

June 2006

Primary Prevention in the 21st Century : A Dollar of Smoking Cessation

Robert S. Goldsmith

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Primary Prevention in the 21st Century:

A Dollar of Smoking Cessation

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A Thesis Submitted in Partial Fulfillment of the Requirements

for the Degree of Master of Public Health

At the University of Connecticut

2006

Approval Page

Master of Science Thesis

**Primary Prevention in the 21st Century:
A Dollar of Smoking Cessation**

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Preface

My parents, despite advancing age are in wonderful health. Dad, at 86, still works as an upholsterer. My appreciation of their vitality is heightened by the experience of a close personal friend whose father is in the last stages of both small cell and non-small cell lung cancer. While it is simplistic to attribute my parents' relative good health to smoking cessation alone, it is impossible to avoid the observation that they quit cigarettes decades ago, while our friend's father continued. I remember my parents receiving 4 cigarette sample boxes of *Salem's* unsolicited in the mail. They don't recall any specific moment when they decided to quit, but, but were somewhat ahead of their peers in recognizing the risk and acting.

As the lag period between smoking and the development of lung cancer in older Americans comes to a close, there remains a huge opportunity to learn from their illnesses and decrease this risk to those adults approaching middle age, our children and generations to follow. This thesis is dedicated to the hope that more effective tobacco control strategies can be deployed before irreparable harm comes to more Americans and smokers around the world.

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Section I Introduction

- But this same poison, steeped India weed
In head, hart, lunges, do the soote and cobwebs breede
With that he gasp'd, and breath'd out such a smoke
That all the standers by were like to choke.-*Samuel Rowlands, 1601*¹

The totality of healthcare resources in the United States is a relatively finite entity, limited by government expenditures, insurance payment pools, employer budgets and individual savings. Within this universe are competing forces such as the needs of public health to respond to common, communicable and preventable disease, and the expense of patient care for clinical illness and injury. The relative balance dictated by American society between these has varied with innovation, epidemiology of disease, availability of care, political influences, and in no small measure, commercial interests. This thesis will examine the relationship between a public health prevention effort, smoking cessation, and patient care for one of smoking's sequelae, lung cancer. It will analyze the effectiveness of both approaches as a function of survival and cost reduction.

The emergence of public health and patient care

Before the eighteenth century, epidemics such as plague, cholera, and smallpox evoked only limited public health efforts. The lack of understanding of a scientific basis of infection promoted a culture that routinely blamed disease on

¹ Borio, G. Tobacco Timeline: The seventeenth century-the great age of the pipe. *Tobacco.org-news and information*. www.tobacco.org/resources/history/Tobacco_History_17.html

moral impurity and relied on hope and prayer for survival. This is not to imply that public health did not exist prior to the 1700's. Efforts date at least to the Greek and Roman era. In France in 1350 King John II instituted sanitation ordinances among other reforms which provided that, "hogs should not be kept in the cities; that streets should be cleansed, and the offal removed; that butchers should not sell meat more than two days old in winter and one and one-half in summer and that fish should be sold the same day they were caught".²

It may be argued that the first Golden Age of public health began in 1796 and that eight-year-old James Phipps was its herald. In that year Edward Jenner inoculated the child with an extract of pus from a cowpox-infected individual. Subsequently, Phipps was exposed to variola, but did not contract the disease. With this success, the science of primary prevention was born.

An early milestone in population-based disease management was the discovery of the communicable nature and infectious origin of cholera by John Snow and his contemporaries. These revelations formed a basis for modern epidemiology and the application of sanitation to public health practice^{3, 4}. In America, the birth of the modern public health movement may have occurred with the publication of Lemuel Shattuck's *Report of the Massachusetts Sanitary Commission*, an extraordinary analysis of the relation of sanitation to morbidity

² Shattuck, L. et. al. Report of the Sanitary Commission of Massachusetts 1850. Dutton & Wentworth State Printers, Boston. 1850 page 5.
<http://www.deltaomega.org/shattuck.pdf>

³ Smith, G.D., Commentary: Behind the Broad Street Pump: aetiology, epidemiology and prevention of cholera in mid-19th century Britain. Intl. J. Epidem. 31:920-932. 2002.

⁴ Snow, J. Snow on Cholera. The Commonwealth Fund. New York. 1936

and declaration of the responsibility of government to provide a public health infrastructure. Other dramatic advances in public health were the development of a rabies vaccine by Pasteur in 1885, and the principle of antitoxins by van Behring and Kitasato at the turn of the century. The latter part of the 19th century was marked by a change in attitude described as “a great sanitary awakening”, the identification of filth as both a cause of disease and a vehicle of transmission, and the ensuing embrace of cleanliness.⁵ These advances brought the power of disease control to light and generated trust and reliance on public health for protection from disease.

The Spanish flu epidemic of 1918 highlighted both the opportunity and limitation of the public health capabilities of the time. Despite truly global efforts at quarantine and vaccination, somewhere between 25-40 million deaths occurred, 675,000 in the United States alone. A golden era had ended.

At the same time that limits to the effectiveness of public health interventions were realized in the first quarter of the 20th century, medical treatment of ill individuals began to emerge as a legitimate and powerful approach to healthcare. There is no single point where the application of disease management eclipsed the role of prevention in America, but by mid century there was clearly a greater reliance on individual care than population-based intervention. Several key discoveries and applications contributed to this trend, including:

- The purification of morphine and quinine in the 19th century

⁵ Institute of Medicine. *The Future of Public Health*. National Academy Press, Washington, D.C. 1988. page 58

- The first application of X-ray imaging in 1895 (Roentgen)
- Synthesis of acetylsalicylic acid by Bayer in 1897
- The first electrocardiogram, introduced at Presbyterian Hospital, Chicago, 1913
- The discovery of a pancreatic enzyme capable of controlling diabetic hyperglycemia in 1920 and the first use of insulin in 1922.
- Isolation of penicillin in 1929 and the earliest use of antibiotics between 1935 and 1940

Although the influence of public health may have waned in the 20th century, the advancement and application of public health principles did continue, both in the U.S. and abroad. The eradication of smallpox and advances against polio were absolute highlights in global medical history. Another prime example was the global suppression of malaria after the Second World War*. These achievements underscored several aspects of public health initiatives during that era. For one, the greatest successes were seen in underdeveloped or relatively impoverished regions. This was due both to the magnitude of public health and sanitary need and the lack of available medical care. It is possible, in fact, that even today, the age of patient care has yet to arrive in much of the world, where a paucity of physicians, limited access to technology, cultural barriers and inadequate financial resources hinder this advancement. In those regions the role of public health is extremely different than that in America; it remains the primary mode of healthcare.

Another lesson learned in the public health efforts of this century was the influence of politics, budgets and even environmental factors on prevention efforts. A footnote to the malaria eradication effort was the influence of political, and social forces on the program. Despite tens of millions of saved lives, the use of DDT to eradicate mosquitoes is best remembered by the environmental backlash championed by Rachel Carson in, *Silent Spring*. Political forces were more vividly on display in the formation of the public health response to swine flu in 1978, which led to widespread, unnecessary vaccination and a possible surge in reported cases of Guillen Barre syndrome.⁶

The United States CDC lists these ten great public health achievements in the 20th century, and promotes them as a significant cause for the 25-year improvement in life expectancy in this country.⁷

- Immunizations
- Motor vehicle safety
- Workplace safety
- Control of infectious diseases
- Declines in deaths from heart disease and stroke
- Safer and healthier foods
- Healthier mothers and babies

⁶ The development and deployment of DDT saved countless millions of lives. In India, for example, malaria deaths went from nearly a million in 1945 to only a few thousand in 1960.

⁶ Kolata, G. *Flu*. Simon & Schuster Publishing. 1999. 151-185

⁷ Ten Great Public Health Achievements in the 20th Century. *CDC Office of Communications*. 1999. www.cdc.gov/od/oc/media/tengpha.htm

- Family planning
- Fluoridation of drinking water
- Identification of tobacco as a public health hazard

These extraordinary achievements help demonstrate the viability of prevention programs, even during times of exponential advances in surgery, radiology and pharmacology, and will serve as the foundation for re-emergence of population-based efforts for the next generation.

The second half of the last century saw the emergence of a new threat to the public's health, the long-term effects of tobacco use. Within decades of the adoption of cigarette smoking as a socially acceptable and popular habit, the number of cases of lung cancer and chronic obstructive pulmonary disease increased dramatically. The frequency of these diagnoses may have plateaued in parallel with per capita U.S. tobacco consumption. These trends are displayed in figures 1-2.^{8, 9} It is both intriguing and unfortunate to note that the decrease in smoking prevalence has leveled since 1995. Might the incidence of smoking-related cancer and cardiopulmonary disease reflect that limit within the next several decades?

⁸ National Cancer Institute SEER Data. <http://seer.cancer.gov/>

⁹ Tobacco Use: United States, 1900-1999. *Oncology*. 13(12). 1999.

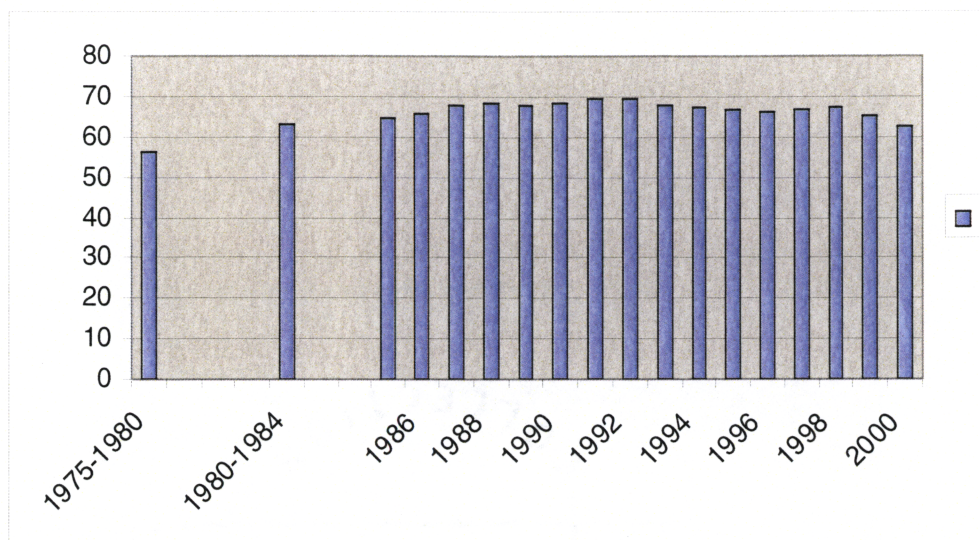


Figure 1. Incidence of Invasive Cancer of the Lung and Bronchus, 1975-2000. Adapted from National Cancer Institute, SEER database

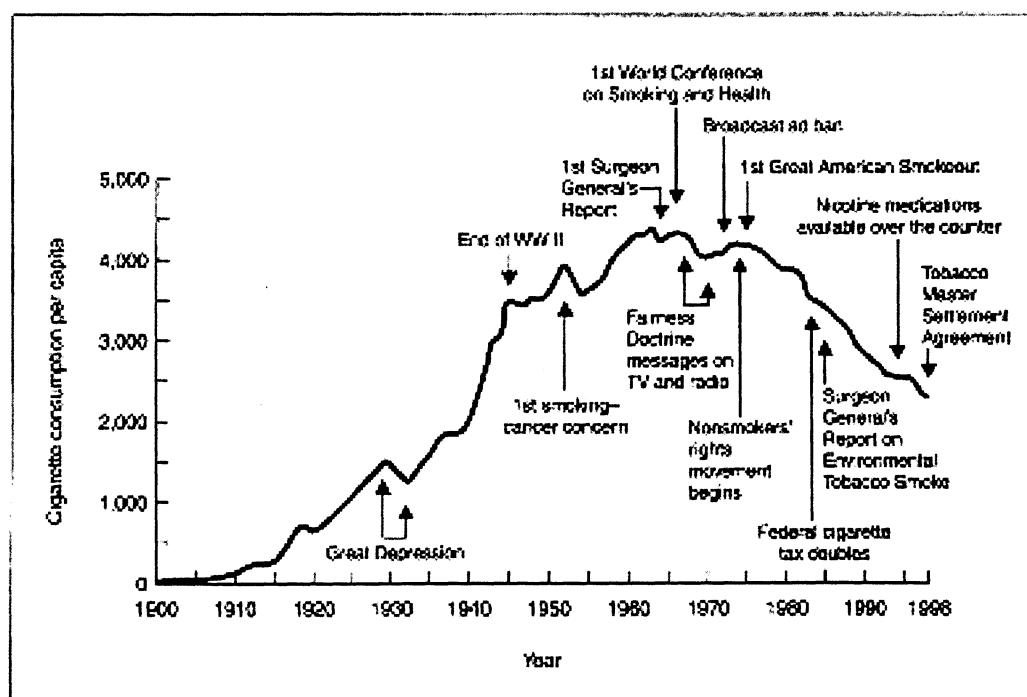


Figure 2. Annual Adult per Capita Cigarette Consumption and Major Smoking and Health Events-United States, 1900-1998. Source of data: U.S. Department of Agriculture, 1986 Surgeon General's report

Patient care and the concept of therapeutic plateau

A theory of **therapeutic plateau** holds that limits exist to the effectiveness of chronic disease management. As medical progress continues, the incremental improvement in outcome slows until the rate of change becomes relatively insignificant. There are three likely scenarios that help define therapeutic plateau. These may be described as follows:

1. Illness is refractory to therapy-There are human diseases that have not and do not respond well to surgical, medical, or other forms of treatment. Improvement in outcome for these illnesses may be graphed as a relatively horizontal line when viewing outcome as a historical function.
2. The illnesses may become refractory to treatment. An example of this phenomenon is the emergence of antibiotic resistance among several species of pathogenic bacteria. Limits may also result from the relative toxicity of treatment.
3. Illness is very responsive to a therapy-In this case a statistical limit to favorable outcome (cure, remission, survival, disease-free period) creates a plateau. Almost invariably, there will be limits to successful treatment. Despite the generally favorable outcome for many illnesses, some minority of patients will be poor responders, either due to late stage at diagnosis, inadequacy of treatment, intolerance of therapy, comorbidity, genetic predisposition, or unusually refractory disease.

In many cases, therapeutic plateaus are temporary phenomena. Dramatic new medical advances, which invigorate treatment protocols, are constantly reported. New fields, such as molecular biology, genetic engineering and immunotherapy will perpetuate outcome improvement for many diseases. Nonetheless, improvement in the health of a population as a function of advances in patient care may not be possible or indefinitely sustainable for any disease state. It is also critical to note that the availability of a physical cure does not relieve the patient of the anxiety associated with diagnosis, discomfort, expense, adverse reactions and inconvenience related to treatment, loss of productivity, and concern for recurrence or second primary recurrence of illness.

This limit of therapeutic plateau may be cause for reappraisal of alternative or additional strategies, such as primary prevention. This thesis will question whether a therapeutic plateau currently exists for lung cancer, and whether the limited effectiveness of cancer treatment should drive an emphasis on population-based smoking avoidance and smoking cessation programs.

Cost of care

Can the amount of money available for patient care continue to support the volume and types of treatment available? Are there cost savings associated with primary prevention that are meaningful to the health of Americans? The answer to these questions is critical in planning American healthcare strategy.

The recovery of the actor Christopher Reeve provides context for these questions. Prior to his death Mr. Reeve made unprecedented (and to some observers unexplainable) rehabilitation progress from an equestrian accident that left him quadriplegic. Despite a prognosis of nil recovery, he regained sensation and modest motor function in both his upper and lower extremities. His recovery argued strongly for accelerated research and implementation of 21st century technology for spinal cord injuries. Lost in the clinical scenario, however, was the cost. Mr. Reeve became relatively ventilator independent as result of implantation of an intra-diaphragm pacing device, a procedure which was neither widely available nor insurance reimbursable. He used an electrical stimulation bike which cost roughly \$100,000, and was supported by a team of 18 healthcare professionals. The cost of his care exceeded five hundred thousand dollars a year, two-thirds of which was covered by health insurance.¹⁰ An extremely difficult decision is whether these extraordinary resources ultimately detract from those available to the population, either by service limitations or affordability of insurance, and whether a greater good might be achieved by applying those funds toward the prevention of similar spinal injuries (via seat belt compliance measures, water safety courses and helmet promotion programs, for example). Even without broad application of the intensive rehabilitation services utilized by Mr. Reeve, car wrecks, debilitating falls and other accidents in the United States

¹⁰ Groopman, J. The Reeve Effect. *The New Yorker*. November 10, 2003. pages 82-93.

account for \$117 billion in cost each year, representing 10% of all medical spending¹¹

In the U.S. the *cost per case* of personal healthcare threatens to choke accessibility to the most modern, most effective treatments. This escalation is due to inflation of medical expenses, the expense of new treatment modalities, and rates of utilization. Outside the U.S. this burden is clearly being translated into clinically important gaps in the availability of patient care. Those limitations include clinically important formulary restrictions for government-sponsored healthcare plans, limitations on covered diagnoses, and basic unavailability of necessary medical care.^{12, 13, 14} It is not farfetched to worry that similar rationing currently exists in limited form (such as formulary restrictions) and could expand in the U.S. At present, several states are considering legislation designed to make “basic-coverage” available to employers and uninsured workers. These carve outs would be considered in the effort to increase the number of Americans with some coverage and reduce states’ Medicaid burdens.¹⁵

As private and public funding of patient care increases, the emphasis on public funding for primary prevention has waned. In fact, the U.S. Centers for

¹¹ Numbers. *Newsweek Magazine*. 17. January 26, 2004.

¹² Gawande, A. Dispatch from India. *NEJM*. 349.25. 2003;2383-2386.

¹³ The World Health Report, 2000. *WHO Publications*. 2000.
<http://www.who.int/whr2001/2001/archives/2000/en/pdf/overview.pdf>

¹⁴ Gill, B., Hewitt, P, and England, R.. China’s Ailing Healthcare and Welfare System. *Global Aging Initiative and Freeman Chair of Chinese Studies, position paper*. Center for Strategic and International Studies <http://www.csis.org/gai/ChinaHealthcare.pdf>. 2003

¹⁵ Freudenheim, M. Broader Health Coverage May Depend on Less. *The New York Times*. January 20, 2004.

Medicare & Medicaid Services lists public health as only one of 14 categories of expenditures.^{16**} Opposing this trend are cost-related efforts in the private sector, where some recognition of the cost-effectiveness of primary prevention is being documented. It is becoming clearer that the chronic disease burden among workers could be reduced through prevention programs targeted at the risk factors associated with the most common disabling conditions.¹⁷

Although the best available patient care is a noble and worthwhile objective, it is quite possible that spending on primary prevention of most injuries and preventable illnesses is of greater value to the U.S population as a whole. This thesis will examine the economics of primary prevention of lung cancer in some detail.

Patterns of Illness and Mortality in the 20th Century and Beyond

It would be an overwhelming task to analyze the contribution of patient care and public health on all illnesses found in the American public. A more reasonable approach is to focus on the most important causes of morbidity and mortality facing Americans today and in the future. Mortality causes in the United

¹⁶ Centers for Medicare and Medicaid Services: national health expenditures aggregate amounts and average change, the type of expenditure 1980-2002
<http://www.cms.hhs.gov/statistics/nhe/historical/t2.asp>

^{**} The 14 are hospital care, physician and clinical services, other professional services, dental services, other personal health care, home health care, nursing home care, prescription drugs, other medical products, government administration and net cost of private health insurance, government public health activities, research, investments, and construction.

¹⁷ Friedman, C. et. al. Assessing the Burden of Disease among an Employed Population: Implications for Employer-sponsored Prevention Programs. JOEM. 46(1). 2004. 3-9.

States in 1890, 1900 and 2000 are provided in table 1. Mortality trends for the period from 1950-2001 are charted in Figure 3^{18,19,20,21}. It is critical to glean from the tables that the leading causes of death at the beginning of the 20th century were infections. Although their prominence in part reflected an immaturity of the public interventions of infection control and immunization, the trend largely speaks to the inadequacies of individual care in the pre-antibiotic era.

Leading Causes of Death in the U.S., 1890, 1900 and 2000

1890	1900	2000
•Consumption	•Pneumonia	•Diseases of the Heart
•Pneumonia	•Tuberculosis	•Malignant neoplasms
•Infant cholera	•Diarrhea and enteritis	•Cerebrovascular disease
•Measles	•Heart Disease	•COPD
•Cancer	•Liver Disease	•Accidents
•Typhoid fever	•Injuries	•Diabetes mellitus
•Diphtheria	•Cancer	•Influenza and pneumonia
•Croup	•Senility	•Nephritis, nephrotic syndrome and nephrosis
•Bronchitis	•Diphtheria	•Septicemia
•Whooping cough		
•Scarlet fever		

Table 1

¹⁸ Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System and unpublished data, 1997

¹⁹ Anderson, RN. Deaths: Leading Causes for 2000. *National Vital Statistics Report*. CDC Report, 2002.

²⁰ Health, United States, 2003. National Center for Health Statistics. <http://www.cdc.gov/nchs/products/pubs/pubd/hs/03tables.htm>

²¹ Richardson, N., Chermayeff, C., and Walker, TK (eds) Medicine's Great Journey: One Hundred Years of Healing. 1992. Callaway Editions, Inc. p. 9.

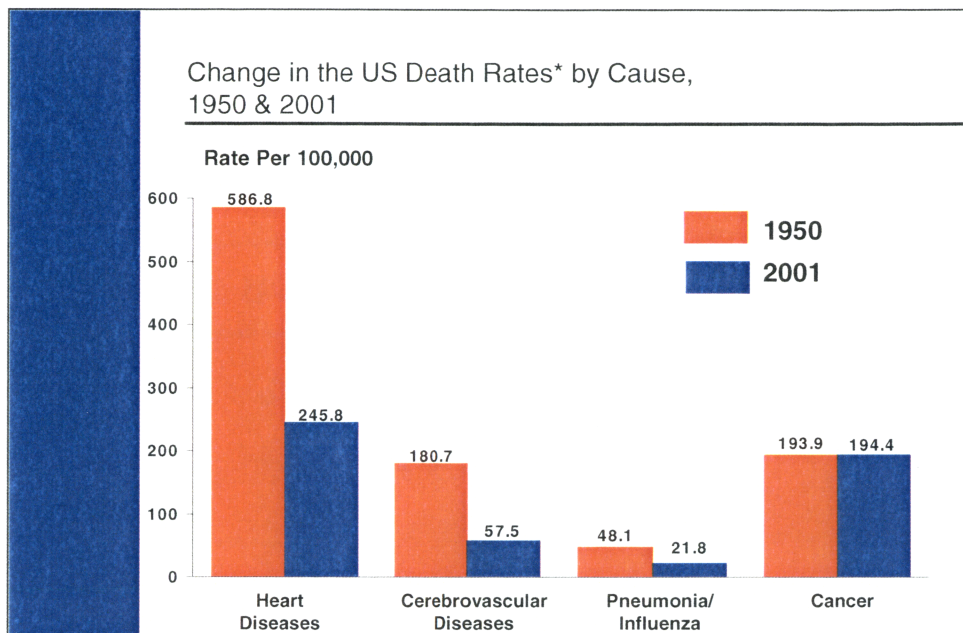


Figure 3-Change in the U.S. Death Rates by Cause, 1950 & 2001. Adapted from *Cancer Statistics 2004*. American Cancer Society. 2004

Infectious diseases were clearly displaced by chronic illness as the century progressed. According to data published for 2001, death from heart disease, for example, is more frequent than death from influenza and pneumonia by a factor of greater than 11. More than 90 million Americans live each day with chronic disease. Heart disease, cancer, diabetes and other chronic conditions now account for 70 percent of all deaths in the United States and for one-third of the years of potential life lost. According to census data the absolute number of deaths in the United States from noncommunicable disease will increase by 77%,

from 28.1 million to 49.7 million in the interval between 1990 and 2020.^{22,23} This increase in the burden of chronic disease is multifactorial and includes an increase in the prevalence of risk factors such as obesity and physical inactivity, the latent emergence of disease from decades-old exposures, treatment improvements and ongoing public health efforts.

