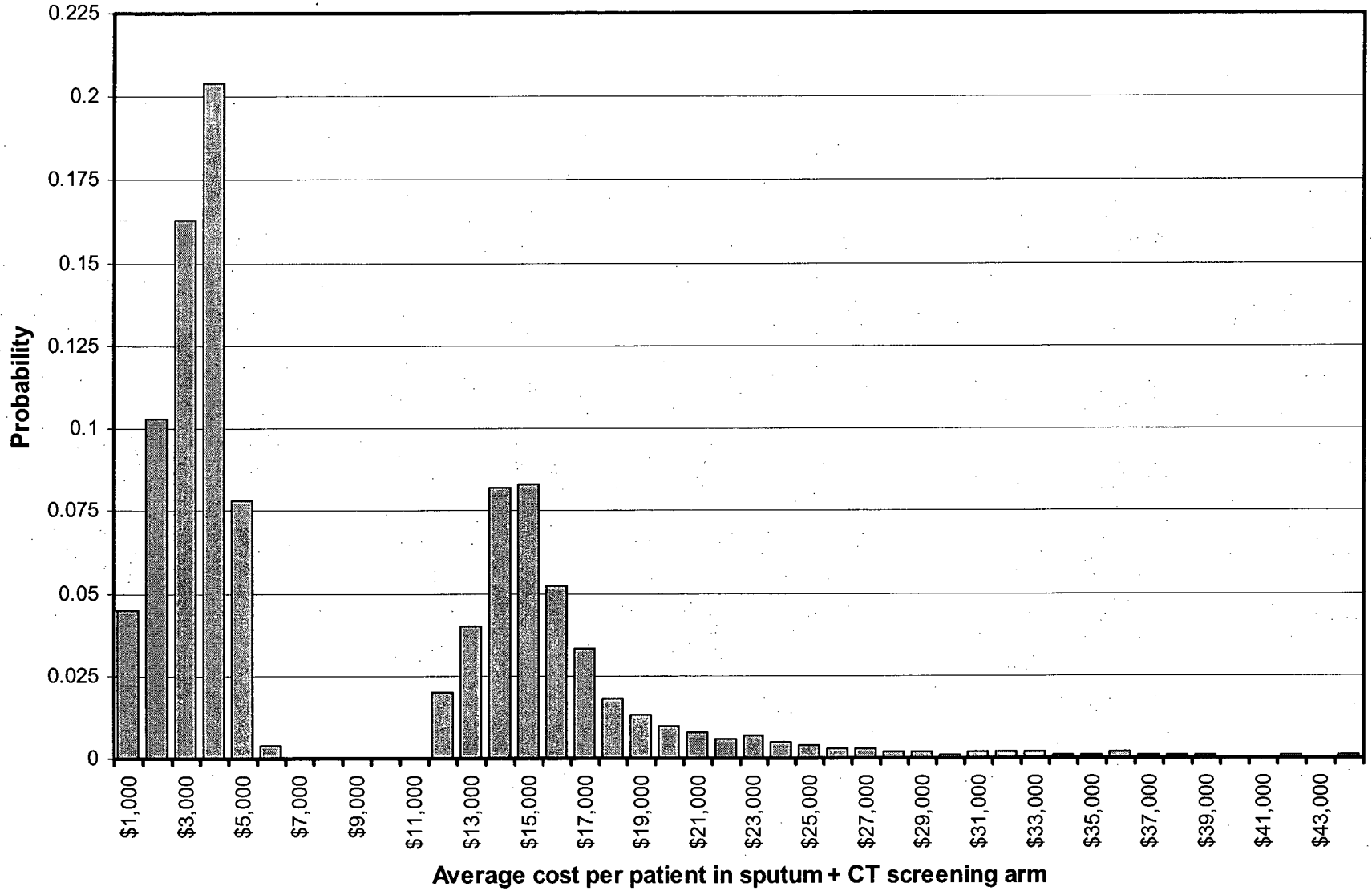

Figure 6.6 Distribution of average costs in the sputum + CT screening arm.