Where will mortality trends evolve in years to come? The possible re-emergence of widespread or epidemic infectious disease cannot be ruled out for several reasons:

- Larger and shifting populations have increased the risk for spread of disease.
- Humans are living in closer proximity to wildlife and livestock than in any previous period.
- Climatic changes have improved the environment for many pathogenic microbes and their vectors.
- Importation of non-native animal species is becoming increasingly common, introducing non-native pathogens to new territories.
- Bioterrorists threaten to release increasingly virulent agents into the environment.

²² Health and Health Care 2010: The Forecast, The Challenge 2nd ed.. Institute for the Future. Josey-Bass Publishers. 2003. p.22.

²³ Public Health's Infrastructure: a status report. Department of Health and Human Services, page ii. 1999.

More likely than the re-emergence of acute illness as a dominant cause of mortality, however, is the continued pre-eminence of chronic disease. Several studies have recently reported an alarming trend in the increase of obesity-related illness and the associated cost. Clearly, diabetes and obesity related heart disease will continue to plague American society for years to come^{24,25,26}.

The Disability Adjusted Life Year (DALY) is a quantitative indicator of burden of disease that reflects the total amount of healthy life lost, to all causes, whether from premature mortality or from some degree of disability during a period of time. Analysis of disease patterns by DALY's in a subset of Americans further demonstrates the burden of chronic disease on the population. A striking prominence is noted in the Pareto of this data (figure 4). Thirty-eight percent of the DALY's were caused by chronic diseases that may in part be prevented by a single primary intervention, smoking cessation¹⁷. The Global Burden of Disease Study (GBD) created a model based on disease and injury trends since 1950. In their model, the leading causes of disability-adjusted life years were (in descending order) ischemic heart disease, unipolar major depression, road-traffic accidents, cerebrovascular disease, chronic obstructive pulmonary disease, lower respiratory infections, tuberculosis, war injuries, diarrheal disease, and

²⁴ Obesity Costs States Billions in Medical Expenses. CDC office of Communications. 2004.

²⁵ Finkelstein, E.A., Fieberkorn, I.C., and Wang, G. State-Level Estimates of Annual Medical Expenditures Attributable to Obesity. Obesity Research. 12 18-24. 2004

²⁶ Mokdad, A.H. et. al. Actual Causes of Death in the United States, 2000. JAMA. 291(10) 1238-1245. 2004.

HIV.²⁷ Certainly the ranking for the United States would differ somewhat from the global expectation, but those discrepancies would most likely occur at the tail end of the list, where infectious disease and diseases of childhood are more prominent. In the U.S. as elsewhere, lifestyle-related chronic disease will continue to pose the greatest threat. The GBD estimates 8.4 million annual smoking-related deaths by 2020. This figure is likely within the same magnitude of the U.S. CDC projection that an estimated 5 million U.S. persons who were aged 0-17 years in 1995 could die prematurely from smoking-related illnesses.²⁸ Will American medicine respond with primary prevention through lifestyle modification or treatment of resultant illness?

²⁷ Murray, CJ and Lopez, AD. Alternative Projections of Mortality and Disability by Cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997 May 24;349(9064):1498-504.

²⁸ Projected Smoking-related Deaths Among Youths, United States. *MMWR Weekly Report*. November 08, 1996 / 45(44);971-974.

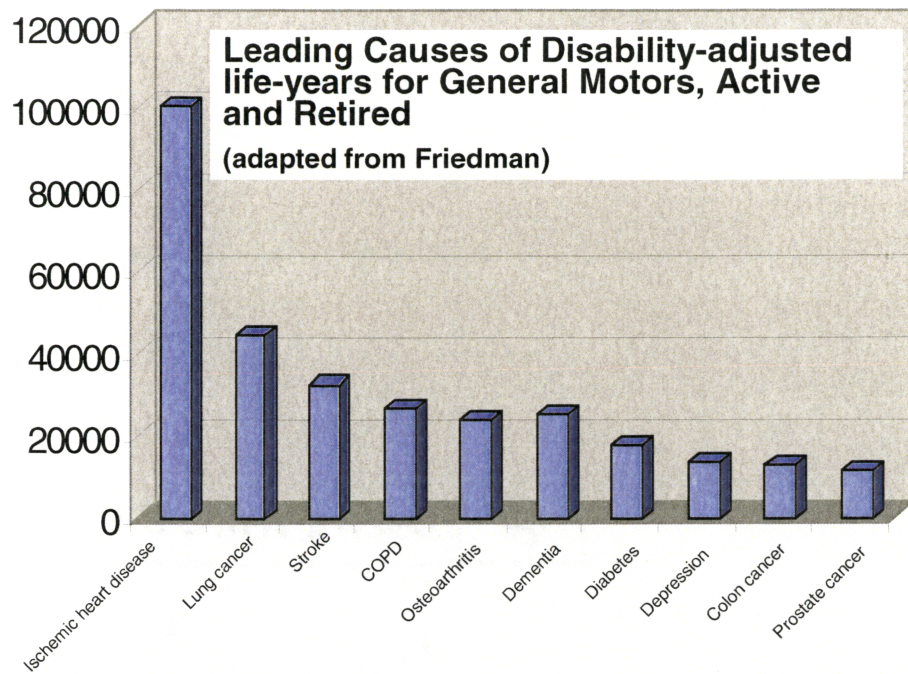


Figure 4

A Brief History of Smoking in America

Tobacco use in the Western Hemisphere

Overwhelming evidence supports the use of tobacco in various forms prior to the arrival of Columbus in the Caribbean in 1492. European efforts to cultivate the plant for export to Europe date to at least 1531 in Santo Domingo and 1580 in Cuba.²⁹ Even as advanced cultivation and trade was germinating, opinion was forming that use of tobacco was both unhealthy and addictive. King James I, in 1604, wrote one of the first essays on the dangers and social impropriety of tobacco, entitled *Counterbase to Tobacco*. In this writing he

²⁹ Borrio, G. *The History of Tobacco, Part I*. History Net.
<http://www.historian.org/bysubject/tobacco1.htm>

stated, “Custome lothesome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs and in the black and stinking fume thereof, nearest resembling the horrible stygion smoke of the bit that is bottomless.” Shortly after publication of the essay, England saw its first tobacco tax. It remains unclear whether the tax was established as a public health measure or convenient means to further the wealth of the monarchy. Within years of *Counterbase to Tobacco*, other prominent subjects also commented on tobacco its adverse effect on health. In 1610, Sire Francis Bacon wrote that, “tobacco use is increasing and that it is a custom hard to quit”.³⁰

These denouncements were certainly not the standard of the period. As smoking and snuff became increasingly popular, there were, on both sides of the Atlantic, continuing stories of its health benefits, including reports of a protective effect against plague.

Through the next centuries, tobacco use in America was transformed from a personal habit to a social phenomenon and financial pillar. Regional economies became dependent on the crop, as did the governments that taxed cigarettes and other tobacco-containing products. The first federal tax on cigarettes was imposed in 1864. During that period a populist health reform movement led to the earliest anti-tobacco movement in this country. The efforts were, however, aimed at moral and hygiene concerns, rather than the health

³⁰ Key Dates in the History of Tobacco. The Ash Organization.
www.ask.org.uk/html/schools/keydates.html.

effects of smoking.³¹ A milestone in the expansion of tobacco use may be marked in the invention of machinery to mass produce cigarettes in the mid 1880's.

The give and take of tobacco use continued into the 20th century. The cachet of smoking, established in earlier eras, continued, as did the backlash. Moralists blasted cigarettes, referring to them as “coffin nails” and “gaspsers”. Henry Ford deemed cigarette smokers unemployable in a 1914 brochure, stating, ““Boys who smoke cigarettes we do not care to keep in our employ. In the future we will not hire anyone whom we know to be addicted to this habit. It is our desire to weed it entirely out of the factory just as soon as practicable....”³²

Smokers were characterized as criminals, neurotics or possibly drug addicts. In 1892 the Senate Committee on Epidemic Diseases agreed that cigarettes were a public health hazard and urged the states to restrict their use. In 1900 an increase in cancer of the lung was noted, particularly by vital statisticians. These calculations are generally described as the first scientific evidence of the relationship between tobacco and chronic disease.³³ Between 1890 and 1930 fifteen states enacted law to ban the sale, manufacture,

³¹ Historical Fact Sheet. CDC Tobacco Information and Prevention Source. www.cdc.gov/tobacco/sgr/sgr_2000/factsheets/factsheets_historical.htm

³² Davis, R. Tobacco Control: How is Michigan Doing? Tobacco-Free Michigan Membership Meeting July 25, 2003 / East Lansing, Michigan

³³ Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. 1964. Page 5

possession or use of cigarettes.³⁴ What changed, however, in the first part of the last century, was the advent of modern advertising. In 1914 the R.J. Reynolds Tobacco Company launched its first national marketing campaign, for Camel cigarettes. Competitors quickly followed.³⁵

The First World War became another major force for the propagation of smoking in America. The United States entered the war under the banner of moral reform, pledging to free the world with an army untainted by alcohol and prostitution. In that context, smoking among the military was considered a reasonable allowance³⁴. Army surgeons praised cigarettes for helping the wounded relax and easing their pain. After the war's end, smoking popularity soared, both by social acceptance and dependence by an ever-increasing percent of the populace.

It was not until the 1940's that a reinvigorated anti-smoking campaign took hold. Different than previous efforts targeting the immorality of smoking, the new program was based on biostatistics and the newly emerging science of epidemiology. Although scientific papers preceded, a study by Lombard and Doering, published in the *New England Journal of Medicine* in 1928, is generally credited with the first true application of the scientific method to the risk of tobacco use. The case-control study demonstrated that smoking was more

³⁴ Tate, C. Cigarette Wars: the Triumph of "the Little White Slaver". Oxford University Press. 1999. pp4-5.

³⁵ Sivulka, J. Soap, Sex, and Cigarettes: a Cultural History of American Advertising. Wadsworth Publishing. 1998. p. 166.

common among cancer patients than an otherwise similar cohort of individuals without malignancy.³⁶

Early research and the apparent emergence of an important number of cases of smoking-related illness, prompted further research, including the landmark prospective studies of Doll and Hill in the U.K. and Hammond and Horn in the U.S. in the early 1950's^{37,38} Mounting and irrefutable evidence on the potential for cigarette smoking to induce lung cancer lead to increased public health scrutiny. In 1957 U.S. Surgeon General Leroy Burney announced that, "The Public Health Service feels the weight of the evidence is increasingly pointing in one direction; that excessive smoking is one of the causative factors in lung cancer"³¹. It is of interest and some importance that the Tobacco Industry Research Committee, representing the scientific findings of tobacco growers, manufacturers, and warehousemen was chartered in the same decade.

A further milestone to the recognition of a public health role for tobacco control was reached with the first Surgeon General's report on Smoking and Health. The report was prompted by, among other concerns, an increase in lung cancer deaths from 3,000 in 1930, to 18,000 in 1950, 27,000 in 1955, and 41,000 in 1962. The report cited 7,000 studies toward a list of conclusions which included that the death rate for smokers of cigarettes only, was about 70% higher

³⁶ 1989 Surgeon General's Report: reducing the health consequences of smoking. 1989. Chapter 1, page 5. http://www.cdc.gov/tobacco/sgr/sgr_1989/1989SGRChapter1.pdf

³⁷ Doll R, Hill AB. Smoking and carcinoma of the lung. Preliminary report. *BMJ* 1950; ii: 739-748.

³⁸ Wynder EL, Graham EA, Croninger AB. Experimental production of carcinoma with cigarette tar. Part 1. *Cancer Res* 1953;13:855

than that for non-smokers. Although no specifics were provided, the report also stated, "Cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action."³³

In the 1960's the percentage of Americans consuming cigarettes began to level. Although the reasons are likely multiple and varied, it is clear that the Surgeon General's report and supporting research sparked some change in social attitudes. Since that time a progressively smaller fraction of Americans have become or remained smokers. This trend is visible in Figure 5. The cause for this decline is likely multifactorial and includes further enlightenment on the health effects of cigarette smoke, changes in the social perception of smoking, the increasing cost of cigarettes and restrictive legislation (Arizona became the first state to restrict smoking as an indoor air pollutant, in 1973). Some highlights of the last 30 years include the 1965 Federal Cigarette Labeling and Advertising Act, the 1988 ban on smoking on domestic commercial airliners, and the 1996 FDA regulations designed to regulate tobacco sales and marketing aimed at minors³¹. It is of some concern, however, that the rate of decline in smoking prevalence has flattened within the past decade. It remains uncertain whether continuing avoidance and cessation efforts will re-energize the curve, or whether a core of incorrigible tobacco users will remain.

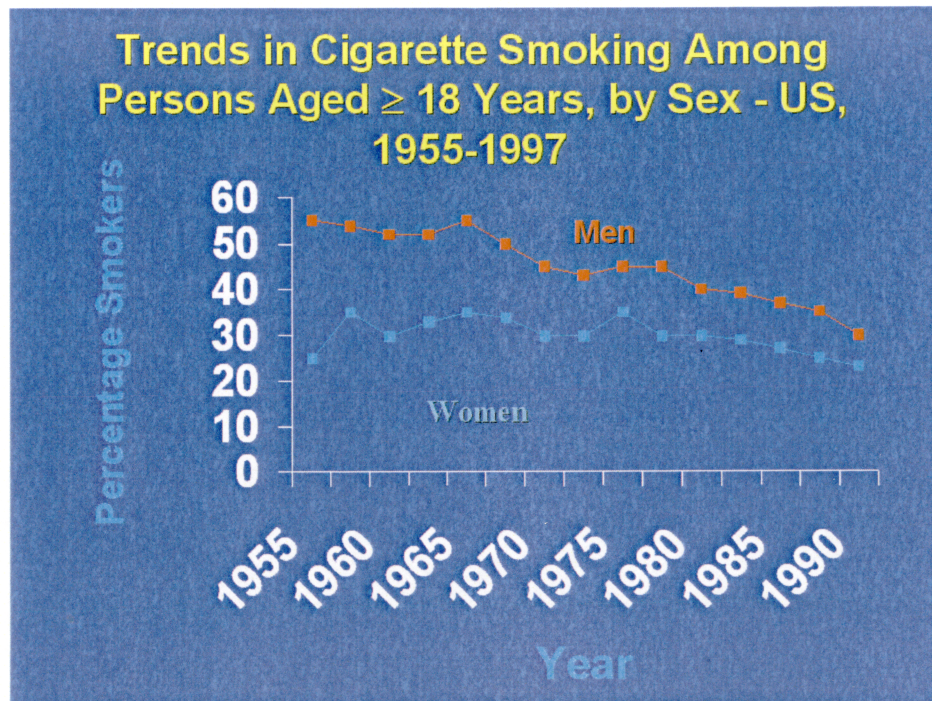


Figure 5. Note that the public health definition of “smoker” was changed in 1992. Source of Data: Current Population Survey, National Interview Survey 1965-1997.

Current Epidemiology of Lung Cancer in America

The epidemiology of lung cancer is relatively unique given the single predominant risk factor, inhalation of the carcinogens produced by the combustion of tobacco. It is also marked by a case fatality rate of 90%, assuring that incidence and mortality rates are nearly equal.

Incidence

Lung cancer is the most frequently diagnosed cancer in the world and the leading cause of death from cancer. In the U.S. it is the second most common cancer diagnosed in men and women and the leading cause of cancer mortality. It is certainly no coincidence that a measurable disease burden from lung cancer

is a relatively recent phenomenon, arising first in Western Countries in the 1930's, with incidence rates rising sharply in subsequent decades.³⁹ Prior to that time a diagnosis of carcinoma of the lung was a very rare phenomenon, accounting for <1% of all recorded tumors in one series reported in 1921^{40*}. It would be overly simplistic to state that lung cancer did not exist before that time. Prior to the 20th century the diagnosis of lung tumors relied entirely on history and physical examination. Even after discovery of the roentgen ray, a considerable period elapsed before its application to diagnostic oncology. Similarly, the bronchoscope, invented in the late 1800's was not frequently used for cancer diagnosis until the 1930's⁴¹. By 1933 the reported incidence of lung cancer had increased to 5-10% of all carcinomas⁴². Between the establishment of smoking as a social phenomenon and today, the incidence and mortality rates have varied in parallel with tobacco utilization trends⁴³. As suggested above, lung cancer is unique among all malignancies in having a single, modifiable risk factor that

³⁹ Smith, R. and Glynn, T. Lung Cancer: epidemiology of lung cancer. Radiologic Clinics of North America 38(3). 2000.

⁴⁰ Smith, A. L. The Prevention and Treatment of Cancer. The Practitioner. 1:189-201. 1921.

*It is of historical interest that this article noted the presence of cancer clusters among family members and those working or residing in close contact with cancer cases. This phenomenon was ascribed to an *infectious* cause for malignant tumors. Non-infectious environmental causes (such as smoking) had yet to be considered.

⁴¹ Meade, R.S. A History of Thoracic Surgery. Charles C. Thomals Publisher. 1961. pages 180-181.

⁴² Graham, E. A and Singer, J.J. Successful Removal of an Entire Lung for Cacinoma of the Bronchus. JAMA. 101:1371-1374. 1933.

⁴³ Alberg, A. and Samet, J. Lung Cancer Guidelines: epidemiology of lung cancer. Chest. 123(1). 2003.

accounts for a high percentage of cases. Compared to individuals who have never smoked, cigarette smokers have an overall 20-fold increase in lung cancer risk. It is currently estimated that up to 8% of all smokers will develop some form of lung cancer during their lifetimes.⁴⁴

State-by-state variations in lung cancer incidence also support the relationship with cigarette smoking. As may be seen in figure 7, Kentucky, which has consistently lead the country in percentage of adult smokers, also has the highest combined male/female mortality from lung cancer. The smoking prevalence is more than twice that of Utah, the state at the opposite pole of the study, and the mortality rate was 300% greater in the years 1996-2000.⁴⁵

As might be expected, the risk of lung cancer among smokers varies tremendously, depending on other related and independent risk factors including age, gender, duration of smoking, and number of cigarettes per day. Smokers with chronic obstructive lung disease (COPD) have a higher risk than those with normal lung function^{46,47}. In one analysis among 18,172 smokers, ten-year cancer risk ranged from 15% for a 68-year-old man who had smoked two packs per day for 50 years, to 0.8% for a 51-year old woman who smoked one

⁴⁴ Siepmann, J.P. Smoking **Does Not** Cause Lung Cancer. J. Theoretics. 1(4). 1999. www.journaloftheoretics.com/Editorials/Vol-1/el-4.htm

⁴⁵ Weir, H.K. et. al Annual Report to the Nation on the Status of Cancer, 1975-2000, Featuring the Uses of Surveillance Data for Cancer Prevention and Control. J. Nat. Cancer Inst. 95(17);1276-1298. 2003.

⁴⁶ Skillrud, D.M., Offord, K.P., and Miller, R.D. Higher Risk of Lung Cancer in Chronic Obstructive Pulmonary Disease. Ann. Int. Med. 105;503-507. 1986.

⁴⁷ Tockman, M.S. et. al Airways Obstruction and the Risk for Lung Cancer. Ann. Int. Med. 106;512-518; 1987.

pack per day for 28 years before quitting 9 years earlier.⁴⁸ Current models have led to the development of a lung cancer risk assessment tool that is publicly available and promoted as part of the prevention program at Memorial-Sloan Kettering Cancer Center.⁴⁹

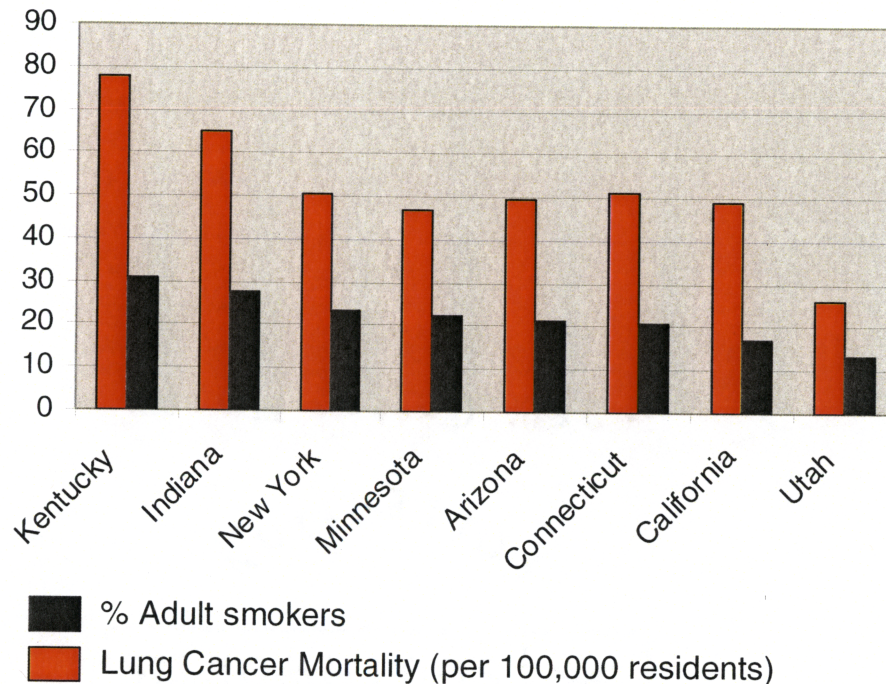


Figure 7 Smoking prevalence and lung cancer mortality in selected states. Smoking data is for 1985, the first year for which comprehensive state-specific data was reported. Mortality data is for the years 1996-2000 (Mortality rates adapted from Weir. Prevalence data derived from The American Lung Association.⁵⁰)

Lung cancer is not a homogenous illness, but rather a group of histologically distinct entities. The main cell types may be roughly categorized by

⁴⁸ Bach, P.B. et. al. Variations in Lung Cancer Risk Among Smokers. JNCI 95(6); 470-478.2003.

⁴⁹ Lung Cancer Risk Assessment Tool. Memorial Sloan Kettering Cancer Center. <http://www.mskcc.org/mskcc/html/12463.cfm>

⁵⁰ Trends in Tobacco Use. American Lung Association Epidemiology and Statistics Unit. 2003. www.lungusa.org/data/smoke/SMK1.pdf

their propensity for early metastasis. Thus, squamous cell, adenocarcinoma and large cell lung cancers all tend to invade locally early in the course of the illness, with late distant spread, while small cell cancer is most often metastatic at the time of diagnosis. The incidence of these subtypes are displayed in figure 8. Of note in the chart is the general trend described previously, where peak incidence is seen in the years just before the rate of smoking in the U.S. began to decline. The exception is adenocarcinoma, which has continued to increase in frequency to the present⁵¹. The trend in adenocarcinoma incidence is likely multifactorial, including changes in diagnostic standards, number of cigarettes consumed by smokers, and changes in cigarette inhalation patterns associated with the introduction of filtered and low tar products over recent decades. It is postulated that smokers of filtered and low tar-low nicotine cigarettes inhale more deeply, exposing deeper lung regions to these carcinogens. Adenocarcinoma of the lung are primarily peripheral lesions, as opposed to small cell and squamous tumors, which most often arise near the hilum.^{52,53}

⁵¹ Wu, A.H Secular Trends in Histologic Types of Lung Cancer. J. Natl Cancer Inst. 77(1). 1986. 53-56.

⁵² Thun, M.J. Cigarette Smoking and Changes in the Histopathology of Lung Cancer. J. Natl. Cancer Inst. 89(21). 1997 1580-1586

⁵³ Morabia, A. Cigarette Smoking and Lung Cancer Cell Types. Cancer. 68(9). 1991. 2074-2078.

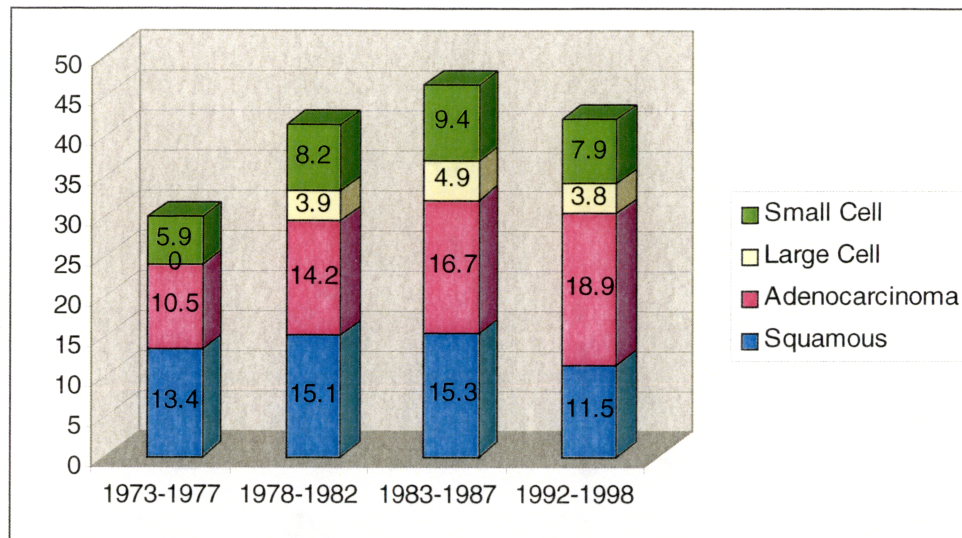


Figure 8 Age-adjusted incidence rates per 100,000 U.S. population of lung cancer by histologic subtype and time period (adapted from SEER data, <http://seer.cancer.gov>)

Mortality

440,000 Americans per year are now dying of smoking-related illnesses, including chronic respiratory disease, cardiovascular disease, stroke, and cancer of the lung, oropharynx, esophagus, stomach, pancreas, kidney, cervix, and blood.⁵⁴ Because of the high case-fatality rate of lung cancer, the incidence and mortality rates are nearly equivalent. Thus, it follows that the death rate has decreased in concert with incidence, in both white and black men since 1993, roughly 30 years after smoking prevalence reached its peak⁴⁵. The relative risk of lung cancer mortality is provided in table 2

In addition to the survival data presented below, evidence indicates that non-smokers with lung cancer have a better chance at longevity than those with

⁵⁴ Olson, E. U.S. Lengthens the List of Diseases Linked to Smoking. *The New York Times*. A15. May, 28, 2004.

a tobacco history. It may be postulated that smokers, by virtue of comorbid conditions or poorer performance status, would have a shorter survival. “Non-smokers” may develop cancer as a consequence of environmental (“second hand smoke”) exposure, and may not have other stigmata of chronic, high intensity cigarette use. Alternatively, It is possible that this phenomenon is not directly linked to smoking at all. Lung cancer in non-smokers may be a distinct pathologic entity with an inherently better clinical outcome.⁵⁵

Study Group	Relative risk	
	Cigarettes per Day	
	1-19	≥20
ACS-CPS I (men)	6.5	13.7
ACS-CPS II (men)	18.8	26.9
ACS-CPS II (women)	7.3	16.3

Table 2-ACS-CPS, American Cancer Society Cancer Prevention Study. Adapted from Hays⁵⁶ and The U.S. Surgeon General's Report on the Health Benefits of Smoking Cessation⁵⁷

Other risk factors

It is long past speculation that cigarette smoking is the major risk factor for lung cancer among Americans. Although tobacco use is clearly associated with all types of lung cancer, nonsmokers also develop these tumors. This suggests that risk factors other than smoking may contribute to pulmonary

⁵⁵ Nordquist, L.D., et. al. Improved Survival in Never-smokers vs. Current Smokers with Primary Adenocarcinoma of the Lung. *Chest* 126(2): 347-51. 2004.

⁵⁶ Hays, J.T. et. al. Trends in Smoking-related Diseases. *Postgraduate Medicine*. 104(6). 1998

⁵⁷ The Surgeon General's 1990 Report on the Health Benefits of Smoking Cessation: Executive Summary-Introduction, Overview and Conclusions. *MMWR* 39(RR-12); 2-10. 1990.

oncogenesis. Although all risk factors have not been clearly identified, it is now known that environmental (“second-hand”) exposure to cigarette smoke, radon inhalation, asbestos, dietary deficiency in antioxidants, HIV, inactivity and certain non-malignant lung diseases play a role^{58,59}. It is of historical irony that as late as two decades ago, cigarette smoking was considered protective against the lung cancer sustained by uranium miners.^{60,61}

Environmental influences aside, there are several genetic factors that have also been implicated in the development of lung cancer, including the CYP1A1 and mu-1 genotypes which influence carcinogen activation and detoxification proteins⁶². In one case control study, individual with low levels of the DNA repair enzyme 8-oxoguanine DNA N-glycosylase (OGG) were up to 124 times more likely to have lung cancer than those with normal levels.⁶³

⁵⁸ Wistuba, I.I. Comparison of Molecular Changes in Lung Cancers in HIV-positive and HIV Indeterminate Subjects. *JAMA*. 279; 1554-1559. 1998.

⁵⁹ Lee, I.M., Sesso, H.D. and Paffenbarger, R.S. Physical Activity and Risk of Lung Cancer. *Int. J. Epidemiol.* 28(4);620-625. 1999.

⁶⁰ Bilello, K.S., Murin, S. and Matthay, R.A. Epidemiology, etiology, and prevention of Lung Cancer. *Clinics in Chest Medicine* 23(1). 2002

⁶¹ Roscoe, R.J. et al. Lung Cancer Mortality Among Nonsmoking Uranium Miners Exposed to Radon Daughters. *JAMA*. 262 (5). 1989. 629-633.

⁶² Wong, MP et. al. Chromosomal aberrations of Primary Lung Adenocarcinomas in Nonsmokers. *Cancer*. 97; 1263-1270. 2003.

⁶³ Bosch, X. Genetic Basis for Lung Cancer Risk in Smokers. *The Lancet Oncology*. 4(10). 2003.

Gender Differences

Women have traditionally experienced lower rates of lung cancer than men, a distinction that is largely related to differences in smoking prevalence. This explanation also helps to explain the recent narrowing of the differential, as the rate of lung cancer begins to reflect the relative increase in popularity of cigarette use among women over the past several decades. That difference first began to narrow in the 1960's as the effects of increased smoking among females emerged⁴³.

Overall, women with lung cancer are younger than men and have smoked less intensively. Females have a disproportionate ratio of adenocarcinoma and small cell lung cancer relative to males. In addition, only 30-40% of females with lung carcinoma are cigarette smokers, as compared to 80% of men. In addition to lung cancer, cigarette smoking among women has been associated with cancer of the bladder, cervix, esophagus, kidney, oropharynx and pancreas.^{62,64}

Recently there has been considerable evidence to support differences, other than prevalence of smoking, to explain variations in lung cancer incidence and response to therapy among women. For example, women may have increased expression of the CYP1A1 oncogene and a lower capacity for DNA repair. It has also been noted that estrogen signaling may have a biological role in lung tumorigenesis. These differences, along with variations in stage at

⁶⁴ Reichert, V.C. et. al. Women and Tobacco Dependence. Med. Clin. North America. 88(6).1-13. 2004.

diagnosis may also explain why women with lung cancer have an overall better prognosis^{65,66,67}

Racial and ethnic differences

There are clear differences in lung cancer incidence between ethnic and racial groups in the U.S. These variations seem to relate both to genetic susceptibility and differences in tobacco use. A comparison in the incidence among major ethnic groups in the U.S. appears in figure 6

⁶⁵ Patel, J.D., Bach, P.B. and Kris, M.G. Lung Cancer in U.S. Women: A Contemporary Epidemic. JAMA. 291(14), 1763-1768.2004.

⁶⁶ Stabile, L.P. et. al. Human Non-Small Cell Lung Tumors and Cells Drived from Normal Lung Expres Both Estrogen Receptor α and β and Show Biologic Responses to Estrogen. J. Cancer Research. 62:2141-2150. 2002

⁶⁷ Radzikowska, E. , Glaz, P. and Roszkowski, K. Lung Cancer in Women: Age, Smoking, Histology, Performance Status, Satge, Initial Treatment and Survival. Population-based Study of 20,561 Cases. Annals of Oncology. 13:1087-1093.2002.

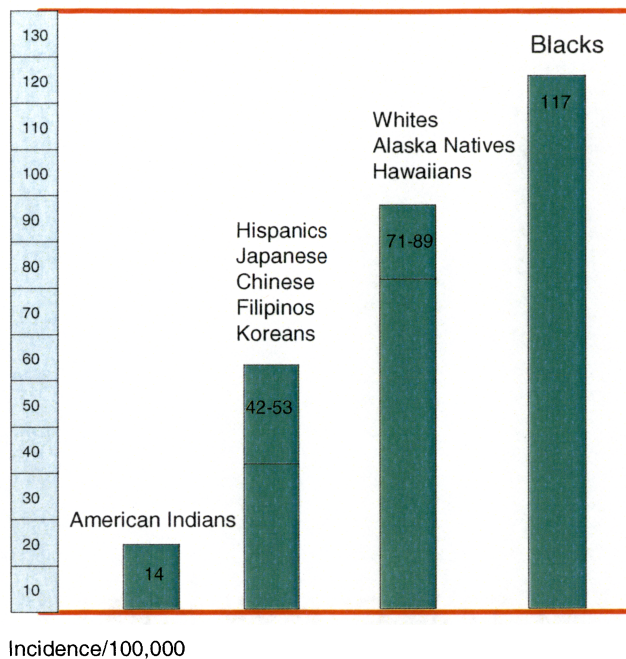


Figure 6. The relative incidence of lung cancer among ethnic groups in the U.S. Adapted from the National Cancer Institute⁶⁸

African American smokers are at greater risk for lung cancer than whites. The conclusion is based on the observation that Blacks with lung cancer report smoking fewer cigarettes per day than affected Caucasians. It is possible that the difference in risk is due to patterns of smoking rather than genetic susceptibility. Cohorts of black smokers have higher levels of serum cotinine than whites smoking the same number of cigarettes. The difference in concentration of this nicotine metabolite suggests that blacks may inhale more deeply than whites. There has also been a suggestion that menthol filtered cigarettes are more carcinogenic than plain filtered, although this has not been

⁶⁸ Lung and Bronchus: U.S. Racial/Ethnic Cancer Patterns. National Cancer Institute Cancer Statistics. <http://www.cancer.gov/templates/doc.aspx?viewid=95260E47-27F9-42BA-AB63-EF7836>

proven in rigorous analysis. A survey published by the Harvard School of Public Health noted that 70% of black smokers use menthol cigarettes. This compares to an average of 25% among all U.S. Smokers⁶⁰.

Smoking Cessation and Lung Cancer Risk Reduction

It is certain that smoking cessation is associated with a long-term decrease in risk for the development of lung cancer^{43,69,70,71}. This holds true for all subpopulations, including the elderly and individuals with underlying COPD.^{72,73} The relationship between smoking cessation and decreasing cancer risk is graphed in figure 9. Attenuation of risk is least pronounced in formerly heavy smokers.⁷⁴ Details of a meta analysis on cessation-related lung cancer risk reduction are presented in Appendix A.

Discontinuation reduces risk in all histologic types, although to various degrees. The highest reduction is in SCLC and squamous cell carcinoma, while

⁶⁹ Ockene, JK. The Relationship of Smoking Cessation to Coronary Heart Disease and Lung Cancer in the Multiple risk Factor Intervention Trial (MRFIT). Am J Public Health. 80(8); 954-958. 1990

⁷⁰ Mortality Rates After 10.5 Years for Participants in the Multiple Risk Factor Intervention Trial. JAMA; 263(13);1795-1801. 1990

⁷¹ Mortality After 16 Years for Participants Randomized to the Multiple Risk Factor Intervention Trial. Circulation. 94;946-951. 1996.

⁷² Appel, DW, and Aldrich, TK. Smoking Cessation in the Elderly. Clinics in Geriatric Medicine. 19(1).2003.

⁷³ Anthonisen, N.R. The Effects of a Smoking Cessation Intervention on 14.5 Year Mortality. Ann. Intern. Med. 142;233-239. 205.

⁷⁴ Ebbert, J.O. et. al. Lung Cancer Risk Reduction After Smoking Cessation: observations from a prospective cohort of women. J. Clin. Oncology. 21(5); 921-926. 2003.

less risk reduction is evident for large cell cancer and adenocarcinoma.⁷⁵ The 1982 Surgeon General report, *The Health Consequences of Smoking* cited studies to indicate that risk reduction is time dependent and concluded, “The more years one is off cigarettes, the greater the reduction in excess cancer risk. Fifteen years after quitting cigarette smoking, the former smoker’s lung cancer risk, for example is reduced close to that observed in nonsmokers”.⁷⁶ This view is far from universal, however⁷⁴. It is possible that smoking-mediated genetic changes persist, independent of removal of the tobacco irritant. Cessation of smoking would not be expected to decrease either the expression or latency of these mutations. This would explain persistent risk in quitters, for whom the stimulus for mutation would be removed, and would also explain some observations of a zero-slope risk reduction over time⁴⁸.

⁷⁵ Khuder, SA and Mutgi, AB. Effect of Smoking Cessation on Major Histologic Types of Lung Cancer. *Chest*. 120(5). 2001.

⁷⁶ The Health Consequences of Smoking: Cancer. Report of the Surgeon General. Viii, 1982

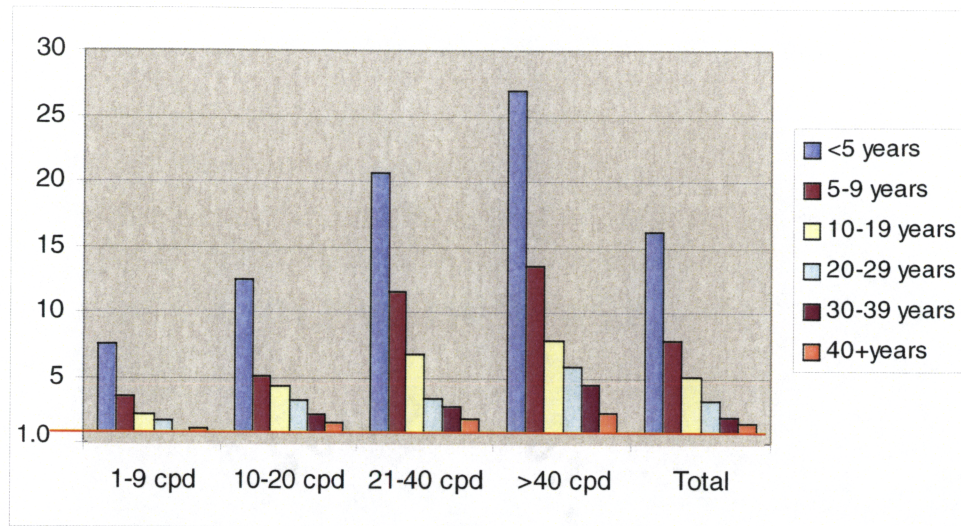


Figure 9 Relative risk of Lung Cancer among Ex-Smokers Relative to Never-Smokers. Adapted from Hrubec and McLaughlin.⁷⁷

A History of Lung Cancer Treatment

Ancient times-1970

It is likely that the earliest attempts to cure cancer were primarily surgical resection. Documentation of surgical oncology dates to at least the 17th century. During that period a visionary of modern surgery, Fallopius commented, “*Quiescente cancro, medicum quiescendum*” (If cancer does not bother, leave it alone”). A contemporary, Fabricius de Aqua-Pendente was similarly skeptical of the ability to surgically cure tumors. He commented, “*nam amputates cancer redit vel in eodem loco vel in hapte, liene, utero...*” (Removal of a tumor is easy but prevention of local recurrences and of metastases to the liver, lung, uterus,

⁷⁷ Hrubec, Z and McLaughlin, J.K. Former Cigarette Smoking and Mortality Among US Veterans: a 26-year follow-up, 1954-1980. In Burns, D.M., Garfinkel, L., and Samet, J.M. eds. *Changes in Cigarette-related Disease Risks and Their Implication for Prevention and Control*. Bethesda, MD: U.S. Government Printing Office, 501-530. 1997.

etc. is the problem). This notion of the incurability of cancer persisted into the earliest 20th century, when anecdotal reports of spontaneous remissions and metastatic regression after surgical debulking began to accumulate. Still, with high surgical mortality rates in the early part of the century, the technique may not have been useful therapy. The first modern report of pneumonectomy for lung cancer was reported in 1933⁴². This milestone provided the first opportunity for survival from a previously hopeless disease⁷⁸. Surgical resection of lung cancer became a treatment standard in the mid 1930's when the technique for pulmonary lobectomies was devised. Early surgical mortality rates were in the range of 65%. By the end of World War II, the introduction of more limited procedures and streptomycin had reduced the primary death rate by more than three-quarters. It remains invaluable as primary treatment for non-small cell lung cancer to date.⁷⁹

The therapeutic use of radiation might be as old as man himself. At minimum, the curative effects of sunlight are documented from antiquity. Roentgen's discovery of X-rays in 1896 set off a flurry of research on the therapeutic effects of ionizing radiation. Clearly, radiation had the capacity to cause skin burns. In 1902 the development of cutaneous squamous cell cancer after exposure to radiation was documented. An early milestone in the development of the science of radiobiology was the discovery in 1906 that rapidly

⁷⁸ Baue, A.E. Evarts A. Graham and the First Pneumonectomy. JAMA. 251:261-264. 1984.

⁷⁹ Peller, S. Cancer Research Since 1900: An evaluation. Philosophical Library, New York. 1979. 215-241

dividing cells are more susceptible to radiation than those which are relatively senescent.⁸⁰

The birth of chemotherapy for cancer may be traced to chemical warfare agents of the First World War. Specifically, the ability of nitrogen mustard and its analogues to produce leukopenia was noted during that period, even though the mechanisms of action were not completely understood.⁸¹ Despite the recognition of the mustards as myelotoxic, therapy with alkylating agents was slow to develop. A recognized highlight in the pharmacologic treatment of cancer was the adaptation of folic acid antagonists, such as methotrexate for the treatment of childhood leukemia. This effort was pioneered by Farber, beginning in the period directly after World War II.⁸²

1970-present

A reasonable starting point for the documentation of modern treatments for lung cancer is 1971. By that time surgical oncology had matured, chemotherapy was in common use both as primary and adjuvant therapy, radiation therapy had proven its value in cancer care, and the promise of immunotherapy had begun to blossom. That year President Richard Nixon proposed in his State of the Union

⁸⁰ Sanders, C. Basis of Radiotherapy. Gail's Books . 2003.
<http://www.gailsbooks.com/chap27.htm#subhead1>

⁸¹ Parnham, M.J. and Bruinvels, J.(eds) Discoveries in Pharmacology, volume 3. Elsevier Publishing, New York. 1986. pp353-365.

⁸² Farber, S, et. al Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonists 4-Aminopteroyl-Glutamic Acid (Aminopterin). NEJM. 238(23). 1948. 787-793

Address, “an intensive campaign to find a cure for cancer.” His commitment was codified in December of that year with enactment of the National Cancer Act (NCA). This legislation clearly promoted research and implementation of new cancer treatments. At its core, the legislation provided the following stipulations⁸³:

- (1) that the incidence of cancer is increasing and cancer is the disease which is the major health concern of Americans today;
- (2) that new scientific leads, if comprehensively and energetically exploited, may significantly advance the time when more adequate preventive and therapeutic capabilities are available to cope with cancer;
- (3) that cancer is a leading cause of death in the United States;
- (4) that the present state of our understanding of cancer is a consequence of broad advances across the full scope of the biomedical sciences;
- (5) that a great opportunity is offered as a result of recent advances in the knowledge of this dread disease to conduct energetically a national program against cancer;
- (6) that in order to provide for the most effective attack on cancer it is important to use all of the biomedical resources of the National Institutes of Health; and
- (7) that the programs of the research institutes which comprise the National Institutes of Health have made it possible to bring into being the most

⁸³ The National Cancer Act of 1971. The National Cancer Institute.
<http://www3.cancer.gov/legis/1971canc.html>

productive scientific community centered upon health and disease that the world has ever known.

- (8) It is the purpose of this Act to enlarge the authorities of the National Cancer Institute and the National Institutes of Health in order to advance the national effort against cancer.

The legislative initiative provided \$150 million for National Cancer Institute funding of new and improved treatment regimens and was clearly a milestone in the modern history of cancer care.⁸⁴

Peller's review of Cancer Research, published in 1979, provides a comprehensive view of the capabilities of lung cancer treatment in that decade⁷⁷. At that time surgery had become well established as primary therapy for solitary nodules (regardless of histology) and single metastases. Of those patients deemed operable and who accepted surgery (roughly one-third of all cases) in two major centers, 10-25% were dead within 4 weeks. Of those who survived surgery, however, 25% remained alive at 5 years, as compared to 1% of patients who were ineligible or refused lobectomy.