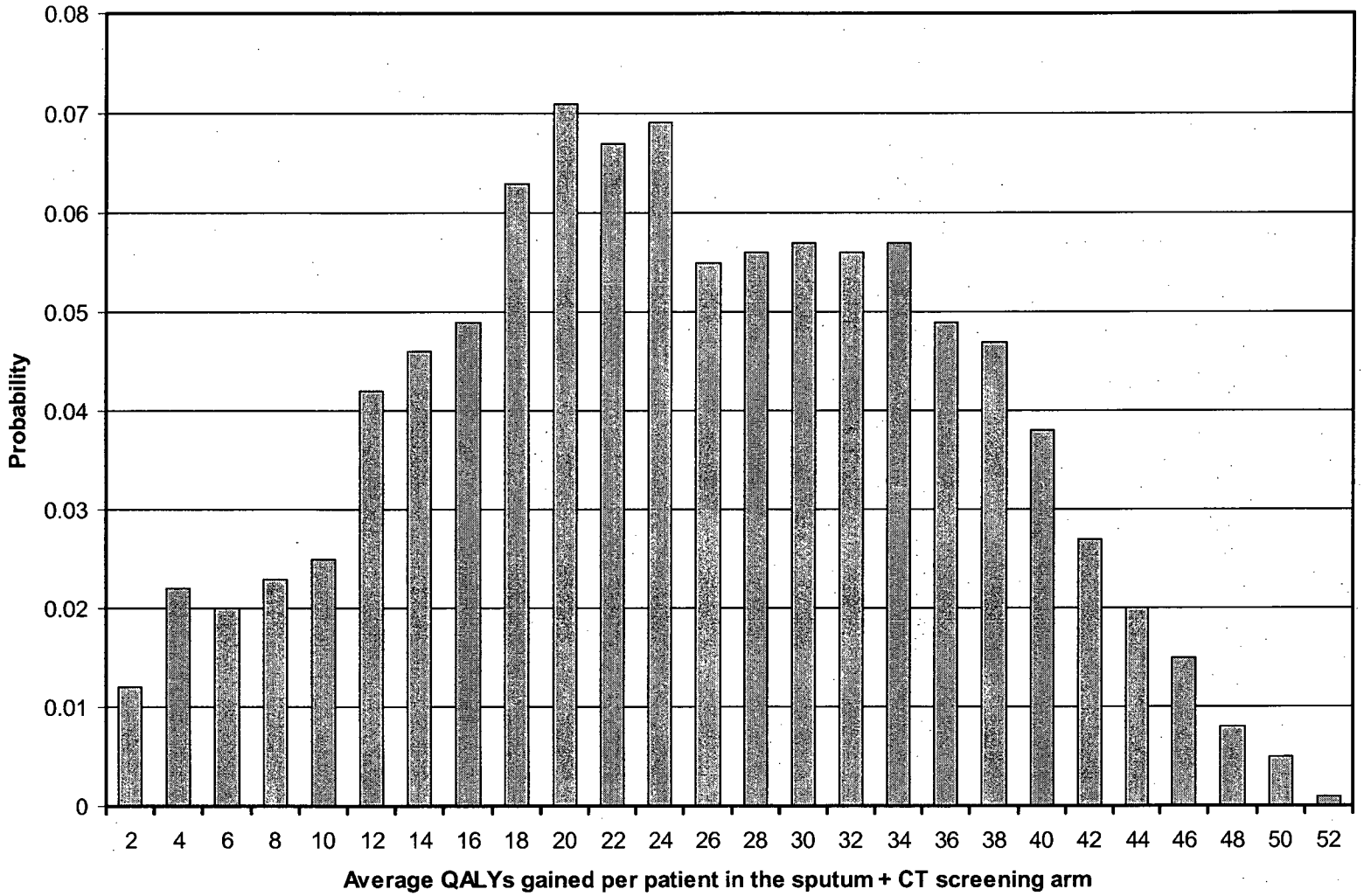

Figure 6.7 Distribution of average QALYs in the sputum + CT screening arm.