Chemotherapy in the 1970's was a poor therapeutic alternative, particularly for those patients who had sustained brain metastases. Only two agents, cyclophosphamide and methylnitrosourea had been shown to cross the blood-brain barrier. To maximize the odds of local and metastatic response, a combination of 3 drugs, including methotrexate, adrimycin and vincristine, was

⁸⁴ Leaf, C. Why We're Losing the War on Cancer. *Fortune Magazine*. March, 2004. pages 76-98.

added to the CNS regimen. This protocol was highly toxic and largely ineffective, with a maximum improvement in survival rate of no greater than several months.

Observing recent advances in cancer therapy requires more than tracking the introduction of new chemotherapeutic agents. During the past 25 years, changes in surgical oncology and radiation therapy have been profound. In addition the formulation of complex multi-modality protocols has changed the face of therapy. Neoadjuvant chemotherapy has provided greater opportunities for surgery or higher dose targeted radiation.

Immunotherapy has been under development as therapy for lung cancer since the 1970's. BCG was the first agent recognized as a therapeutically active immunomodulator. Morton and Pinsky and Oettgen simultaneously observed the dramatic regression of melanoma after cutaneous injection of BCG during that period⁸⁵. Since that time dramatic refinements, including enhanced immunomodulation and increased tumor specificity have significantly broadened the applications for this modality. Although immunotherapy has not had a major impact on survival from lung cancer to date, several agents, such as BEC-2 continue to show promise and remain under investigation.

Recent changes in standard chemotherapy protocols for small cell and non-small cell lung cancer are outlined in tables 3 and 4. As table 1 suggests, the key change in therapy for small cell cancer has been a migration from cyclophosphamide-based therapy (which remains a second-line choice) to

⁸⁵ Tumor Immunology (II): Strategies for Cancer Therapy. *Science*. 184. 652-654. 1974.

platinum-based therapy. Neoadjuvant therapy for non-small cell cancer remains considerably less effective for inducing remissions or improving survival, although recent data suggest a clear advantage.⁸⁶ The limits of treatment for non-resectable NSCLC are evident from a recent study from Schiller and the Eastern Cooperative Oncology Group. Among 1155 eligible patients who were randomized to one of four combinations of cisplatin, carboplatin, paclitaxel, docetaxel, and gemcitabine, the response rate was only 19 percent and the two-year survival rate was 11%.⁸⁷ As data suggesting somewhat improved survival became available, recommendations for chemotherapy-containing regimens were endorsed for stage III, and then stage II disease. It should be noted that significant regimen variability exists between treatment centers and that several agents, not listed in these tables are active against SCLC, NSCLC, or both. An extensive meta-analysis reported in 2004 demonstrated a significant improvement in response rate and a modest 1-year survival rate increase for multi-agent chemotherapy regimens over single-agent treatment for NSCLC, regardless of combination. Unfortunately, additive or synergistic toxicity limits the usefulness of combination therapy with currently available drugs.⁸⁸

⁸⁶ Carbone, D.P. and Minna, J.D. Chemotherapy for Non-small Cell Lung Cancer: A meta analysis suggests that the benefits are small. *BMJ* 311(7010). 1995. 889-90

⁸⁷ Schiller, J.H. et. al. Comparison of Four Chemotherapy Regimes for Advanced Non-Small Cell Lung Cancer. *NEJM*. 346:92-98. 2002.

⁸⁸ Delbaldo, C, et. al. Benefits of Adding a Drug to a Single-agent or a 2-Agent Chemotherapy Regimen in Advanced Non-small-cell Lung Cancer. *JAMA* 292(4). 470-484. 2004

Considerable research is ongoing toward the evaluation of novel approaches to the treatment of advanced NSCLC. Perhaps the most promising is the development of agents directed against the epidermal growth factor receptor tyrosine kinase. This enzyme is frequently overexpressed in common solid tumors. Three such drugs, gefitinib, erlotinib and cetumixab (EGFR's) are currently available in the U.S. Phase II and III trials have recently begun to clarify the drugs' treatment potential. They appear to improve disease-related symptoms and induce radiographic tumor regression, but have not clearly been shown to prolong survival. Clearly, survival data will change as duration of experience with this class of drugs increases.^{89,90,91}. A closer analysis demonstrates heterogeneity of response. Roughly one in ten NSCLC patients treated with epidermal growth factor inhibitive therapy show dramatic response and possible long-term benefit.^{92,93,94}

⁸⁹ Kris, M.G. et. al. Efficacy of Gefitinib, an Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients with Non-Small Cell Lung Cancer. *JAMA*. 290(16). 2149-2158. 2003.

⁹⁰ Herbst, R.S. et. al. Gefitinib in Combination with Paclitaxel and Carboplatin in Advanced Non-Small-Cell Lung Cancer: A Phase III Trial-INTACT 2. *J. Clin. Oncology*. 22:785-794. 2004.

⁹¹ Fukuoka, M. et. al. Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients with Advanced Non-Small-Cell Lung Cancer. *J. Clin. Oncology*. 21(12);2237-2246. 2003.

⁹² Pollack, A. Genetic Link Seen in Cancer Drug's Power. *The New York Times*. A-14. April 30, 2004.

⁹³ Green, MR. Targeting Targeted Therapy (editorial). *NEJM* 350(21). 2004.

⁹⁴ Argiris, A. and Schiller, J. Can Current Treatments for Advanced Non-small-cell Lung Cancer Be improved? *JAMA*. 292(4). 499-500. 2004.

<u>1979</u>	Procarbazine plus 5-fluorouracil
<u>1982</u>	Cisplatin <i>plus</i> cyclophosphamide, doxorubicin, vindesine
<u>1990</u>	Cisplatin, cyclophosphamide and doxorubicin <i>or</i> Cisplatin and vindesine
<u>1992</u>	Cisplatin, cyclophosphamide and doxorubicin <i>with or without</i> etoposide
<u>1997</u>	Cisplatin and mitomycin <i>with or without</i> ifosfamide
<u>2004</u>	Cisplatin/Carboplatin plus etoposide <i>for extensive</i> <i>disease add</i> irinotecan. Consider gefitinib.

Table 3. Conventional chemotherapy for small cell lung cancer in 1979⁶⁸, 1982⁶⁹, 1990⁷⁰, 1992⁷¹, 1997⁶⁷ and 2004⁷²

<u>1979</u>	Vincristine plus doxorubicin plus cyclophosphamide
<u>1982</u>	Cyclophosphamide plus at least two of the following: vincristine, doxorubicin, CCNU, procarbazine, etoposide, vindesine or hexamethylmelamine.
<u>1990</u>	Vincristine plus doxorubicin plus cyclophosphamide <i>or</i> Cisplatin plus etoposide
<u>1992</u>	Vincristine plus doxorubicin plus cyclophosphamide, <i>with or</i> <i>without</i> Cisplatin or etoposide
<u>1997</u>	Vincristine plus doxorubicin plus cyclophosphamide, <i>with or</i> <i>without</i> Cisplatin or etoposide
<u>2004</u>	Cisplatin/Carboplatin plus etoposide <i>for extensive disease add</i> irinotecan

Table 4. Conventional neoadjuvant chemotherapy for non-small cell lung cancer in 1979⁹⁵, 1982⁹⁶, 1990⁹⁷, 1992⁹⁸, 1997⁹⁹ and 2004¹⁰⁰

⁹⁵ Dorr, R.T. and Fritz, W.L. Cancer Chemotherapy Handbook. Elsevier Publishing, New York. 1980 pp.65-66.

⁹⁶ Cancer: A Manual for Practitioners. American Cancer Society Massachusetts Division. 1982. pp158-168.

Smoking Cessation

Each year, 40% of all American smokers attempt to quit. At any given time, approximately half of those are ready to take action¹⁰¹. Of those 20 million, however, only about 6% succeed over the long term.¹⁰² The percentage of those who succeed has much to do with commitment to the effort, duration of smoking, number of cigarettes, genetic predisposition toward dependent behavior, and supportive therapy. Among smokers with insurance coverage for comprehensive smoking cessation therapy who wish to quit, only about half take advantage of their insurance benefits. The other half attempt to quit without assistance¹⁰³. Variables statistically associated with higher and lower abstinence rates include the following¹⁰⁴:

⁹⁷ Skeel, T.T. (ed.) Handbook of Cancer Chemotherapy. Little Brown and Company, Boston. 1991. pp158-166.

⁹⁸ Rubin, P. Clinical Oncology: A Multidisciplinary Approach for Physicians and Students. 7th edition. W.B. Saunders Company, Philadelphia. 1993. pp. 645-666.

⁹⁹ Felip, E. and Rosell, R. Neoadjuvant Chemotherapy in Non-small Cell Lung Cancer. *Current Medicinal Chemistry*. 9(8);893-898. 2002.

¹⁰⁰ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. 2004.
www.nccn.org.

¹⁰¹ Prochaska, J.O., and DiClemente, C.C. Stages and Processes of Self-change of Smoking: Toward an integrative model of change. *J. Consult Clin Psychol* 51;390-395. 1983.

¹⁰² Smoking Cessation During Previous Year Among Adults-United States 1990 and 1991. *MMWR* 42; 504-507. 1993.

¹⁰³ Curry, S.J. et. al. Use and Cost Effectiveness of Smoking-cessation Services Under Four Insurance Plans in a Health Maintenance Organization. *NEJM*. 339(10) 673-679. 1998.

¹⁰⁴ Treating Tobacco Use and Dependence. U.S. Department of Health and Human Services. 55. June, 2000.

High abstinence rates

High motivation
Ready to change
High self-confidence
Supportive social network

Low abstinence rates

High nicotine dependence
Previous failed attempts
Psychiatric comorbidity
High stress level

This overall rate has remained relatively constant, although the addition of behavioral therapies, nicotine replacement products, acupuncture, hypnosis, anxiolytics, and antidepressants has had a dramatic impact in the cohort of smokers using them. A comparison of meta-analyses for various medications is in figure 10. Studies have now demonstrated 22%-38% long-term (>6 months) abstinence rates with combined therapy.¹⁰⁵ It is reasonable to anticipate that a program utilizing combined therapy, including counseling, nicotine replacement and bupropion or tricyclic antidepressants will have a long-term success rate of about 25% among smokers who are motivated to quit. Data showing the success rates for entire populations of smokers (including those who are coerced into enrolling into cessation programs) are not available.

¹⁰⁵ Jorenby, D. et. al. A Controlled Trial of Sustained Release Bupropion, a Nicotine Patch, or Both for Smoking Cessation. NEJM 340(9); 685-691. 1999.

An effective approach to smoking cessation

There is no single method of enrolling, encouraging and enabling cessation for all smokers. There are clearly person-to-person differences in acceptability, safety and tolerance to therapy. Strategies may be categorized as follows:

1. Effective for the patient willing to quit
2. Appropriate for patients unwilling to quit
3. Maintenance therapy for patients who have recently quit

The cost, approach and effectiveness of the third category are beyond the scope of this report. An approach to current smokers is represented in figure 11.

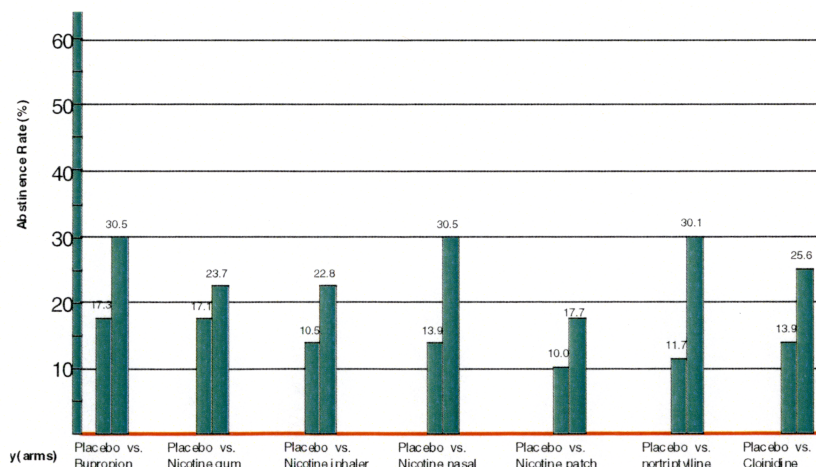


Figure 10. A comparison of medications for smoking cessation (Adapted from *Treating Tobacco Use and Dependence* U.S. Department of Health and Human Services)

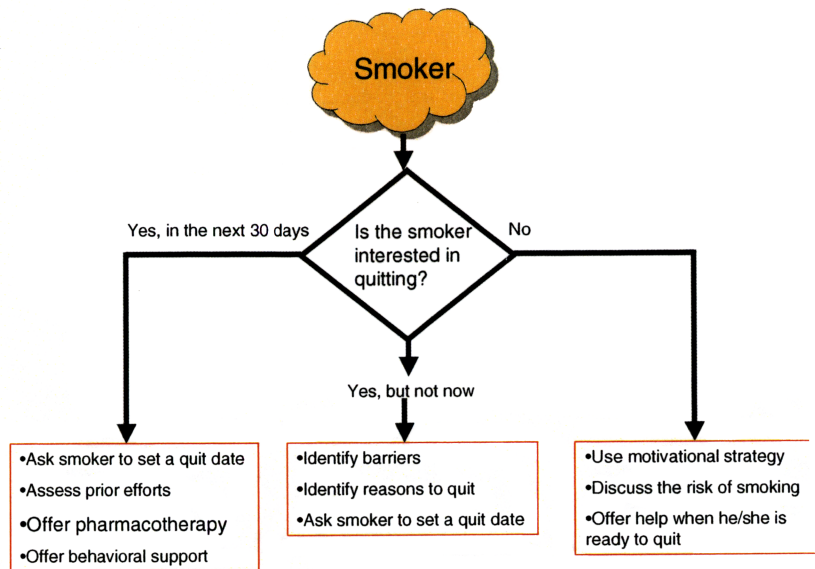


Figure 11. An evidence-based smoking cessation strategy for physicians. Adapted from Rigotti¹⁰⁶

It is reasonable for patients to self-enroll in smoking cessation programs. Primary care practitioners, through contacts during ill visits, hospital care, and primary prevention counseling can encourage smokers to quit and provide the expertise to tailor a cessation program to their personal needs. This thesis examines the cost effectiveness of these and other interventions relative to the tertiary treatment of carcinoma of the lung.

The Financial Burden of Smoking in the United States

There is little question that the effects of cigarette smoking place a financial burden on government, private and personal finances. The National Medical Expenditures Survey (NAMES-2), for example, provided a

¹⁰⁶ Rigotti, N.A. Treatment of Tobacco Use and Dependence. NEJM. 346(7); 506-512. 2002.

comprehensive analysis of these costs. The study group evaluated the effect of smoking history on the presence of smoking-related medical conditions (heart disease, emphysema, arteriosclerosis, stroke, and cancer), calculated probabilities and applied that data to the cumulative cost of treatment. Hospital expenses, physician fees, pharmacy expenses, home health care and nursing home charges were summed to reach the total smoking attributable cost. In 1987 alone those charges added to \$21.9 billion.¹⁰⁷ By 1998 that total had increased to \$75.5 billion.¹⁰⁸ The breakdown of these expenses is diagrammed in figure 12. This estimate was confirmed in published data, where the smoking-attributable fraction of healthcare cost was calculated to be somewhere between 4-7%¹⁰⁹. The incremental increase occurred despite a declining prevalence of cigarette smoking in this country, and likely reflects both the increase in cost-per-service and the latency of smoking-related illness. Almost half of Medicare's drug budget of \$10.5 billion went for cancer drugs in 2003¹¹⁰.

*Asymptomatic brain metastases, common in small cell lung cancer, were virtually impossible to diagnose in the pre-CT era. Thus dissemination to the central nervous system was a more frequent and severe complication.

¹⁰⁷ Medical-care expenditures attributable to Cigarette Smoking-United States, 1993. MMWR 43(26). 1994 469-472.

¹⁰⁸ Smoking-Attributable Expenditures 1998. CDC National Center for Chronic Disease Prevention and Health Promotion.
http://apps.nccd.cdc.gov/sammec/show_same_data.asp

¹⁰⁹ Miller, V.P., Ernst, C, and Collin, F. Smoking-attributable Medical Care Costs in the USA. *Soc. Sci. Med.* 48;375-391. 1999.

¹¹⁰ Harris, G. Proposal Would Cut What Medicare Pays for Cancer Drugs. *The New York Times*. July 27, 2004. C1.

Unfortunately, there are also program cost savings associated with smoking that somewhat offset the incremental increase in healthcare expenditures. Frank A. Sloan, director of the Center for Health Policy, Law and Management at Duke University calculated that the decreased life expectancy associated with cigarette smoking resulted in Social Security savings of \$1,519 for a 24 year-old female smoker and \$6,549 per 24 year-old male.¹¹¹ Also to be considered are savings in Medicaid payments for custodial care and government administered payments for the non-smoking-related illnesses of the elderly.

The cost of medical care in the United States is clearly linked to coverage and reimbursement of private insurers. This model has seen dramatic change with the proliferation of managed care in the 1990's. The burden of lung cancer on insurance carriers has been studied in the context of this paradigm shift. A benchmark was established in 1998 based on the analysis of Hillner's group. His study estimated that the cost of care for patients with non-small-cell lung cancer, who survived less than one year was \$47,280.¹¹² Despite an intuitive conclusion that smoking is associated with increased health care costs, the Kaiser Foundation found no difference in a tightly controlled managed care environment. Although smokers experienced a higher rate of hospitalization, this increase in utilization was offset by a lower frequency of outpatient service utilization. The suggested explanation for this phenomenon was that smokers have a lower

¹¹¹ Smith, H. The High Cost of Smoking. MSN Money.
<http://moneycentral.msn.com/content/Insurance/Insureyourhealth/P100291.asp>

¹¹² Hillner, B.E. et. al. Costs of Care Associated with Non-Small-Cell Lung Cancer in a Commercially Insured Cohort. J. Clin. Oncology. 16(4);1420-1424. 1998.

concern for health and a correspondingly reduced tendency to seek medical care until it is absolutely necessary.¹¹³

Private industry must also contend with the cost of absenteeism and poor productivity among workers. These too have been studied in the context of smoking. Not only do workers who use tobacco experience higher absenteeism and less productivity than their non-smoking counterparts, the differences attenuate after smoking cessation.¹¹⁴

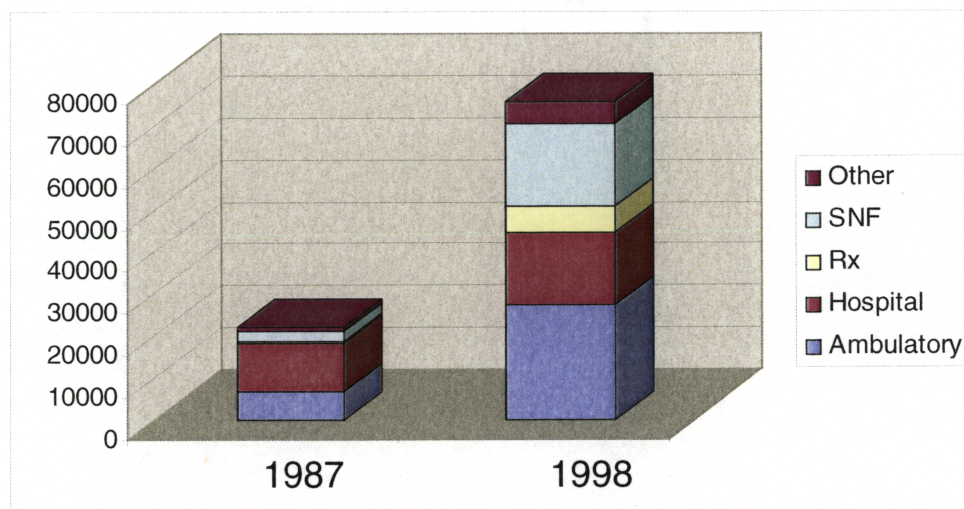


Figure 12 Relative expenditures for smoking-related chronic illness in the U.S. Key: SNF-nursing home care, Rx-prescription medications, Hospital-all hospital related care, Ambulatory-home health care. Adapted from NMES-2 and CDC Smoking Attributable Mortality, Morbidity and Economic Cost (SAMMEC)

The financial burden of lung cancer

¹¹³ Vogt, T.M. and Schweitzer, S.O. Medical Costs of Cigarette Smoking in a Health Maintenance Organization. *Am. J. Epidemiology*. 122(6);1060-1066. 1985.

¹¹⁴ Halpern, M.T., Shiklar, R. Rentz, A.M., and Khan, Z.M. Impact of Smoking Status on Workplace Absenteeism and Productivity. *Tobacco Control*. 10; 233-238. 2001'

Some analysts have proposed that lung cancer is a relatively inexpensive disease to treat. They argue that bronchogenic carcinoma is a quick and efficient killer, which spares society the burden of paying for more insidious diseases such as chronic heart failure, and senility^{115,116}. This theory ignores several key points:

- Lung cancer risk reduction strategies do not exist in a vacuum. In parallel with this effort are advances in risk reduction for a wide variety of illnesses.
- Morbidity and mortality costs associated with lung cancer do not reflect the cost burden of lost productivity, especially in pre-retirement years.
- Smoking cessation will reduce the expense associated with other pulmonary and cardiac diseases such as emphysema and myocardial infarction¹¹⁷.
- Reduced passive exposure to cigarette smoke can decrease the burden of disease among non-smokers. Roughly half of the smoke generated by cigarette combustion enters a local environment as sidestream smoke. The associated effects are similar to those of smokers and include low birth weight (due to exposure during

¹¹⁵ Sturm, R. The Effects of Obesity, Smoking, and Drinking on Medical Problems and Costs. *Health Affairs*. 21(2):245-253. 2002.

¹¹⁶ Leu, R.E. and Schaub, T. Does Smoking Increase Medical Care Expenditures? *Soc. Sci. Med.* 17; 1907-14. 1983.

¹¹⁷ Ibid Surgeon General's 1990 Report on the Health Benefits of Smoking Cessation... below.

pregnancy), sudden infant death syndrome, acute lower respiratory tract infections, asthma, middle ear infections, and chronic respiratory symptoms in children, lung cancer, nasal sinus cancer, and coronary heart disease.¹¹⁸

As the cost of patient care for smoking-related disease increases it is reasonable to ask several questions:

1. Have advances in patient care for smoking-related cancer result in improved survival?
2. How does medical inflation impact on the cost of care
3. In addition to lung cancer expenses, are medical costs increased in smokers for comorbid smoking-related illnesses as well?
4. Might additional resources and emphasis on primary prevention (through avoidance and cessation programs) result in a net healthcare savings by reducing the burden of lung cancer?

This thesis will examine these questions as reflected by the effectiveness and cost of treatment for primary carcinoma of the lung and airways. It will graph the survival from these diseases over the past thirty years and look at recent trends in cost-for-treatment. It is anticipated that these analyses will facilitate decisions concerning resource allocation and the emphasis of primary prevention

¹¹⁸ Environmental Tobacco Smoke. National Cancer Institute Cancer Facts. 2000. http://cis.nci.nih.gov/fact/10_18.htm.

relative to acute and chronic care.

Calculating the Cost of Smoking Cessation

This introduction has documented the relationship between cigarette smoking and lung cancer as well as the association between smoking cessation and decreased cancer risk. Clearly, quitting cigarette use saves lives. It is intuitive that broad application of cessation would decrease smoking-related lung cancer costs and result in an associated health care savings. Although there is a large body of evidence in its favor, this theory has not been unequivocally established. Wagner, et. al., for example, showed a relative net **increase** in hospital costs for ex-smokers during the first year after cessation, followed by progressive decreases in healthcare utilization for the next 5 years¹¹⁹. The “break even” point of utilization occurred during year 4. Other authors have replicated this data.¹²⁰ It was concluded that the increase in early cost was due to underlying acute or progressive disease that often was the *motivating force* for individuals to discontinue cigarettes^{121,122}.

¹¹⁹ Wagner, E.H. et. al The Impact of Smoking and Quitting on Health Care Use. Arch Int Med. 155. 1789-1795. 1995.

¹²⁰ Warner, K.E. The Costs of Benefits: Smoking Cessation and Health Care Expenditures. *American J. Health Promotion*. 18(2): 123-124. 2003

¹²¹ Martinson, B.C., O'Connor, P.J., Pronk, N.P., and Rolnick, S.J. Smoking Cessation Attempts in Relation to Prior Health Care Charges: The Effect of Antecedent Smoking-related Symptoms? *American J. Health Promotion* 18(2) 125-132. 2003.

¹²² Munisch, S.et. al Pattern of Medical Charges After Quitting Smoking Among Those with and Without Arthritis, Allergies, or Back Pain. *American J. Health Promotion* 18(2) 133-142. 2003.

The net healthcare savings (or cost) of smoking cessation is a function of numerous variables, which may be categorized as follows:

Primary costs associated with smoking cessation (paid through public health, private insurance, NGO-sponsored programs or individuals)¹²³

- Cost of clinicians screening the U.S. population
- Cost of advertising and promoting smoking cessation
- Cost of medical care for counseling and medication therapy
- Motivating unwilling smokers to try and quit
- Direct intervention costs including educational materials, counseling, medications and alternative therapies

Secondary costs associated with smoking cessation

- Inevitable cost of diagnosis and treatment of non-smoking related illness
- Healthcare costs associated with increased longevity, such as those associated with custodial care

Healthcare savings from smoking cessation

- Reduced number of screening procedures for smoking-related disease
- Fewer diagnostic tests for evaluation of smoking-related disease
- Less treatment for smoking-related disease, including surgery, medical therapy, and radiation therapy
- Lower therapeutic (other than smoking cessation) pharmacy costs

¹²³ Cromwell, J, et al. Cost-effectiveness of the Clinical Practice Recommendations in the AHCPR Guideline for Smoking Cessation. JAMA 278(21);1759-1766. 1997.

- Reduced rehabilitation costs
- Reduced medical expenses from individuals exposed to second hand smoke

This project will scrutinize the current approach to lung cancer in America as measured by the effectiveness of treatment and relative cost-effectiveness of prevention. The former will be determined by analysis of recent trends in lung cancer survival. Cost effectiveness has been defined by Doubilet as a given intervention that (i) achieves a given quantified objective at a lower cost than all alternative interventions intended to achieve the same objective or (ii) achieves more of the desired objective than do the alternatives when identical levels of resources are devoted to each intervention¹²⁴. Other applications of the term include the criterion of having an additional benefit worth the additional cost.¹²⁵ Thus, cost-effectiveness will be calculated as the differential between the cost of lung cancer treatment and the net cost of primary prevention through smoking cessation programs. Evaluation of these parameters will allow for restatement of the current balance between prevention and patient care efforts in lung cancer care. Recommendations for social policy realignment will follow.

Achieving these goals will require consideration of four questions, which may be stated as follows:

¹²⁴ Warner, K.E. Cost Effectiveness of Smoking-Cessation Therapies. *Pharmacoeconomics*. 11(6); 538-549. 1997.

¹²⁵ Doubilet, P., Weinstein, M.C., and McNeil, B.J. Use and Misuse of the Term "Cost Effective" in Medicine. *NEJM*. 314(4); 253-256. 1986.

1. Despite numerous important advances in the treatment of lung cancer, have the One, three, five, and ten-year survival rates improved?
2. What is the cost of treating lung cancer?
3. What is the real cost of a comprehensive smoking cessation program?
4. Is primary prevention through smoking cessation effective and efficient relative to treatment for lung cancer?

The findings of this study will be based on available statistical records and a cohort analysis of Americans diagnosed with lung cancer. Per capita medical costs, hospital admissions/100 cases, total annual hospital days/100 cases, ambulatory visits and cancer-related cost will be compared with a peer group of individuals who have not been treated for this disease.

Section II Methods

-As an example to others, and not that I care for moderation myself, it has always been my rule never to smoke when asleep and never to refrain when awake.-Mark Twain on his 70th birthday

Survival from lung cancer

Historical data on lung cancer survivability will be gleaned from CDC-SEER tables and other sources available by Med Line, MD Consult, FIRSTConsult and manual literature reviews¹²⁶. Data will be presented graphically, so as to best display improved survival (or lack thereof) over time and a therapeutic plateau, if one exists.

Cost-effectiveness of primary prevention relative to patient care for lung cancer

The methods described below will compare the cost of lung cancer care for beneficiaries that smoke but do not access enhanced smoking cessation therapy to the cost of care plus the cost of a program providing comprehensive smoking cessation therapy for beneficiaries who choose to enroll. It will utilize data from the U.S. workforce and adult beneficiaries of a single large multinational corporation. Total cost of the cessation benefit group is the sum of 1) treatment cost for continuing smokers who develop cancer, plus 2) the cost of care for quitters who develop cancer, plus 3) the cost of smoking cessation therapy. Determination of diagnosis will be based on insurance billing records accrued in the MedStat database for the employer (>200,000 U.S. adult beneficiaries) for the years 2001-2004. Included are all inpatient claims,

¹²⁶ National Cancer Institute Surveillance, Epidemiology and End Results.
<http://seer.cancer.gov>

outpatient claims ancillary service claims (such as physical therapy and nutritional counseling) and inpatient pharmacy costs. The cost of mental health care, outpatient pharmacy and dental services is not included. To minimize age bias, only records of individuals between 40-65 years of age will be included. Groups will be compared for the frequency of diabetes (types I and II), hypertension and coronary artery disease (all diagnoses, including angina and myocardial infarction), three significant comorbidities. Cost data will be presented for all cancers of the trachea, lung and bronchus, which have been grouped and coded among the CDC designated smoking-related cancer group¹²⁷:

ICD 162: Malignant primary neoplasm of trachea, bronchus and lung

ICD 231.2 Cancer in situ of bronchus and lung

ICD 235.7 Neoplasm of uncertain behavior in trachea, bronchus, lung

Medstat has created the database from claims data submitted by multiple company insurers, and provided the basic tabular form used in this report. Absent from this compilation are employees who use non-company benefits (such as those provided by a spouse's employer), non-U.S. employees, contractors, and other individuals not receiving medical services as a core company benefit.

¹²⁷ International Classification of Disease Codes. CDC.
http://apps.nccd.cdc.gov/sammec/icd_codes.asp

*Calculated as the cost of medical care (which includes the cost of inpatient and office pharmacy) + the cost of outpatient pharmacy

Individuals who are billed for a diagnosis of lung cancer on consecutive (or non-consecutive) years are included separately for each year.

Cost of care will be calculated as the sum of the cost of inpatient and outpatient medical services. Chemotherapy and inpatient pharmacy costs will be considered in the calculations, while outpatient pharmacy costs will not.

The relative cost of smoking and smoking cessation will be calculated as follows:

1. The Cost of Care for Lung Cancer:

This model calculates this cost by estimating the risk of cancer among smokers, the cost of yearly care as determined by Medstat statistics, the cost of care for those smokers who do not develop bronchogenic carcinoma, and the average longevity of patients with lung cancer. The formula may be written as follows:

, where

S=Number of individuals in the smoking cohort (persons)

P₁=Ten year probability of lung cancer among the cohort of smokers

C=Average differential in cost of care for beneficiaries with lung cancer per year, including outpatient care, inpatient care and pharmacy costs. (Dollars/year)

L=Average longevity of a lung cancer patient in the cohort (Years)

Prevalence variations for comorbid diseases such as coronary heart disease, diabetes, and hypertension may suggest that lung cancer patients have increased risk for other smoking and non-smoking-related chronic diseases. For that reason and because some of the cost of care for lung cancer may be

obscured because of billing under a comorbid diagnosis, this study uses *total cost of care* used by lung cancer patients for financial analysis, rather than *cost of lung cancer treatment alone*.

2. The Cost of Smoking Cessation Benefits

The cost of smoking cessation may be calculated as the medical care cost of lung cancer patients who had succeeded in long-term cessation, plus the care cost for those who attempted, but were unsuccessful, plus the medical cost for individuals who did not attempt to quit despite the availability of cessation benefits, plus the cost of smoking cessation programs. This concept is represented graphically as figure 13 and may be disassembled to the following equations:

R =The fraction of smokers that will attempt to quit. The value for R was been documented earlier in this report and is in the range of 40%¹⁰³.

Q =Overall quit rate among smokers entering comprehensive cessation programs. A discussion of this value follows below.

P_2 =Ten year probability of lung cancer among the U.S. population of “typical” former smokers

Lung cancer cost of those who do not attempt to quit despite the availability of a cessation program (\$/smoker) = $S \times (1-R) \times P_1 \times C \times L/S \times (1-R)$

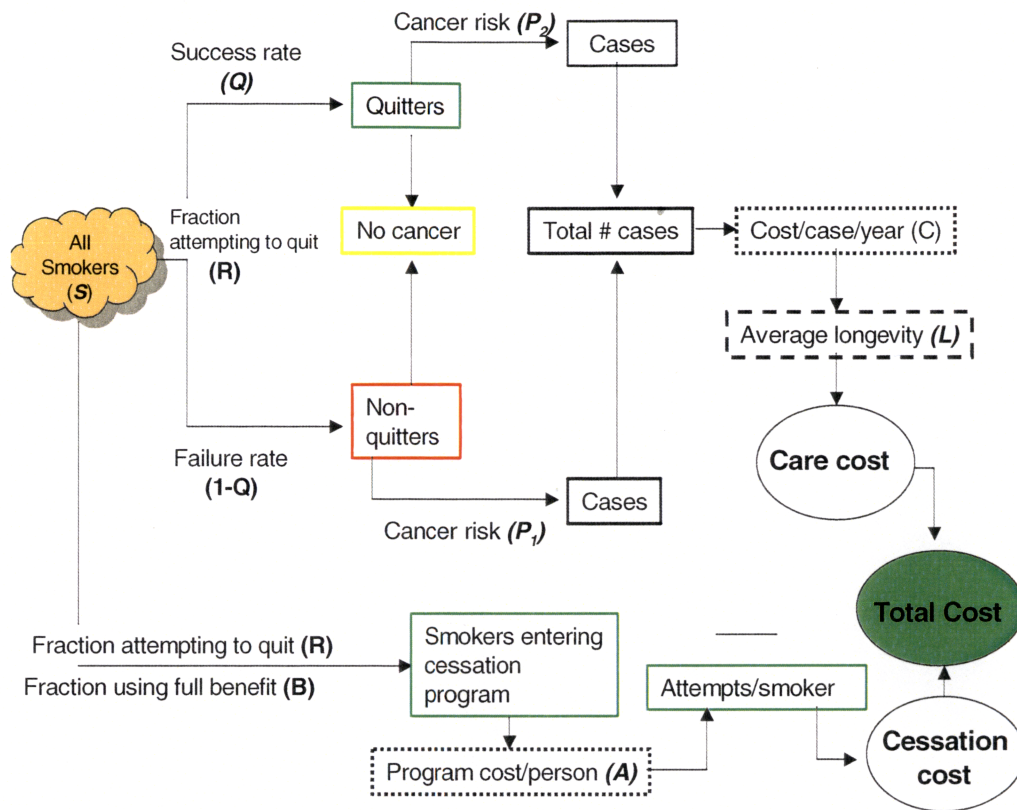


Figure 13. Determining the cost of care and cessation in a population of smokers

Cost of cessation (\$/successful and unsuccessful quitters) = $S \times R \times B \times A$

B=Fraction of program entrants that will utilize offered services, rather than quitting on their own.

A=Cost of a comprehensive multi-modality smoking cessation program.

(\$/attempt)

These calculations may be vastly simplified by removing the cost of cancer care from both sides of the equation. Calculations then simplify to the following:

Net savings from avoided cancer cases

(-) Cost of smoking cessation program

Net savings (or cost) of primary prevention

Assumptions

Demographic differences between cohorts

It is likely that significant demographic differences will be uncovered between the lung cancer and non-lung cancer groups. The several decade lag period between smoking onset and lung cancer favor an older age for individuals with bronchogenic carcinoma. Differences in smoking prevalence between men and women and changes in prevalence over the past several decades may also skew the relative percentages of men with and without cancer. Unless these differences obviously impact the results of this study, they will be assumed to have no bearing on the analysis.

Interpolation of U.S. and referenced data

No data is available for the prevalence of smoking among the population examined in this study. This analysis will assume that it is similar to that of the U.S. public as a whole-23.1%. Thus, an estimate for the number of smokers in this population of 200,000 beneficiaries is 46,200 (**S**). This study will assume

that the lung cancer risk and treatment outcome (longevity) among active and former smokers in this population is identical to those of the American public as a whole. In terms of smoking cessation, these calculations are based on the anticipation that the utilization, efficacy and cost of a multi-modality cessation program is the same for both this population and those of referenced studies.

Lung cancer risk (P_1)

To calculate a reasonable expectation for the risk of lung cancer among smokers, a “typical” cigarette user profile needs to be established. For the purposes of this thesis, such an individual is 50 years of age, male, has not experienced asbestos exposure and has smoked one pack of cigarettes per day since age 15. According to the Memorial Sloan-Kettering model, 3% of these people develop some form of respiratory cancer within 10 years.

Longevity after diagnosis of lung cancer (L)

Obviously longevity is dependent on numerous factors including stage at diagnosis, histology, comorbid conditions, performance status, and even access to healthcare services. Curves have been generated based on staging, one of which is presented as figure 14. To calculate an average period during which care (and expense) for lung cancer needs to be provided this study assumes an equal distribution of patients at each pathologic stage. By this calculation, a “typical” lung cancer patient survives for an average of 30.25 months (2.52 years) (L).

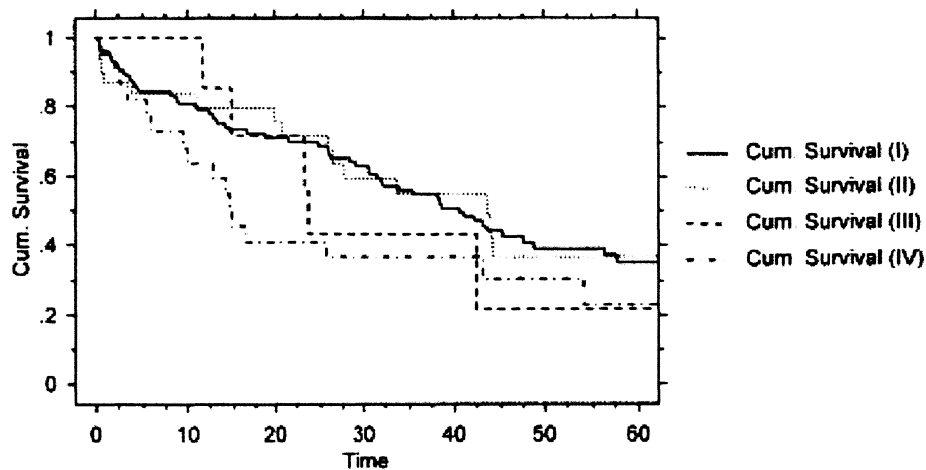


Figure 14 Kaplan-Meier survival curves of lung cancer survival by stage, incorporating all causes of mortality¹²⁸

Smoking cessation success rate (Q)

For the purpose of these calculations a cessation success rate of 0.25 will be used. This value considers the published data and is a reasonable approximation of what might be anticipated from the combination of intervention with practitioner enrollment, nicotine replacement, bupropion therapy and behavior modification¹⁰³⁻¹⁰⁵.

Incorrigibility

Previously cited studies estimated that each year 40% of smokers in the U.S. attempt to quit. Despite all types of motivation and strategies, the majority fails to stop using cigarettes in any given year. This thesis assumes that the treatment failures rejoin the general pool of smokers for the purposes of estimating number of quitters, for the succeeding three years. Those individuals

¹²⁸ Reed, M.F. Survival After Resection for Lung Cancer Is the Outcome That Matters. Am. J. Surgery. 188(5). 598-602. 2004.

who have failed to quit by year three will be considered incorrigible and will be calculated as part of the smoker cohort for purposes of estimating lung cancer prevalence and cost.

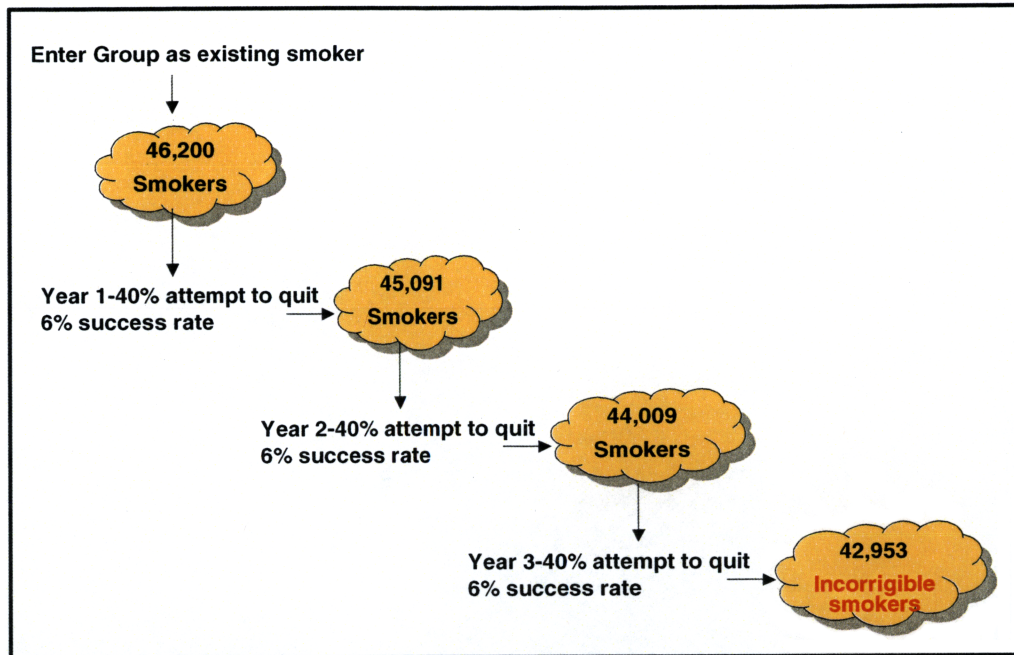


Figure 15. The effect of successive years of unassisted attempts on the number of smokers within the study population, in the absence of a supported cessation program. The third year value is used further in the study as the number of “net smokers” who might access a comprehensive cessation program.

Spontaneous smoking cessation

The studies cited previously demonstrate the relative success (or failure) of smoking cessation programs. They also note that roughly 40% of smokers will attempt to quit in a given year and that the overall success rate without support is 6%. The impact of unsupported smoking cessation on the study population of smokers is demonstrated in Figure 15.

*The rate of risk reduction after smoking cessation (**P₂**)*

The Sloan Kettering model notes a 67% reduction in 10-year lung cancer risk among ex-smokers. This figure reflects average risk reduction during that period, from effectively zero at the moment after the last cigarette is extinguished, to greater than two-thirds for ex-smokers who remain cancer-free for the next decade. Given the estimation of a 3% 10-year risk for “typical” active smokers, the average 10-year lung cancer risk of 1% will be used as an average for the cohort of former smokers.

Re-use of smoking cessation benefits

No data was found to show the rate of re-enrollment of failed smoking therapy patients into programs in succeeding years. This study will assume that individuals who fail cessation therapy re-enter the general cohort of smokers and are as likely as the therapy naïve group to utilize smoking cessation benefits in the succeeding three years. After three years, these individuals, as incorrigibles, would not further re-use these benefits at any significant rate.

*Fraction of attempting quitters using available services (**B**)*

At least one previously cited study has shown that only half those offered comprehensive therapy will take advantage of the service. Those who do utilize the benefit have a far superior quit rate than those attempting self-cessation.

Cost of an average smoking cessation program (A)

There are myriad permutations of treatments for nicotine dependence. Their cost ranges from trivial (“learn to quit” literature) to very expensive (combined modalities). As demonstrated above, there is reasonable correlation between the type of therapy and success rate. The calculations in this report are based on the provision of a highly effective, multimodality program. The charges used in this calculation, therefore, reflect 2005 expenses for practitioner intervention, nicotine replacement, bupropion therapy and Internet-based behavioral therapy. The cost for each of these interventions is based on typical charges or average wholesale prices for medication. Not entered into this calculation is the cost of advertising and promotion of smoking cessation programs. This expense will be considered in the discussion section, however.

Statistical relationship between smoking and lung cancer

The calculations in this paper rely on data demonstrating that the overwhelming majority (90%) of Americans with lung cancer are smokers⁴⁴. Also to be considered in the real world are those who develop lung cancer as a result of sidestream or mainstream environmental cigarette smoke (“second hand smoke”). Individuals who develop lung cancer as a result of environmental tobacco smoke are not factored into the cost of care calculations, and are not considered in the potential impact of smoking cessation. Clearly the relationship between quitting cigarettes and risk reduction is different between smokers and

those exposed to exhaled smoke. This distinction, however, is considered to be non-significant for the purposes of this thesis.

Baseline medical costs

These formulas assume that the per-member-per-month (PMPM) medical expenses accrued by all individuals who do not develop lung cancer are equivalent and that this baseline applies to those with cancer as well. The assumption allows the incremental cancer expense to be calculated as the PMPM for the cancer group minus the PMPM for the non-cancer cohort.

Adjustments for inflation

These statistics assume that the patterns of inflation for general care and care for individuals with lung cancer continue to follow the same slope of the years referenced in the study. The raw data suggest zero inflation for the cancer group and a 27.4% average (non-compounded) increase in general medical expenses for the entire 4-year period (6.8% per year). The cost differential over a 10-year follow-up period, baseline medical expenses will reflect an averaged adjustment of 34% above the 2004 baseline PMPM. It should be noted that this rate is significantly lower than the national medical inflation average for the period studied and may not be reflective of future increases.

Pharmacy costs

Chemotherapy costs, which may be substantial, are captured within the cost of inpatient and outpatient services. Although several types of drugs (such as analgesics) are frequently used by cancer patients, it is reasonable to anticipate that relative outpatient pharmacy costs will not be significantly impact the relative cost of care for the treatment of lung cancer.