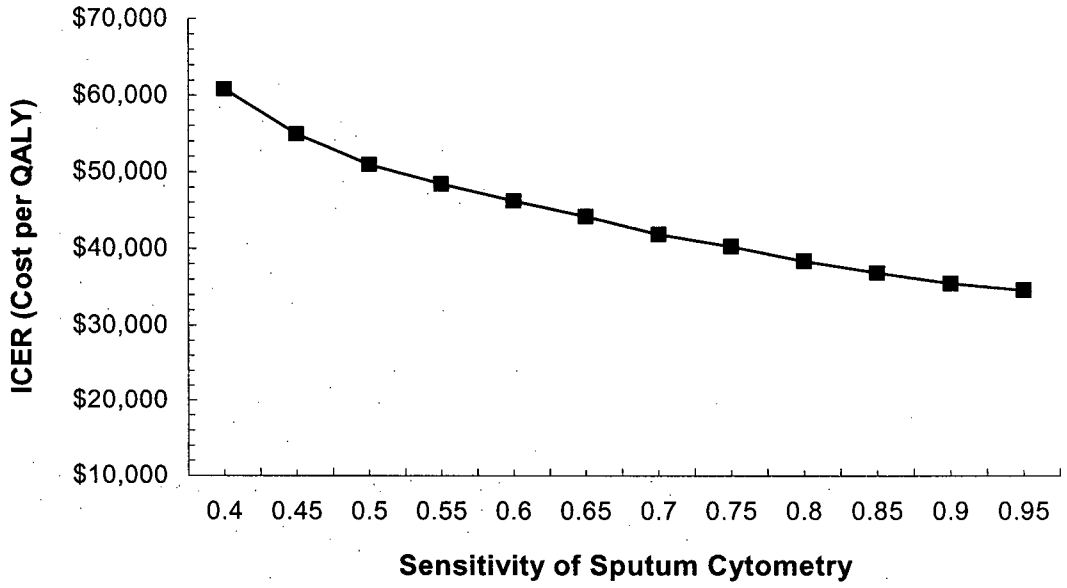

Figure 6.8 Sensitivity analysis on sensitivity of sputum cytometry test

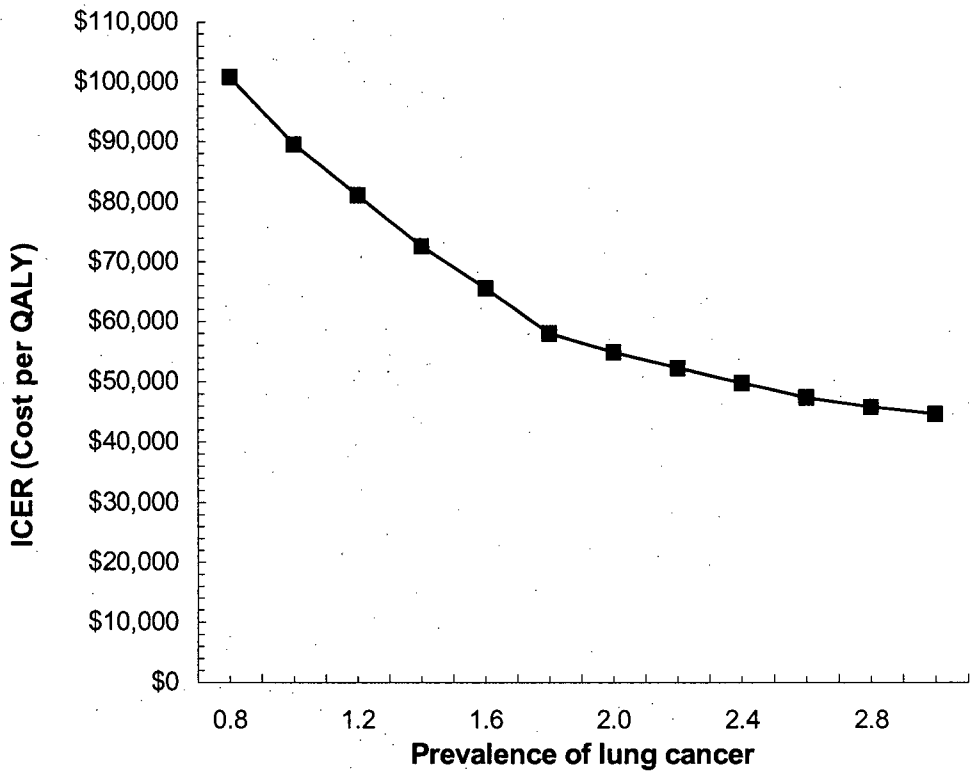

Figure 6.9 Sensitivity analysis on prevalence of lung cancer

6.4 Limitations and Feasibility

There are a number of limitations in this model that should be addressed. Firstly, the timing of lung cancer diagnosis can results in lead time bias. Overestimation of survival time, due to the backward shift in the starting point for measuring survival was not taken into consideration. Marshall et al., (2001) used a 1-year decrease in survival benefit as a proxy for a 1-year lead time bias and found that the cost-utility of CT screening increased from$19,533/QALY (US$ 1999) to $50,473/QALY. Two other important bias are likely to have an effect on outcomes in this economic model. Over-diagnosis bias, meaning those lung cancers detected through screening do not actually cause clinical disease and length time bias, in which tumours detected are very slow growing with long latency periods, have not been addressed in the model.

Costs incorporated in the decision analysis algorithm do not include indirect costs such as those attributed with diagnostic complications or opportunity costs such as travel time and lost productivity as a result of screening. As the age of screening candidates increases it is assumed that foregone opportunity costs would decrease as many patients would no longer be in the work force. The model also assumes that the capital equipment and resources for such a screening programme are already in place and so represents the 'steady state' when such a programme would be operating. This is considered a reasonable assumption for the model with respect to current clinical practice in diagnosing lung cancer using CT scans and fluorescence bronchoscopy, it does not however take into account the initial cost of setting up a laboratory with the proposed sputum cytometer to analyze clinical slides. Capital cost estimates related to the design, construction and set-up of a sputum cytometer have been estimated by PMI to be approximately $65,000. Practical considerations and policy issues raised by implementation of lung cancer screening such as how individuals at high risk for lung cancer would be targeted are not addressed in the model.

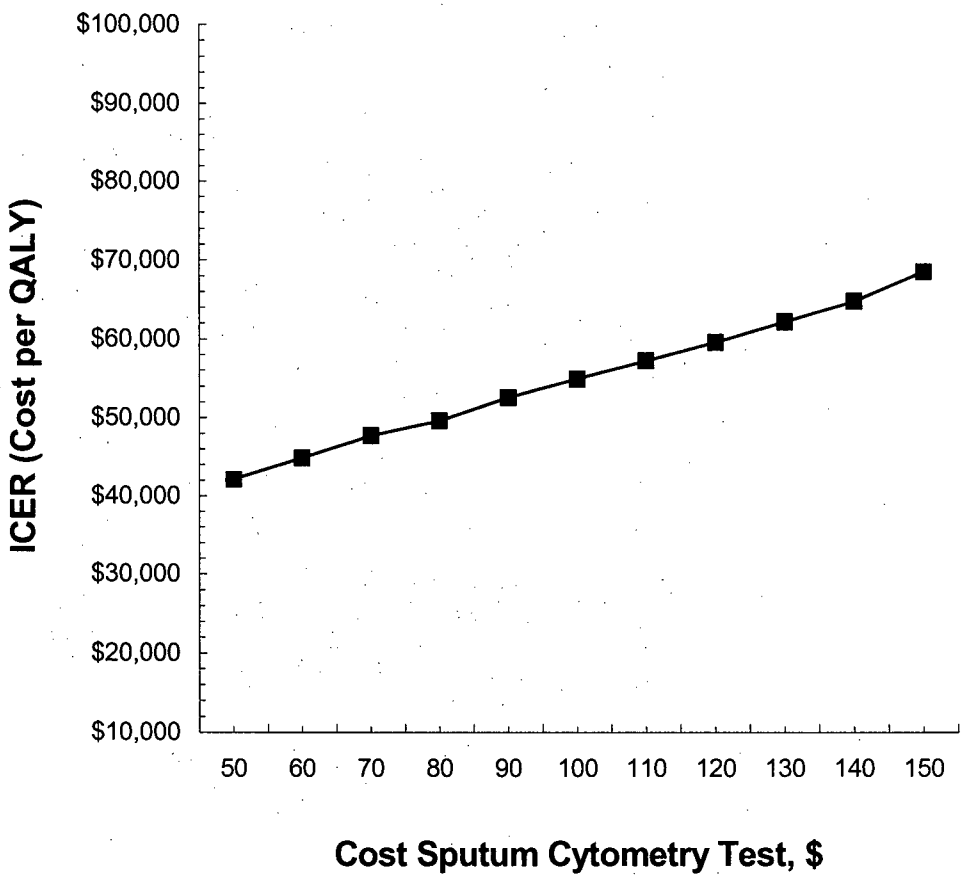

Figure 6.10 Sensitivity analysis on cost of sputum cytometry test

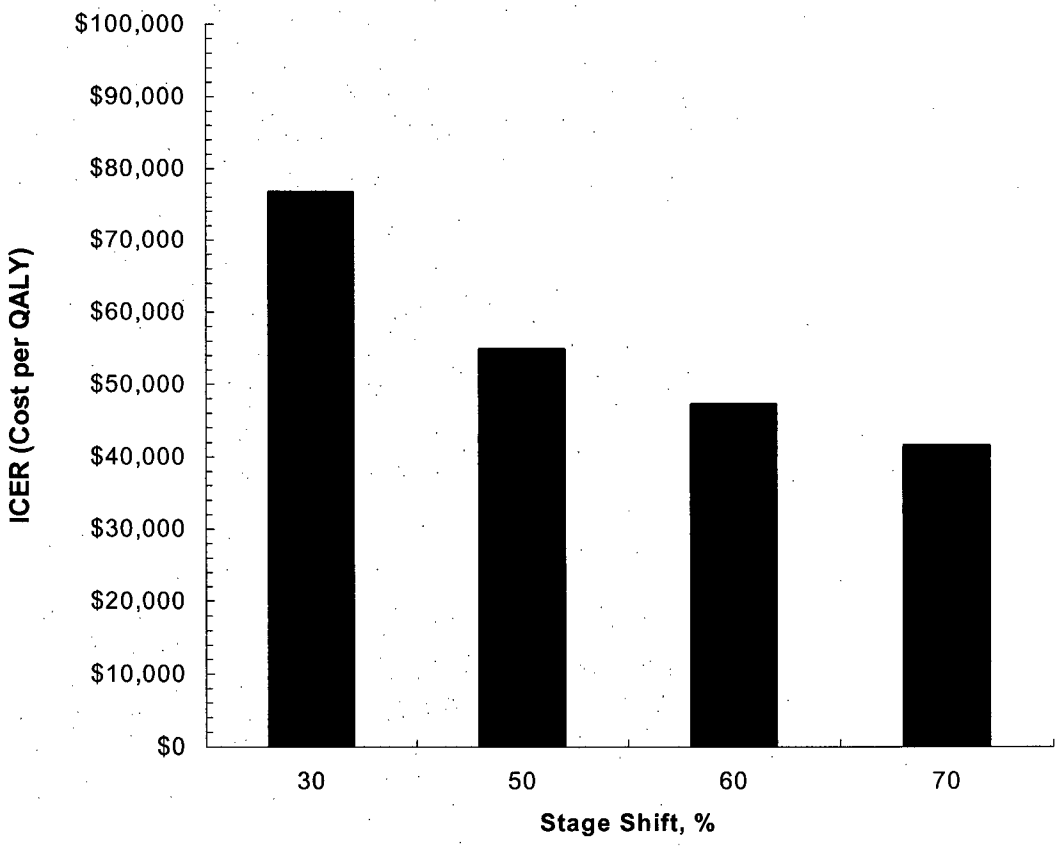

Figure 6.11 Sensitivity analysis on degree of stage shift from advanced to local stage lung cancer

Table 6.10 Multi-way Sensitivity Analyses of Lung Cancer Screening with Sputum Cytometry

Analysis Variable Description	ICER (Sputum + CT Screening vs. No Screening) (2002 CDN$/QALY)
Base-case Scenario Prevalence of lung cancer 0.019 Cost of sputum cytometry $100 Sensitivity of screening test 0.45	$54,923/QALY
Two Way Sensitivity Analyses	
A. Sensitivity 0.7 Prevalence 0.3	$54,116/QALY
B. Sensitivity 0.7 Cost of test $150	$67,408/QALY
C. Sensitivity 0.7 Stage Shift 70%	$57,322/QALY
D. Specificity 0.95 Sensitivity 0.40 (MAC as biomarker)	$66,571/QALY
Multi-way Sensitivity Analyses	
Most Favourable Scenario (favourable estimates from Table 6.3)	$34,388/QALY
Least Favourable Scenario (against screening estimates from Table 6.3)	$94,171/QALY

It is assumed that the entire cohort is screened and that there is full compliance with screening protocols. This is rarely this case in true clinical practice and an annual non-adherence rate has been shown to affect the ICER in other lung cancer screening models (Mahadevia et al., 2003). Clearly, if < 100% of the cohort is screened and complies with follow-up diagnostic testing, the ICER will increase. Annual non-adherence rates reported in lung cancer screening literature range from 3% to 18% (Henschke et al., 2001, Sone et al., 2001, Swensen et al., 2002). Finally, lung cancer disease progression was not stratified according to sex which may affect the outcome since men and women have slightly different survival rates.

6.5 Discussion