Section III Results

...as the search (for a cancer cure) moved on toward final solution, beams of light are focused on enlightening discoveries which save more and more lives, and now if everyone would only take advantage of all knowledge and treatment available, one in two could be cured-

-“The Search Goes On” Publication of the New York chapter of the American Cancer Society. 1975

Demographics

As demonstrated in table 5 the age and gender distribution is different for the cohorts under study for this thesis. The average age for a lung cancer patient is 57.15 years, while individuals without lung cancer (within the age 40-65 parameter for the study) average 51.78 years. The lung cancer group is 46% male, while the unaffected cohort is 49% male. These differences are statistically significant, but are unlikely to measurably affect the cost of care..

Lung Cancer				
Ages 40 - 65				
3 Years Incurred Data				
4Q01 - 3Q04				
	Average Age			
	2001	2002	2003	2004
p value	0.0041	0.0022	<.0001	0.0002
Lung Cancer Patients	57.1	57.0	57.3	57.2
male	57.5	57.3	57.3	57.1
female	56.8	56.8	57.3	57.2
% male	46%	48%	46%	44%
Control Group	51.6	51.7	51.8	52.0
male	51.7	51.7	51.9	52.0
female	51.6	51.7	51.8	51.9
% male	49%	49%	49%	49%

Table 5 Demographic Comparison of Cohorts

Survival Rates

There has certainly been improvement in survival from lung cancer over the past half-century. In the period from 1950-1954 the relative 5-year survival rate for all cases was 6%, compared to the 1992-1996 rate of 15.1%. It is reasonable to conclude that treatment advances improved survival during that interval. Hidden in those statistics, however, is lead time bias related to improved imaging (primarily CT and MRI) and invasive diagnostic procedures (such as via thoracoscopy and image guided needle biopsies). Also inevident is the effect of increasingly sophisticated treatment for comorbid conditions and non-smoking-related illness. In 1950 the average life expectancy (male and female combined) in the U.S. was 68.07 years. That average increased to 76.9 years in 2000 and 77.6 years by 2003.^{129,130} More accurate, and of greater relevance for this discussion, is a review of survival data for the period between enactment of the National Cancer Act in 1971 and today. Data for the past quarter-century has been collated by the National Cancer Institute into the SEER database. Progression of cancer survival is graphed in figure 16.

¹²⁹ Simao, Paul. Life Expectancy in U.S. Hits Record High. Reuters. News. March 1, 2005

¹³⁰ Life Expectancy. National Center for Health Statistics.
www.cdc.gov/nchs/faststats/lifexpec.htm.

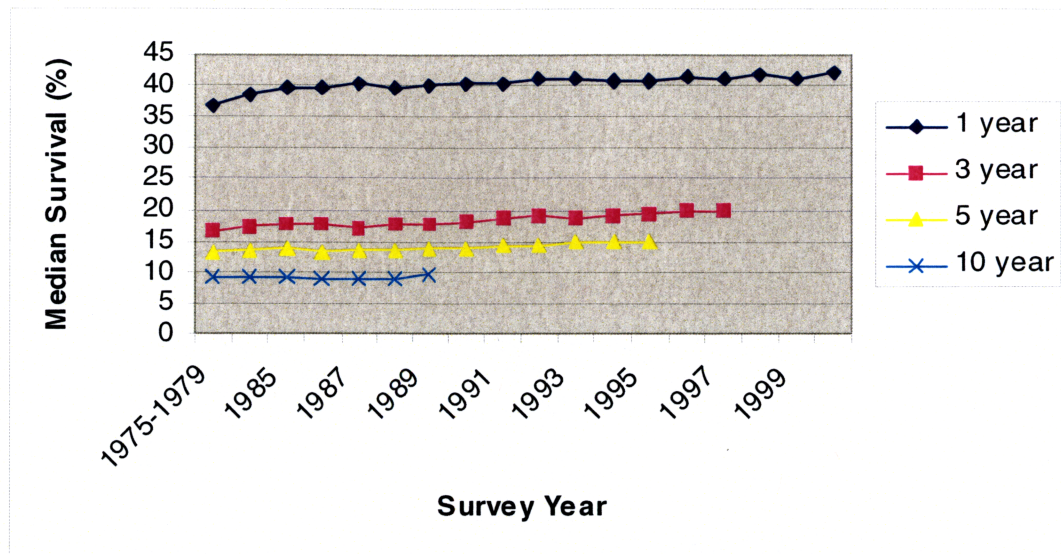


Figure 16 Changes in survival for cancer of the lung and bronchus. (Adapted from the National Cancer Institute, SEER Cancer Statistics Review 1975-2000)

These results demonstrate an extremely modest correlation between modernization and improvement in one, three and five year survival and a relative lack of correlation between year and 10-year longevity.

The notion of a therapeutic plateau for lung cancer is not entirely new. Scagliotti et. al. described the lack of additional efficacy from three platinum-based chemotherapy regimens in advanced non-small cell lung cancer and concluded that therapy had reached a plateau.¹³¹ However, journal, conference and media reports tout steady advances. A recent news item reported, “Treatment advances ranging from drugs to surgery are prolonging survival and improving quality of life for victims of lung cancer, based on new post-operative chemotherapeutic regimens for NSCLC”. This opinion was provided even though

¹³¹ Scagliotti, G.V. et. al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. Clin. Oncol. 20(21);4285-91. 2003.

the survival advantage for the surgery-plus-chemotherapy group was only 5% greater than that for patients treated with surgery alone¹³²

The Cost of Lung Cancer Treatment

The cost of medical care for the employee population studied is presented in table 6. Not evident from the table is the reality that lung cancer treatment costs in the U.S. reflect wide practice variations. Although these differences often are reflected in variations in outcome, such is not always the case.¹³³ The data presented in this table suggest that the PMPM cost of medical care for lung cancer patients is between \$2,990-\$3,713. The average PMPM during the study interval was \$3,261. The net PMPM (lung cancer medical cost minus baseline medical cost, adjusted for inflation) is \$2,823 or \$33,876/year. This value will be used (as “C”-the average cost of care for individuals with lung cancer per year) in the calculations to follow. Of note is the complete lack of inflationary pressure on the cost of care for patients with lung cancer. Although an in-depth analysis of the cause of this phenomenon is outside the scope of this thesis, two possible cost savings mechanisms are evident from the available data:

1. Decreased rate of hospitalization
2. Shorter average hospital length of stay

¹³² New Advances in Lung Cancer Therapy. MSNBC. 2003
<http://www.msnbc.msn.com/id/3076870/>

¹³³ Hoverman, J.R. and Robertson, S.M. Lung Cancer: A Cost and Outcome Study Based on Physician Practice Patterns. Disease Management. 7(2); 112-123. 2004.

Both of these phenomena suggest that the increasing use of outpatient services is helping to control the cost of care. It cannot be determined whether these efficiencies can continue to stabilize overall expenses. If not, the cost of care should rise in step with general medical inflation, further magnifying any advantage of primary prevention.

As might be expected, the prevalence of comorbid conditions is substantially higher in the cohort of employees with lung cancer than the control group. This relationship is greatest with individuals with coronary artery disease, which would be expected, given the association between both atherosclerosis and lung cancer among smokers. Although there is no direct link between smoking and diabetes or hypertension, it may be postulated that the same social forces and personality patterns that induce smoking also contribute to obesity and excess sodium consumption, risk factors for those illnesses.

Lung Cancer ICD-9 162								
All U.S. Employees								
Ages 40 - 65								
3 Years Incurred Data								
3Q01 - 2Q04								
	2001¹		2002		2003³		2004²	
	Lung Cancer	Control Group	Lung Cancer	Control Group	Lung Cancer	Control Group	Lung Cancer	Control Group
Prevalence	404	200,000	610	200,000	742	200,000	629	200,000
Incidence	404		301		309		130	
Lung Cancer Rate	1.90		2.67		3.32		3.02	
Admissions								
Admits/1,000	1,360.1	73.1	1,024.7	80.9	909.6	77.3	740.5	76.1
ALOS	7.23	4.83	6.50	4.61	6.17	4.63	5.26	4.27
Net Pay/Admit	12,340	9,470	13,196	10,190	13,188	11,025	11,530	10,954
Net Pay/Day	1,707	1,962	2,031	2,210	2,136	2,382	2,193	2,567
Outpatient Utilization								
Office Visits/1,000	28,052	6,495	23,089	6,759	21,444	6,842	21,019	7,107
ER Visits/1,000	979	151	969	180	1,031	178	911	170
Prescriptions/1,000	36,151	12,475	36,428	13,368	36,560	13,045	38,209	13,703
Lab Svcs/1,000	48,420	6,559	34,706	6,836	30,473	6,651	28,171	7,012
XR Svcs/1,000	32,132	2,277	29,085	2,561	22,944	2,485	22,057	2,589
PMPM Total	\$3,713	\$257	3,154	\$290	3,186	\$307	2,990	\$327
Comorbid Prevalence								
Coronary Artery Disease	12.59	5.54	13.16	4.30	11.80	4.31	14.77	7.25
Diabetes	16.79	10.27	12.84	7.06	13.38	7.42	24.79	16.35
Hypertension	27.05	21.57	21.67	17.17	24.00	18.01	41.14	31.24

Table 6. The Cost of Lung Cancer Treatment for a Large U.S. Corporation. The cohort includes all U.S. beneficiaries (employees and covered family members), participating in company-sponsored health insurance plans, who are between the ages of 40-65. Those identified as having lung cancer have filed at least a single claim for coverage using a lung cancer diagnosis during the year referenced.

Effectiveness of Smoking Cessation Efforts (R x Q)

It has been previously documented that 40% of smokers attempt to quit each year (**R**) and that at any given time, 20% of smokers in the U.S. are ready to take action. It has further been estimated that 10% (half of those attempting to quit) of smokers with full coverage for cessation therapy will use this benefit. The one-year quit rate for smokers who do not utilize cessation therapy is roughly 6%. The success rate for multi-modality therapy can be averaged at 25% (**Q**). Thus the overall success rate of a fully covered, multi-modality cessation program may be estimated as shown in the following graphic (figure 17):

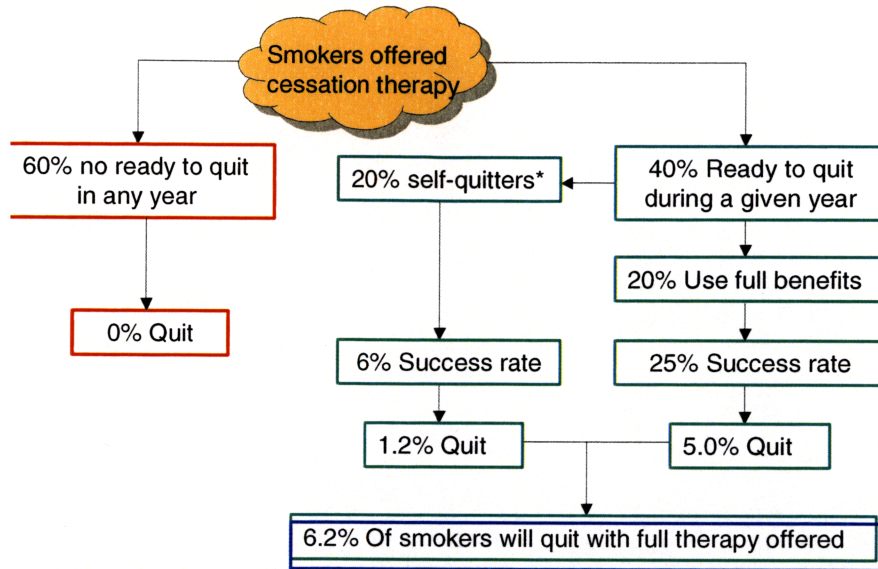


Figure 17. Estimating the percentage of smokers who will quit in a given year when offered full therapy. The model incorporates the observation that 40% of all smokers will attempt to quit when offered entry into a program **(R)**. This figure displays the rate of smoking cessation for all smokers offered entry into a comprehensive multimodality program in a given year. **(R x Q)**. Adapted from Prochaska and Curry

As demonstrated above, 6.2% of the smoking population might be reasonably expected to quit in any given year if offered full coverage and access to multi-modality cessation therapy.

The cost of smoking cessation

In one series the calculated cost to health plan and individual for maximum effective therapy (nicotine replacement and behavioral therapy) was \$333.76/program entrant (approximately \$430 in 2005 dollars, given an average inflation rate of 5.0%.) Another computed a cost of \$441/successful quitter using nicotine replacement gum and group intensive counseling (adjusts to \$595 in

2005 dollars). This estimate adds the cost of physician or nurse enrollment and pre-treatment counseling.^{103,123}

A contemporary estimate of the cost of smoking cessation considers the cost of practitioner services (enrollment into a comprehensive treatment program, prescriptions and oversight of prescription therapy), Internet-based counseling (such as QuitNet), the cost of a seven-week course of bupropion, and nicotine replacement. The cost may be estimated as follows¹³⁴:

• Practitioners services-2 office visits @\$50/visit	\$100.00
• 30 days therapy with transdermal nicotine replacement	102.00
• 7 weeks therapy with bupropion (Zyban)	115.00
• Enrollment fee for QuitNet (lifetime membership)	<u>99.95</u>
Total cost per enrollee	\$416.95

Using the use of average wholesale prices for bupropion, this value is in line with those of the studies cited and will be used as **(A)** for the calculations to follow.

The total number of individuals using (and re-using) smoking benefits is based on the utilization rates graphed in figure 17. Over a three-year period, 24,206 smoking cessation packages will be used. Some smokers will use the package on up to three attempts. Derivation of this total is displayed in figure 18.

¹³⁴ Expenses derived from *Treatment Guidelines from the Medical Letter*. 1(10); 65-68. 2003.

The cancer rate among former smokers

As demonstrated in figure 18, the availability of a benefit for comprehensive smoking cessation therapy would result in 7,504 smokers “kicking the habit”. According to the Sloan Kettering model, their risk of developing lung cancer over the next 10 years is one-third that of those who continue to smoke (1% vs. 3%). Calculating through, this group will experience 75 lung cancers during that interval and will have avoided twice that number. Those who do not attempt to quit or who are unsuccessful will continue to constitute the vast majority within the smoking population and will account for most of the lung tumors.

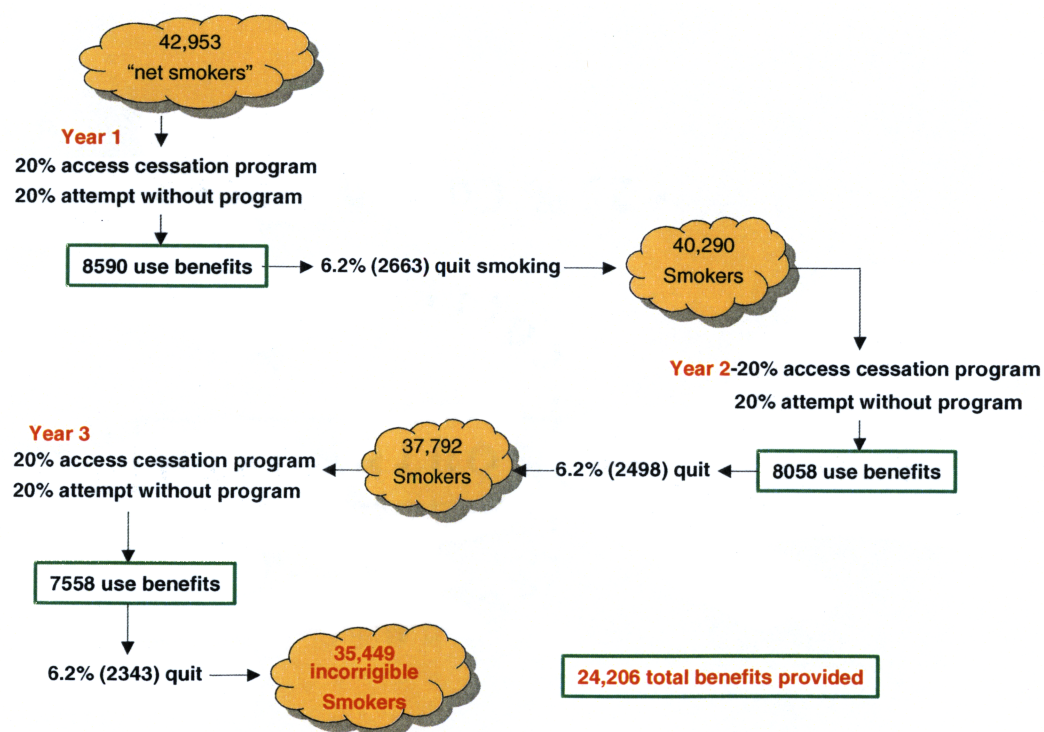


Figure 18. Calculating the number of quitters and benefits packages used. When the numbers of quitters for each year are summed, the total=7,504.

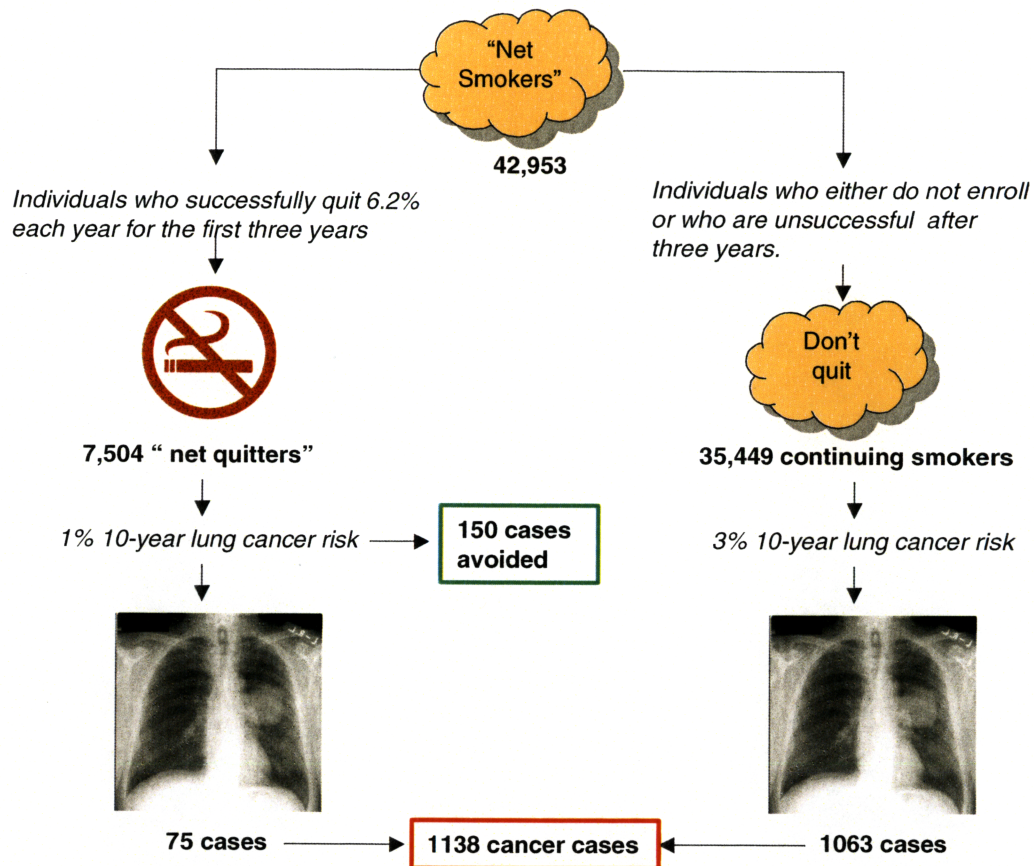


Figure 19 The impact of smoking and cessation on the number of anticipated lung cancer cases over a 10-year period

Calculations:

Using the calculations and referenced values provided above, the cost of treatment and full smoking cessation efforts can be compared as follows:

1. Determination of the number of "net smokers":

It was previously determined that 2.4% of smokers, even without a cessation therapy benefit, will quit each year (40% annual attempt-to-quit rate X 6% success rate). To accurately determine cost savings, these spontaneous quitters need to be deducted from the group to whom

intervention is provided. Thus, the number of “net smokers” is 42,953 (calculation demonstrated in figure 15, above).

2. Cost of care in the absence of a smoking cessation program:

Of the 46,200 smokers, 40% will attempt to quit each year for the first three years (after which they are presumed to be incorrigible). In the absence of a cessation benefit, the expected cessation rate is 6%.

Thus, after the first three years, 42,953 smokers will remain.

Treatment costs-3% 10-year risk x 42,953 smokers x

\$33,876/case/year x 2.52 years=**\$110,003,734 over 10 years**

3. Cost of a comprehensive smoking cessation program

24,206 program enrollees x \$416.95/enrollee=**\$10,092,692 over 10 years**

4. Savings from cancer avoidance

150 cases avoided X \$33,876/case/year X 2.52 years=**\$12,805,128 over 10 years**

Overall savings = \$12,804,128 - \$10,092,692 = \$2,712,436

Section IV Discussion

-Over the last century we have extended life expectancy by 30 years, but that only 8 of those years can be credited to medical intervention.-Hillary Rodham Clinton, 2004¹³⁵

The Value of a Dollar of Prevention

This study has demonstrated that each dollar of primary prevention through a comprehensive cessation program yields only a small direct savings over simply caring for smokers who develop lung cancer. This difference is unlikely to be significant in the context of unmeasured expenses and savings. Although the calculations demonstrate no significant difference, this should be viewed as only one savings stream among a variety of smoking-related illnesses and costs. Not considered is the cost of caring for other smoking-related illnesses such as emphysema and coronary artery disease. It excludes likely indirect savings on disability costs, the expense associated with exposure to second-hand tobacco smoke, and lost productivity related to smoking-related disease. Although not calculated for this thesis, those savings would likely increase the total by a magnitude of 5.0-6.0^{136,137}. It is most critical for the reader not to lose sight of the greatest savings demonstrated in this study. **A**

comprehensive, fully funded smoking cessation program can prevent roughly 350 cases of a horrible and essentially incurable disease per

¹³⁵ Clinton, H.R. Now Can We Talk About Healthcare? *The New York Times Magazine*. April 18, 2004. 26-76.

¹³⁶ Health Canada. *Economic burden of illness in Canada, 1998*. Ottawa: Health Canada, 2002

¹³⁷ Weissflog D, Matthys H, Hasse J, Virchow Jr JC. Epidemiology and costs of lung cancer in Germany. *Pneumologie*. (translated from German) 55(7). 2001:333-8.

100,000 smokers, over a 10-year period. Thus, it should be concluded that aggressive smoking cessation strategies could be financially sound and are definitely in the interest of the public's health.

Treatment for Lung Cancer-Why Isn't Survival Improving?

It would be incorrect to deny the extraordinary advances that have occurred in the fields of oncology since the advent of modern medicine and especially within the last quarter century. Certain neoplasms such as gestational choriocarcinoma, childhood acute lymphoblastic leukemia and Hodgekin's lymphoma may be cured with currently available chemotherapy. Improvements in treatment of cancers of old age, such as carcinoma of the prostate have prolonged survival past the average life expectancy for many with these diseases. It is clear, however, that advances for lung cancer have not been nearly as successful.