Under the assumptions of the base-case scenario in this model it was determined that in a high risk cohort of patients between 45 and 74 years of age, annual 5 year screening for lung cancer using sputum cytometry followed by CT scan appears to be cost-effective at $54,923/QALY (base-case results). Sensitivity analyses conducted on various influential parameters in the economic model generated cost-utility ratios ranging from $34,338/QALY to $100,845/QALY. Using the U.S. cut-off of $50,000 US per life year gained (Goodwin, 1998) or $65,340 CDN (based on exchange rate of 0.765061), results from the base-case scenario in this model are within the accepted level of cost-effectiveness. It is important to remember that this is a 5 year annual screen and lifetime screening of elderly patients were certainly increase the costs while gains in QALYs may be expected to plateau.

Comparing these results to other published cost-effectiveness studies (described in Chapter 4, Table 4.4) on screening for lung cancer, an ICER of $54,923/QALY is within an acceptable range for such a programme. Unfortunately, it is difficult to make direct comparisons across studies since the degree of variation in the model design is quite high. No other economic evaluation focused on using sputum cytometry as a first step in screening a high risk cohort for

lung cancer. Only one other study took into account quality of life and under most favourable estimates had an ICER of $42,500/QALY (US$) for CT screening (Mahadevia et. al., 2003). However, the study modeled annual screening for 20 years with a follow-up of 40 years which would add significantly to the baseline cost of any lung cancer screening programme. This time frame for screening appears excessive and somewhat unrealistic and the authors show that both costs and QALYs gained reach a steady state after approximately 25 years. The fact that the QALYs gained in this study are less than those reported by Mahadevia et al. can be partly attributed to the age of the initial screened cohort. It can be argued that a screening programme beginning at age 60 would not capture as many life years as one where screening began at age 50.

Based on recommendations from cervical screening programmes (BCCA, 2003), which use similar cytological screening techniques, it seems highly unlikely that annual screening for lung cancer using sputum analysis would be advocated. Mahadevia et al. (2003) reported a baseline cost-utility of $116,300/QALY, far above the $50,000/QALY cut-off and suggest that annual CT screening is not cost-effective. Rather, a screening programme that screens a high risk cohort every 2 to 3 years seems more plausible and the model constructed in this chapter is currently being reanalyzed in order to assess the cost-utility of bi-annual screening intervals. All other detailed economic evaluations calculated cost per life year gained (Table 4.4) and cost-effectiveness values are therefore expected to be underestimates since fewer life years would be gained had quality of life been considered. In addition, two studies discounted only costs and not life years and so although Chirikos et. al. (2002) calculated the cost-effectiveness of annual 5-year CT screening to be $35,400 per life year gained this again should be considered an underestimate.

Quality of life was not considered in the Marshall studied and assuming a lung cancer prevalence of 2.7%, with the incorporation of a one year 1 year lead time bias, the cost per life

year was reported to be $62,828 per life year. The high risk cohort was between the ages of 60-74 yrs old.

Lung cancer is estimated to account for approximately 20% of all the cancer care costs in the United States (Desch, 1996). This represents 2% of all health care costs. In absolute dollars, lung cancer costs the American health care system $8 billion annually, and the Canadian health care system $328 million annually (Evans, 1995). Extrapolating results from other cost-effectiveness studies the total cost for annual helical CT screening programme is very high. There are an estimated 50 million men and women in the United States classified as current or former smokers between the ages of 45 and 75 years old. If 50% of this group received periodic annual screening, the programme costs would be approximately $115 billion dollars (Mahadevia et al., 2003). Adding screening with sputum cytometry for a 5 year period would increase this amount by another $5.8 billion.

Until the clinical effectiveness of lung cancer screening has been widely proven there is little likelihood that a population based screening programme will be implemented. The most widely accepted end point in randomized cancer screening trials in disease-specific mortality (Black, 2002). If mortality is the proper measure of effectiveness, sputum cytometry for lung cancer will have to be clinically proven to contribute to a reduction in disease related death. On the other hand, if stage distribution and long-term survival are accurate measures of effectiveness, costing analyses such as this one suggest that screening for lung cancer is a worthy pursuit.

In summary, this economic model allows for a preliminary analysis of using sputum cytometry to screen for lung cancer. The CT screening arm is a weakly dominated strategy and should not be implemented as a screening program when sputum + CT screening is available in the health care setting. Estimates of the cost per QALY for sputum screening show it to be slightly more cost-effective than no screening at all in a high risk cohort of current and former

smokers. The results of the current clinical trial (PMI, Vancouver, B.C.) using sputum cytometry are highly anticipated and will provide more accurate parameters for use in such modeling. It can be concluded that using sputum cytometry in combination with CT scans in patients at high risk for lung cancer holds promise as a cost-effective lung cancer screening strategy. Research in this area will continue as screening algorithms and techniques improve resulting in a higher proportion of early stage lung cancer detection.

APPENDIX A Calculation of Pack Years in Smokers

Assuming 1 pack of cigarettes has 20 cigarettes in it.

Pack years equal the number of years you smoked times the number of packs per day.

For example:

Patient A: Smoked 2 packs a day for 20 years
Therefore Patient A has a 40 (2x20) pack year history.

Patient B: Smoked 3 packs a day for 10 years = 3x10 = 30
and Smoked 2.5 packs a day for 20 years = 2.5x20 =50
Therefore Patient B has an 80 (30+50) pack year history.

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