Analysis of year-to-year variations (or lack thereof) in survival from lung cancer is more complex than the data might suggest on first pass. Numerous confounders and significant bias create the potential for misinterpretation of this crude data in both directions. These include the following:

- Stage at diagnosis-SEER data on lung cancer does not stratify survival based on presenting stage. Thus advances in early detection may influence outcomes.
- Histology-Unquestionably, tumor histology has bearing on response to treatment, especially between small cell tumors and non small-cell

varieties. It was documented earlier in this thesis that the relative mix of these histologies has, in fact, changed over recent decades. The raw data presented in the SEER table does not permit identification of trends within histologic categories, and certainly provides no insight into treatment success among subcellular subtypes.

- Lead time bias-Not only will early detection improve overall survival rates, patients who are identified earlier in the course of their disease enter the survival databank before those for whom the diagnosis is delayed. This likely contributed in part to the improvement trend that was noted.
- Comorbidity-Several aspects of comorbidity and the treatment of coexistent illness may impact on survival data. The crude statistics cited on the SEER database are not age adjusted and not adjusted for such confounders as non-cancer related disease (such as emphysema or coronary disease) that might limit the potential for surgical resection or the tolerability of chemotherapy. Non-smoking related illness, more prevalent in the aging population, is also not considered.

Despite the recognition that bias and confounding inherent in SEER data may alter the statistics, it still remains clear that the slope of survival over the past quarter century has been extremely flat. The probability of surviving for 5 years clearly plateaued before 1975 and remains constant, at least in practical terms. Lung cancer, and especially locally invasive or metastatic cancer remains a killer.

There are common difficulties to the development of effective therapy for all malignancies. They include the following:

Developing strategies that specifically or preferentially target tumors

Clearly cancer therapy is limited by toxicity to normal tissues and adverse reactions. Novel treatments are needed that either are tumor specific or are bound to tumor specific delivery agents. Although not yet clearly evident in mortality data, emerging chemotherapeutic advances are being designed for tumor specificity. One such formulation, Abraxane, encapsulates the chemotherapy agent paclitaxel with albumin, a transport protein that can carry the drug directly to cancer cells¹³⁸. Similarly, advances in endoscopic therapy, microsurgery, cryotherapy and brachytherapy have advanced treatment effectiveness, although these modalities remain largely palliative. Completely novel approaches, including gene therapy offer significant theoretical promise as well.

Bypassing physical and biological separations, such as the blood-brain barrier

SCLC, in particular has a propensity for early metastasis, especially to the central nervous system. This and other safe harbors complicate the total eradication of tumor by chemotherapy. There have been significant advances in understanding the various processes that “protect” the CNS from foreign substances, including mechanisms specific to tumors. Clearly tumor interactions with microglia and various matrix proteins, cytokines and growth factors have a

¹³⁸ New Therapies in Lung Cancer. Newsletter of the Memorial Sloan-Kettering Cancer Center. 2005

central role¹³⁹. In parallel with these insights have been the development of strategies to bypass the barrier and effectively limit the potential and effect of brain metastases. These include prophylactic intracranial irradiation, and conjugation of neuroactive medications with peptidomimetic ligands^{140,141}.

Limitations of current preclinical modeling

Advanced preclinical research typically involves observing the behavior of specific tumors in animals, most often mice. There are significant shortcomings in this approach that diminish research yield. For example, the genetic similarity between mice and men does not uniformly translate into similarities in natural history of disease or response to therapy. Animal research also assumes that a cancer line is genetically static, when in fact continuing mutations impact the clinical effectiveness of most therapies⁸⁴.

Tumor heterogeneity

Most if not all cancer types are, in fact, a highly heterogeneous series of relatively distinct diseases, which share a predilection for genesis in a specific organ. Thus, one would not expect a single treatment breakthrough to be uniformly effective. Lung cancer is no exception. Beyond the histologic

¹³⁹ Subramanian, A. et. al Metastasis to and From the Central Nervous System-the "Relatively Protected Site". *The Lancet Oncology*. 3(8);498-507. 2002.

¹⁴⁰ Le Pechoux, C. and Arriagada, R. Prophylactic Cranial Irradiation in Small Cell Lung Cancer. *Heme/onc Clin North Am*. 18(2); 355-372. 2004.

¹⁴¹ Cornford, E.M. and Cornford, M.E. New Systems For Delivery of Drugs to the Brain in Neurological Disease. *The Lancet Neurology*. 1(5);306-15. 2002.

characteristics of SCLC and NSCLC are myriad subcellular variations. It has now been determined that susceptibility to at least some forms of therapy depends on tumor genes and their expression. Implications of the emergence of genomics in clinical care are discussed below.^{92,142}

That some patients with advanced lung cancer will have a dramatic or prolonged response to therapy is a critical point that should not be overlooked. Each year, for example, 140,000 patients with NSCLC are identified in the United States alone. If only 10% respond to advanced therapy such as gefitinib, the benefit in life-years and DALY's is enormous⁹³.

Why Smoking Cessation Was Not Cost Effective in this Analysis

In this study “an ounce of prevention” did not lead to “a pound of cure”. However counterintuitive, it should not be surprising that a comprehensive smoking cessation does not lead to more substantial reductions in lung cancer cases and net savings in lung cancer treatment. This study provides insight into counterbalance between lung cancer treatment savings and cessation costs. These include the following:

1. Lung cancer is an efficient killer-By and large, bronchogenic carcinoma should not be considered a chronic disease. Unlike diabetes or coronary insufficiency, lung cancer is not, on average, compatible with prolonged

¹⁴² Lynch, TJ et. al. Activating Mutations in the Epidermal Growth Factor Receptor Underlying the Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib. NEJM. 350(21). 2004

survival. Though expensive to treat on a monthly basis, these costs do not accrue over many years.

2. Contemporary cessation programs still lack general effectiveness-Though a marked improvement over single modality therapy and “cold turkey” cessation efforts, the average one-in-four success rate of multi-modality cessation programs do not reduce smoking prevalence at a high enough rate for cost effectiveness to be demonstrated. Even the maximum reported success rate of 35% is inefficient toward that goal.
3. Relatively few smokers are ready to quit-Despite the availability and affordability of sponsored smoking-cessation programs, the lure of nicotine is too strong for 60% of smokers to seriously attempt to kick the habit in any given year. Thus, the number of longer-term and incorrigible smokers drives the total cost of cancer care.
4. Cessation benefits are underutilized-Only half of smokers motivated to quit will access a paid smoking cessation benefit. The rationale for declining support is not clear and is beyond the scope of this report. Nonetheless, these smokers are less likely to achieve the goal of becoming cigarette-independent.
5. Measurable cancer risk persists after smoking cessation-For reasons previously described, quitters experience a 67% decrease in lung cancer risk over 10 years. Despite this important reduction, the absolute risk to this group remains significant.

Neither current nor impending science will influence limitation five. The other constraints, however, may be loosened by improvements in, or increased utilization of currently available smoking cessation resources. More effective therapy for lung cancer would both improve average longevity and shift the financial balance toward smoking cessation. The other drivers of prevention cost-effectiveness relate to the success and utilization of cessation programs and smoking avoidance. All are discussed in the balance of this thesis.

Obstacles to Comprehensive Smoking Cessation Efforts

Broad-based smoking cessation efforts require two components:

1. Activation and engagement of the smoking public
2. Deployment of tools for overcoming the physical, social and psychological addiction to cigarettes.

Specific drivers within each of these elements provide the needed force to enable cessation. Each driver has inherent advantages, limitations, resource requirements and counter-forces. A discussion of the tools for smoking cessation therapy has previously been discussed. The obvious shortcomings of most forms of therapy include cost, social stigma, effectiveness and tolerability. Suffice it to say that improvement in therapy for tobacco addiction will enhance the success rate.

Cessation treatment is also unlikely to be consistently effective if smokers are not truly motivated to quit. Considerable attention has been addressed to identifying and targeting those within the cohort who are actively prepared to

undergo smoking cessation¹⁴³. Approaches to smoker activation may be described as follows:

- Personal efforts
- Direct-to-consumer promotional efforts, including not for profit, government-sponsored and commercial activities
- Clinician-based efforts
- Employer and insurance-sponsored efforts
- Government and non-government public health efforts
- Taxation and other legislation

Each of these approaches has a specific message and audience. Some attempt to appeal to a segment of smokers (such as youth, women or a specific ethnic group), while others are directed to the entire cohort. Often recruitment efforts are broadcast to an entire population, smokers and non-smokers alike. Each type of effort is restricted by the availability of resources or competing agendas. Some are relatively cost-effective while others are either relatively ineffective or inefficient.

Personal efforts

Individual attempts to induce smoking cessation include family intervention and self-motivation. These efforts are mildly effective, and are often

¹⁴³ Goldberg, D., Hoffman, A. and Anel, D. Understanding People Who Smoke and How they Change: a foundation for smoking cessation in primary care, part 1. Disease-a-month. 48:6. 385-439. 2002.

unfocused. They attempt to force activation rather than leverage personal readiness. Within the data presented above are statistics that demonstrate the lack of efficacy of unguided, unaided efforts. Exceptions to this rule may be smokers who become activated during acute or decompensated chronic illness.

Direct-to-consumer (DTC) efforts

DTC messages are those provided in print and the audiovisual media. Included are paid advertising, public service announcements and other publications and broadcasts. Although such messages are effective for commercial ventures, most share a common inefficiency; they are difficult to target. Smokers in particular, are such a heterogeneous group that it is hard, if not impossible, to direct a message specifically to them. By definition, the message will be largely irrelevant to more than three-quarters of the audience. The smokers that receive quit messages are also a mixed group. This approach cannot be concentrated on those who are activated and ready to quit. There is also evidence that DTC medical advertising has a limited and transient impact on consumers. This phenomenon has been cited in the dramatic decrease in utilization of total body CT scans for cancer screening in the U.S. over the past two years¹⁴⁴.

¹⁴⁴ Kolata, G. Rapid Rise and Fall for Body-scanning Clinics. *The New York Times*. January 23, 2005.

Clinician-based efforts

Medical practitioners have unique opportunities to convey the best possible message directly to smokers. They further have the ability to both activate smokers who are not ready to quit and provide immediate therapy to those who are motivated. By definition, medical practitioners have direct access to those most likely to quit, patients with acute smoking-related illness. It has been demonstrated that brief advice provided during routine office visits are at least as cost-effective as other preventive medical practices, such as the treatment of mild to moderate hypertension or hypercholesterolemia¹⁴⁵.

Despite claims to the contrary, neither capitated nor fee-for-service insurance plans provide physicians with reasonable incentives to provide comprehensive smoking cessation services. Two ICD-9 codes are used for treatment. 305.1 may be used for tobacco dependence. V15.82 designates history of tobacco use. By and large, the existing reimbursement structure favors disease treatment over complex, often time consuming primary prevention efforts.

Employer and insurance sponsored programs

For most employers, medical services may be considered partly a tandem effort between business and insurer. Employers' interest in smoking cessation has several sources. First is the recognition that smoking-related illness impairs productivity and drives medical and disability costs, a factor that was considered in the introduction of this thesis. Second is an attempt to differentiate a business

¹⁴⁵ Cummings, S.R. Rubin, S.M., and Oster, G. The Cost-effectiveness of Counseling Smokers to Quit. JAMA. 261(1). 75-79. 1989.

as an “employer of choice” by providing smoking cessation therapy as part of a health maintenance package. Finally corporate benevolence, though far from universal, may influence decisions in support of smoking cessation efforts. Countering these influences is the employee longevity factor. Given the decades-long latent period for smoking-related illness, it is quite possible that a smoker-employee will no longer be actively employed or connected as a beneficiary when lung cancer is diagnosed. In this context it would run counter to corporate fiduciary interests to fund cessation programs.

Aside from acting as the healthcare management agents of sponsoring businesses and individuals, the insurance industry experiences mostly a marketing gain from smoking cessation efforts. The increase in claims or death benefits is underwritten into smoker’s policies. It is likely that the cost of second-hand smoke is factored into premiums as well. Thus, the cost is passed along to consumers, employers and governments.

Company-sponsored pharmacy benefits most often emphasize care over prevention. Smoking cessation serves as a case in point. Bupropion in the U.S. is available under two brand names. Wellbutrin is marketed for clinical depression, while Zyban, an identical formulation is indicated for smoking cessation. The former brand is universally available through private pharmacy benefit management (PBM) companies (albeit, at times with required prior authorization), while the latter is highly restricted. In a recent survey, only 40% of large employers using a PBM’s covered Zyban. The majority had no coverage for any prescription or non-prescription cessation medication. Companies that

included Zyban in their formularies most often limited the drug's use through restricted coverage, capped maximum expenditures, or enacted higher copays¹⁴⁶. Non-prescription medications, such as nicotine replacement patches are most often excluded from coverage as well, although some employers allow for these items to be purchased with designated pre-tax funds.

There is evidence that uncovered, and even subsidized expenses for cessation therapy may pose a significant obstacle for smokers considering quitting. In an unpublished study at General Electric Company, a smoking cessation program that promoted QuitNet was instituted. The cessation initiative was marketed to 300,000 employees and spouses. The first 300 enrollees into the program received lifetime subscriptions to the service. Subsequent enrollees were required to pay \$65, a price that was markedly discounted from retail. The courtesy subscription limit was reached within the first 30 days of the program. In the following 30 days, only a single eligible beneficiary signed on for the discounted Quitnet package¹⁴⁷.

With virtually no cost, employers may restrict the locations at which employees may smoke and the time available to do so. Evidence indicates that workplace smoking bans are associated with higher rates of cessation attempts, lower rates of relapse in smokers who attempt to quit and a 10% decrease in smoking prevalence among employees.^{148,149}

¹⁴⁶ Jay, G. Medco Health Solutions. Personal communication.

¹⁴⁷ Doran, B. General Electric Company. Personal communication.

¹⁴⁸ Farkas, A.J. et. al. The Effects of Household and Workplace Smoking Restrictions on Quitting Behaviours. *Tobacco Control* . 8; 261-265. 1999.

Government and government-funded public health efforts

As the 21st century begins, a debate has emerged on the state of public health in the U.S. The CDC, OSHA, FDA and other government agencies promote the continued potency of their programs. There is a counter view, however, claiming that public health directed prevention activities in the United States have been severely curtailed in recent decades and are grossly inadequate. The Institute of Medicine's reports, *The Future of Public Health*, and *The Future of the Public's Health in the 21st Century*, argue that, "this nation has lost sight of its public health goals and has allowed the system of public health activities to fall into disarray".^{150,151} In the U.S. only 9% of all health care expenditures, including the budgets of The National Institutes of Health and the Centers for Disease Control and Prevention, are directed toward public health efforts.¹⁵² At present a disproportional allocation of public health resources is earmarked for tertiary prevention and administration. At the state level (1996 figures), two-thirds of spending is for personal health services, whereas spending for population-based primary prevention services is only one percent of total

¹⁴⁹ Farrelly, M.C., Evans, W.N., and Sfekas, A.E.S., The Impact of Workplace Smoking Bans: Results from a National Survey. *Tobacco Control*. 8;272-277. 1999.

¹⁵⁰ Ibid Future of public health.

¹⁵¹ Institute of Medicine. *The Future of the Public's Health in the 21st Century*. National Academy Press, Washington, D.C. 2003.

¹⁵² Phalen, K. Public Health: A Victim of its Own Success? *AMNews*. 2001.
<http://www.ama-assn.org/amednews/2001/12/24/hlsa1224.htm>

health care expenditures.¹⁵³ In addition to diverting essential funds from primary prevention programs, this disparity has led to confusion among many between public health services and welfare.¹⁵⁴

These limitations clearly extend to smoking cessation programs. In 2002, for example, only two states offered Medicaid coverage for all recommended medication and counseling treatments for tobacco dependence, whereas 11 states covered no tobacco-dependence treatments.¹⁵⁵

Taxation and other legislation

As detailed in table 7, The United States has by far the lowest tax rate for cigarettes in the industrialized world.

¹⁵³ Measuring Expenditures for Essential Public Health Services. Public Health Foundation for the Office of Disease Prevention and Health Promotion, Office of Public Health and Science, U.S. Department of Health and Human Services, November 1996, Washington, D.C.

¹⁵⁴ A Systematic Approach to Health Improvement. Healthy People 2010. www.healthypeople.gov/document/html/uih/uih_bw/uih_2.htm

¹⁵⁵ State-Specific Prevalence of Current Cigarette Smoking Among Adults --- United States, 2003. *MMWR*. 53(44); 1035-1037. 2004

	Price	Total Taxes	Tax Rate
Norway	\$14.44	\$11.43	79.2%
United Kingdom	\$12.09	\$9.61	79.5%
United States-highest	\$10.16	\$3.90	
Ireland	\$8.51	\$6.73	79.0%
Australia	\$7.67	\$5.28	68.9%
Hong Kong	\$7.59	\$3.94	51.9%
New Zealand	\$7.41	\$5.52	74.5%
Canada	\$7.27	\$5.20	71.6%
Denmark	\$7.20	\$5.88	81.7%
Sweden	\$6.95	\$4.90	70.5%
Finland	\$6.75	\$5.13	79.0%
United States-lowest	\$6.25	\$1.06	
Germany	\$5.28	\$3.63	68.9%
France	\$5.27	\$3.98	75.5%
Belgium	\$5.02	\$3.73	74.4%
Netherlands	\$4.89	\$3.57	73.0%
Austria	\$3.71	\$2.51	67.7%
Luxemburg	\$3.71	\$2.51	74.7%
Italy	\$3.68	\$2.75	74.7%
Greece	\$3.42	\$2.48	72.8%
Spain	\$3.16	\$2.25	71.2%
Portugal	\$3.11	\$2.51	80.7%

Table 7. Relative cost and tax rate for cigarettes in various industrialized countries. U.S. rates include federal state and city taxes. The highest rate is for New York, lowest for Kentucky. All prices are in 2002 Canadian Dollars (conversion CAD \$1.00=USD \$0.64). Adapted from *Global Cigarette Taxes and Prices*¹⁵⁶.

This reality clearly impacts on reduction and cessation efforts. Evidence from multiple studies suggests that smoking prevalence and cessation rates are directly linked to the cost of a pack of cigarettes.^{157,158} In California an increase

¹⁵⁶ *Global Cigarette Taxes and Prices*. Non-Smokers' Rights Association of Canada. www.Nsra-adnf.ca/news_info.php?news_id=57

¹⁵⁷ Beiner, L. Impact of the Massachusetts tobacco control programme: population based trend analysis. *BMJ*. 321(7257); 351-354. 2000.

¹⁵⁸ Heloma, A. et. al. Smoking Prevalence, Smoking-Related Lung Diseases, and National Tobacco Control Legislation. *Chest*. 126(6);1825-1831. 2004.

in cigarette taxation in 1989 was associated with a decline in per capita cigarette consumption of 2.72 packs/year relative to the concurrent decline in total U.S. smoking. This improvement decreased to 2.05 packs/year when the program was scaled back in 1992¹⁵⁹. Even in selected subpopulations, this relationship holds. Among pregnant women, a 10% increase in the price of cigarettes has been associated with a 7% decrease in smoking prevalence.¹⁶⁰ The benefits of higher cigarette taxes go beyond direct disincentives. Additional revenue may be used to improve funding of public and private smoking cessation programs. Two theoretical shortcomings of increased taxation may exist, however. First is the possibility that raising the cost of a pack of cigarettes will to some extent decrease the rate of personal consumption without impacting cessation. Smokers may drift into lower risk categories by cutting down, but will not receive the full benefit of quitting. Second, increasing revenues from cigarette taxes may foster a government reliance on propagation of the U.S. tobacco industry. At some point the government may become more dependent on cigarettes than the public it seeks to protect.¹⁶¹

The U.S. government has traditionally supported tobacco farming through direct subsidies and tax incentives. This trend, however, may be receding. A

¹⁵⁹ Fichtenberg, C.M. and Glantz, S.A. Association of the California Tobacco Control Program with Declines in Cigarette Consumption and Mortality From Heart Disease. *NEJM*. 343;1772-1777. 2000.

¹⁶⁰ Ringel, J.S. and Evans, W.N. Cigarette Taxes and Smoking During Pregnancy. *Am. J. Public Health* 91(11); 1851-1856. 2001.

¹⁶¹ Payne, T.J. Who profits the most from cigarettes? Government. *CalNews.com* October 23, 2002. <http://www.calnews.com/archives/payne01.htm>

recent government-sponsored cigarette control effort used farm subsidies to encourage conversion from tobacco to other crops. (The Flake-Van Hollen amendment to legislation approved in July, 2004 prohibits the use of taxpayer funds for tobacco farm buyouts). It is unlikely, however, that these efforts will decrease the availability or increase the cost of cigarettes. The U.S. cigarette industry has already begun to convert from domestic to foreign tobacco as a cost containment strategy.¹⁶²

The CDC and other public health groups have realized limits to the effectiveness of voluntary population-based efforts. Recently they have begun to actively work with their legislative partners on an active program of developing and implementing a framework as a tool for preventing chronic diseases and addressing the growing epidemic of obesity, heart disease, stroke, and other chronic diseases and their risk factors. It is hoped that these efforts will eventually lead to legally mandated prevention programs including smoking cessation and obesity deterrence.¹⁶³ The California tobacco control program as well as designed studies strongly suggest that restricting the locations where individuals may smoke decreases exposure to second hand smoke, decreases

¹⁶² American Lung Association Commends House Defeat of Tobacco Buyout. American Lung Association News. July 13, 2004.

¹⁶³ Mensah, G.A. et. al. Law as a Tool for Preventing Chronic Diseases: Expanding the Range of Effective Public Health Strategies. Preventing Chronic Disease 1:1. 2004; <http://www.cdc.gov/pcd/issues/2004/jan/mensah.htm>

per capita consumption of cigarettes, increases the likelihood that smokers will attempt to quit and decreases the prevalence of smoking.^{157,164,165}

What Needs to be Done to Reduce the Toll of Lung Cancer in the U.S.

1. Provide Insurance Coverage and a Framework for Screening High Risk Individuals at High Risk for Lung Cancer

Figure 14 demonstrated that survival from lung cancer is directly related to stage at diagnosis. Thus it may be inferred that earlier diagnosis is associated with more favorable outcomes. Application of this theory, however, is hindered by the question of who and how to screen. Expansion of most medical screening programs has been hampered by inadequate predictive values of available tests applied to a general or at risk population. This limitation is certainly true for smokers and smoking-related illness. Multiple studies have demonstrated a lack of survival benefit for individuals diagnosed via chest X-ray or standard sputum cytology and these tests have not been recommended for broad screening purposes among smokers.¹⁶⁶ Compelling data, however, now favors the use of limited testing for cardiovascular and pulmonary disease in this high-risk

¹⁶⁴ Impact of Workplace Smoking Restriction-Impact on Smoking Prevalence. *Health Canada-The Facts About Tobacco*. 2002. www.hc-sc.gc.ca/hecs-sese/tobacco/facts/workplace/part3_impact_prev.html.

¹⁶⁵ Brownson, R.C., Hopkins, D.P., and Wakefield, M.A. Effects of Smoking Restrictions in the Workplace. *Ann. Rev. Pub. Health*. 33;333-348. 2002.

¹⁶⁶ Humphrey, L.L., Teutsch, S. and Johnson, M.S. Update for the U.S. Preventive Services Task Force: Lung Cancer Screening with Sputum Cytologic Examination, Chest Radiography, and Computed Tomography. Agency for Healthcare Research and Policy. 1-11. 2004.

population. The United States Preventive Services Task Force, for example, now recommends abdominal ultrasound scans for elderly smokers and estimates that 3,000 lives could be saved each year by the detection and resection of smoking-related abdominal aortic aneurysms¹⁶⁷. An accumulating body of evidence, including the Early Lung Cancer Action Project (ELCAP) suggests that CT screening of long-term smokers could more accurately diagnose lung cancer and could identify tumor nodules at an earlier stage. The ELCAP data is striking. In that series, 96% of CT diagnosed cancers were resectable and 85% were Stage I. Use of this technology in high risk individuals may be clinically effective, associated with relatively few unnecessary invasive procedures and is cost-effective. Coupling CT scanning with automated quantitative image cytometry, which detects gross genomic aberrations, may further improve diagnostic yield.^{168,169,170}

2. Improve Lung Cancer Treatment

Use of agents like gefitinib and erlotinib may offer a glimpse of the potential of “personalized medicine” to transcend the existing lung cancer survival plateau. Clearly, the promise of the field of genomics is extraordinary. Genetic alterations

¹⁶⁷ Kolata, G. Aneurysm Scans are Urged In Older Men Who Smoked. *The New York Times*. .A15. February 1, 2005.

¹⁶⁸ Henschke, C.I. Early Lung Cancer Action Project: Overall Design and Findings from Baseline Screening. *Cancer*. 89(11 supplement) 2474-2482. 2000.

¹⁶⁹ Henschke, C.I. et. al. Guidelines for the Use of Spiral Computed Tomography in Screening for Lung Cancer. *European Respiratory Journal*. 21;45S-51S. 2003.

¹⁷⁰ McWilliams, A. et. al. Lung Cancer Screening: a Different Paradigm. *Am. J. Respir. Crit Care Med*. 168;1167-1173. 2003.

in various progression stages of lung cancer cells have been studied. These alterations can be regarded as molecular *footprints* representing the individual processes within the transition to cancer.¹⁷¹ Thus, advances in genomics may lead to novel therapies that will have an impact on the survivability of lung cancer. More likely (at least over a shorter term), however, is the identification of individuals at genetically increased risk for lung cancer and pre-treatment selection of patients most likely to respond to currently available therapy, such as EGFR's. For the former group, aggressive avoidance of controllable risk (such as smoking and enhanced screening) could result. In the latter, patients who are unlikely to benefit from potentially toxic therapy may be spared exposure.

Gene therapy offers the promise of previously unheard of forms of treatment. Development of a mechanism for repairing smoking related nuclear damage or inserting healthy tumor immunotherapy genes into cells could revolutionize care. Although no practical breakthroughs against lung cancer can be reported to date, an estimated 60% of gene therapy trials are now aimed at cancer therapy¹⁷².

Other novel treatments including targeted therapy and vaccine-mediated stimulation of the immune system are being actively studied for use in both small cell and non-small cell lung cancer. Their potential is significant.

Regression analysis cannot predict the future. Certainly, continuing advances in diagnostics, cytotoxic chemotherapy, radiation therapy, and surgical techniques will have an impact. It remains impossible to predict whether the next

¹⁷¹ Yokota, J. and Kohno, T. Molecular Footprints of Human Lung Cancer Progression. *Cancer Science*. 95(3):197-204. 2004.

¹⁷² Begley, S. Why Gene Therapy Still Hasn't Produced Major Breakthroughs. *The Wall Street Journal*. B1. February 18, 2005.

breakthrough in conventional therapy will elevate the benefit of treatment above the current plateau. Even less certain is the future impact of the novel therapies including anti-angiogenesis, gene therapy, monoclonal antibodies, and genomics. Compounding this uncertainty is the question of whether new technology will be affordable or even available to the entire at-need population.

3. Improve the Effectiveness of Smoking Cessation Programs

Advances in the science of addiction may yield additional mechanisms and therapies for smoking cessation. In addition to the development of new products, a shift from poorly effective and single-modality treatments to those proven to be most effective should increase the quit rate. Smokers are not a homogeneous group. Variations in psychological, physiological, social and demographic forces affect the suitability of each type or combination of therapy. Even such basic distinctions as gender affect treatment outcomes for different modalities. Unlike men, women most often cite potential weight gain as a major obstacle for smoking cessation. In addition, the likelihood of success of cessation therapy, and especially nicotine replacement, has been linked to the female menstrual cycle¹⁷³. Further study is required to determine subsets of smokers for whom the effectiveness of specific combinations of treatment modalities would be most effective. Healthcare practitioners require additional training on the selective use of each type of cessation therapy. Additional effort

¹⁷³ Allen, S.S. Effects of Transdermal Nicotine on Craving, Withdrawal and Premenstrual Symptomatology in Short-term Smoking Abstinence During Different Phases of the Menstrual Cycle. *Nicotine Tob. Res.* 2(3);231-241.2001.

should also be given to determination of the utility of non-traditional forms of cessation therapy such as aversion therapy and homeopathic care, many of which have demonstrated some degree of effectiveness. Hypnotherapy, for example, has produced 20-40% 6-month quit rates among well-motivated patient groups. Even higher success rates have been associated with individualized induction, greater clinical experience, and greater patient hypnotizability¹⁷⁴. Acupuncture may also be modestly effective for smoking cessation. A review of randomized control trials for this modality appears in table 8.

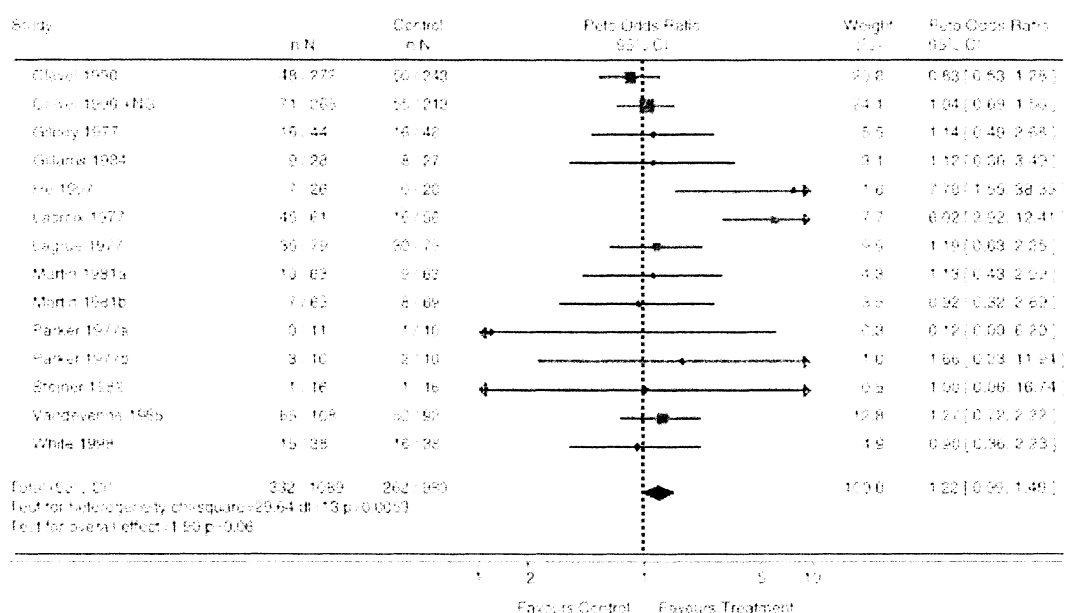


Table 8. Summary of studies of acupuncture versus sham for effectiveness in smoking cessation. Adapted from Villano and White.¹⁷⁵

4. Specifically target “activated” smokers for cessation efforts

¹⁷⁴ Ockene, J.K., Kristeller, J.L. and Donnelly, G. Tobacco. In The American Psychiatric Press Textbook of Substance Abuse Treatment. Second edition. American Psychiatric Press. Washington, D.C. 215-238. 1999.

¹⁷⁵ Villano, L.M. and White, A.R. Alternative Therapies for Tobacco Dependence. Med. Clin. North Am. 88;1607-1621. 2004

As referenced in this thesis, smoking cessation programs are a modestly cost-effective alternative to lung cancer treatment. This differential can be further improved by targeting smokers (as opposed to broad marketing campaigns that reach smokers and non-smokers alike), those who are motivated to quit, and especially smokers with acute or recurrent illness.

Research discussed previously suggests that broad marketing campaigns that reach both the smoking and non-smoking populations are relatively inefficient tools for promoting cessation programs. Directed outreach, even to healthy, poorly motivated smokers may offer an important resource advantage. Consideration should be given to providing concentrated outreach in areas and groups where smokers are likely to congregate. These include the following:

- Geographic regions where smoking is highly prevalent
- “Smoking rooms” in offices and smoking-permissible areas in public buildings.
- Bars and taverns
- Smoking-permissible rooms in hotels

Hospitalized smokers are among the most highly motivated to stop. Using only nicotine replacement therapy, they are much more likely to quit and remain off cigarettes for 6 months or more than the smoking population in general. Nurse led intervention has been associated with a 50% 12-month quit rate among patients hospitalized with coronary artery disease^{176,177}. As

¹⁷⁶ Simon, J.A. et. al. Intensive Smoking Cessation Counseling Versus Minimal Counseling Among Hospitalized Smokers Treated with Transdermal Nicotine Replacement: a randomized trial. *Am. J. Med.* 114(7);555-562. 2003

referenced previously, the elderly and smokers with underlying obstructive pulmonary disease still experience a substantial lung cancer risk reduction after cessation. Statistical opportunity seems to exist up to the development of irreversible oncogenic mutation. Maximum effort should be directed at prompting acutely ill smokers to quit. This may be achieved through physician offices, by providing materials and programs tailored to smokers who are under evaluation or care for acute or chronic (smoking or non-smoking related) illness. Pharmacies may be another contact point for ill smokers. Adult patients receiving prescriptions for medications for acute respiratory infections or COPD should receive information on how to access smoking cessation services, including the scope of available insurance benefits.

Hospitals should actively identify inpatient and outpatient smokers and designate a counselor to recruit them into cessation programs. (Hospitalization alone provides a springboard into abstinence. Often patients will traverse physical withdrawal during their stay). Pilot smoking cessation programs were begun in hospitals over 20 years ago. Still, in a recent survey, only 30% of hospital web sites contained information relating to smoking cessation programs and only 47% of hospital switchboards had smoking cessation programs available for phone inquiry^{178,179}. Electronic medical records systems should be

¹⁷⁷ Brown, D. Nurse-led Intervention Increases Smoking Cessation Among People with Coronary Artery Disease. *Evidence-Based Healthcare*. 8;128-131. 2004.

¹⁷⁸ Andrews, J.L. Reducing Smoking in the Hospital: An Effective Model Program. *Chest*: 84(2) 206-209. 1983.

¹⁷⁹ Denny, J.T. Hospital Initiatives in promoting Smoking Cessation: A Survey of Internet and Hospital-Based Programs Targeted at Consumers. *Chest*. 122(2);692-698. 2002.

adapted to flag smokers at the time of admission, such that the counselor may identify and provide services to all. The medical standard of care should dictate that all smokers receive counseling and the opportunity to begin cessation therapy prior to hospital discharge.

Expensive smoking cessation resources, such as pharmacotherapy should be concentrated on smokers who are most likely to respond to their use. An algorithm for the efficient use of pharmacotherapy as part of an overall smoking cessation strategy was previously provided as figure 11.

6. Concentrate Smoking Cessation Efforts on Young Smokers

Smoking cessation does not eliminate the risk for lung cancer for several reasons. An early cancer, though not clinically apparent, may be present at the time of cessation. Taken a step earlier, irreversible oncogenic mutations may have occurred prior to cessation that will generate lung cancer, irrespective of removal of the causative irritation. It thus makes complete sense to concentrate resources on the subpopulation of smokers for whom the potential for cancer avoidance is greatest. Activating and identifying young smokers who are motivated to quit would further improve program efficiency. A scheme for focusing cessation efforts to this group appeared as figure 20.

Beyond the promotion of cessation programs, a second strategy for preventing, minimizing, and terminating cigarette use in young people is to raise tobacco excise taxes. Studies have shown that youth, minorities, and low-

income smokers are two to three times more likely to quit or smoke less than other smokers in response to price increases¹⁸⁰.

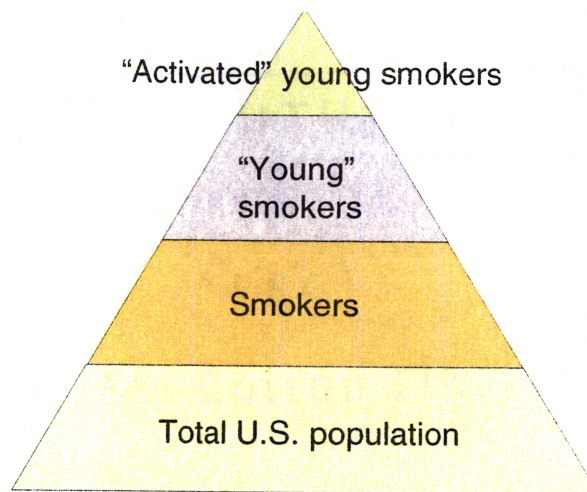


Figure 20. A scheme for optimal utilization of smoking cessation resources. In this plan resources would be concentrated on young smokers who have the greatest likelihood of reducing cancer risk. Strategies targeting the entire population or all smokers would receive less emphasis.

6. Enhance the Role of Clinicians in Smoking Cessation

It is intuitive that physicians and nurses take a leading role in smoking cessation. This responsibility has been defined within the scope of their services since at least 1982¹⁸¹. Current clinical practice guidelines advise that clinicians should use the “Five A’s”, **A**sk about tobacco use, **A**dvice to quit, **A**ssess willingness to make a quit attempt, **A**ssist in quit attempt, and **A**rrange for follow-

¹⁸⁰ Tobacco Taxation Fact Sheet. CDC Tobacco Information and Prevention Source. www.cdc.gov/tobacco/sqr/sqr_2000/factsheets/factsheets_taxation.htm

¹⁸¹ The Management of Smoking in the Physician’s Workshop. ACCP Committee Recommendations. Chest. 82(3). 359-361. 1982.

up, at each patient encounter¹⁸². Still, the current clinical model favors high volume, short visit care. This dynamic is poorly suited to the intensive evaluation and counseling required for highly effective smoking cessation therapy. Several changes are needed to improve physician-led cessation efforts. They include the following:

- Improve payment incentives provided to medical and mental health practitioners for cessation counseling and treatment
- Provide additional training to allow clinicians to identify activated smokers and match individual smokers to the best personal cessation strategy
- Increase the availability of tools and templates for clinician use
- Promote the use of electronic medical records that can identify and track smokers and cessation efforts
- Create the expectation that cessation therapy will be considered the medical standard of care for all smokers seeking medical attention

7. Improve Insurance Coverage for Smoking Cessation Programs

This thesis adds data to the case that the cost of fully funded, multimodality smoking cessation programs is less than the cost of care for lung cancer. Clearly, full coverage of tobacco dependence treatment has been shown to be an effective and relatively low cost strategy for significantly increasing quit

¹⁸² Reimbursement for Smoking Cessation Therapy: A Healthcare Practitioners Guide. 3rd edition. Professional Assisted Cessation Therapy. 2004.

attempts and quit rates.¹⁸³ Also evident in this review is the demonstrable advantage of multi-modality comprehensive therapy over single agent or “cold turkey” approaches. Basic health insurance should provide not only skeleton coverage, but comprehensive reimbursement for practitioner-based activation efforts, counseling, and proven pharmacotherapy (prescription and OTC). The Public Health Service-sponsored Clinical Practice Guideline, *Treating Tobacco Use and Dependence*, and the Community Preventive Services Task Force recommend that all insurers provide tobacco cessation benefits that do the following:

- Cover at least four counseling sessions of at least 30 minutes each, including proactive telephone counseling and individual counseling.
- Cover both prescription and over-the-counter nicotine replacement medication and bupropion
- Provide counseling and medication coverage for at least two smoking cessation attempts per year.
- Eliminate or minimize co-pays or deductibles for counseling and medications, as even small copayments reduce the use of proven treatments.

Coverage should be provided for smoking cessation and tobacco dependency counseling even in the absence of a related medical condition.

¹⁸³ Schauffler, H.H. et. al. Variations in Treatment Benefits Influence Smoking Cessation: Results of a Randomised Controlled Trial. *Tobacco Control*. 10175-180. 2001.

Health plans should further promote physician efforts by providing quality incentives for their efforts.

8. Improve Funding of Government-sponsored Smoking Cessation Programs

The rationale for government sponsorship of smoking cessation programs as a part of public health policy is even more compelling than the argument for private insurance coverage. The age at which smoking most often begins and the several decade lag between onset of smoking and diagnosis of lung cancer mean that this illness disproportionately affects older Americans. Thus, the burden of paying for lung cancer lies largely within the Medicare program. As demonstrated in this thesis, each dollar of smoking prevention will yield a savings of roughly 7.5% in lung cancer treatment expenses alone. At no additional cost the public will experience savings in treatment of other smoking-related illnesses including obstructive lung disease, cardiovascular disease, stroke, and multiple other malignancies.

Under current government guidelines, Medicare managed care programs are supposed to encourage patients to quit smoking. Unfortunately, that mandate has not routinely translated into coverage for smoking cessation treatments. As of 1998, 13% of all enrollees into a Medicare funded managed care plan were active cigarette smokers¹⁸⁴. Given the data supporting the health effects of cessation in the elderly, this group represents a large opportunity for

¹⁸⁴ Receipt of Advice to Quit Smoking in Medicare Managed Care-United States 1998. MMWR. 49(35);787-801. 2000.

improved geriatric health and cancer avoidance. Traditional Medicare and Medicare managed care programs should provide full smoking cessation benefits.

9. Further Encroachment on the Locations Where Smoking is Allowed

Smoking is a threat not only to the individual who uses cigarettes, but also to the public exposed to environmental tobacco smoke. This reality provides a basis for restricting public locations where cigarettes are consumed. Cigarette smokers should not be accommodated in private or public buildings. Even where allowed by law, smoking rooms and other designated areas should be discouraged. Contrary to the concerns of bar and restaurant owners, banning smoking from public establishments does not decrease business. Rather, patrons are more likely to frequent establishments that are smoke free¹⁸⁵. Although there may be practical limits on the environments and situations in which smoking may be prohibited, surprising leeway exists in many areas. In 20 states it is legal for an employer to mandate that employees not smoke on *and off* the job. One employer placed such a restriction, with fines for employees testing positive for nicotine who refused to commit to counseling or personal quit efforts. As a result, approximately 20 employees (out of a workforce of 200) completely discontinued all use of tobacco products.¹⁸⁶ Restrictions on smoking

¹⁸⁵ Rutenberg, J. and Koppel, L. As Air Clears, Even Smokers are Converted. *The New York Times*. February 6, 2005. page 25, 29.

¹⁸⁶ Peters, J.W. Company's Smoking Ban Means Off-hours Too. *The New York Times*. February 8, 2005.

even induce reduction and cessation in teenagers. This benefit speaks to previous points on the importance of addressing young smokers and should further drive this effort¹⁸⁷

10. Increase Business Efforts Toward Smoking Cessation

Employers must not only recognize smoking cessation as a cost-savings strategy, but must also identify opportunities to provide effective, employee-acceptable cessation resources. Several touch points and strategies have been identified¹⁸⁸:

- Smokers who wish to stop smoking and whose needs include access to high quality treatment (counseling, education, and drug therapies) need assistance in paying for treatment, and a supportive work environment and policies.
- Smokers who are not ready to stop smoking should be motivated through incentives, disincentives, education and workplace policies.
- Recent ex-smokers require follow-up to prevent relapse
- Nonsmokers should not be subjected to environmental tobacco smoke
- Supervisors and managers require practical guidelines for implementing smoking policies and addressing conflicts between smokers and nonsmokers, as well as resources to which they can refer employees who wish to quit smoking.

¹⁸⁷ Wakefield, M. et. al. Effect of Restrictions on Smoking at Home, at School, and in Public Places on Teenage Smoking: Cross Sectional Study. BMJ. 7257;333-337. 2000.

¹⁸⁸ Employers' Smoking Cessation Guide. Professional Assisted Cessation .herapy. 15. 2004.

- Smokers may be enticed or assisted with quitting as part of off-work benefit or communications programs.

There are several inherent advantage of employers' participation in smoking cessation efforts. Businesses have the organizational structure to identify and communicate with smoking employees. They may use the leverage of peer-pressure; over two-thirds of all employees are non-smokers. Employers certainly can leverage purchasing power to reduce the cost of cessation efforts.

Non-proprietary educational and cessation materials should be promoted for business customization and use. Business leaders need to recognize the value of smoking cessation programs and need to access (or develop in house) the tools to encourage (or force) their employees to quit.

Employees also bear part of the responsibility of smoking cessation in the workplace. Unions should not view smoking restrictions as an adversarial strategy. Rather, they should embrace this effort as an opportunity for a cooperative effort for employee health and safety.

Section V-Conclusion

**-Economics has been described as the science of allocating scarce resources-
David M. Eddy, M.D. PhD. 1981¹⁸⁹**

Americans, as both individuals and a society have become significantly dependent on cigarette smoke. It has become habit to 60,000,000 citizens and is ingrained in our culture. Although recent trends in smoking prevalence and the potential for breakthrough treatments in lung cancer are cause for optimism, the toll from this disease remains staggering. This thesis has added to an impressive body of evidence suggesting that primary prevention of lung cancer and other smoking-related illnesses could be a more cost-effective strategy for managing the financial burden of lung cancer than patient care. It has shown the poor correlation between modern medical advances and survival and has documented the potential for savings associated with the provision of comprehensive, multi-modality smoking cessation tools relative to surgery, radiation and chemotherapy.

It would be unfair to claim that cigarette smoking continues unabated in this country. Legislation, changing attitudes, improved cessation methods, litigation, and cigarette cost increases continue to separate individuals from a highly addictive habit. Even more dramatic than the overall decline in prevalence has been the recent decrease in smoking behavior among our youth (figure 21). Although the slope has decreased in recent years, there is every reason to believe that the absolute decline in smoking prevalence witnessed over the past decade will continue into the future.

¹⁸⁹ Eddy, D. The Economics of Cancer Prevention and Detection: Getting More for Less. Cancer. 47;1200-1209. 1981

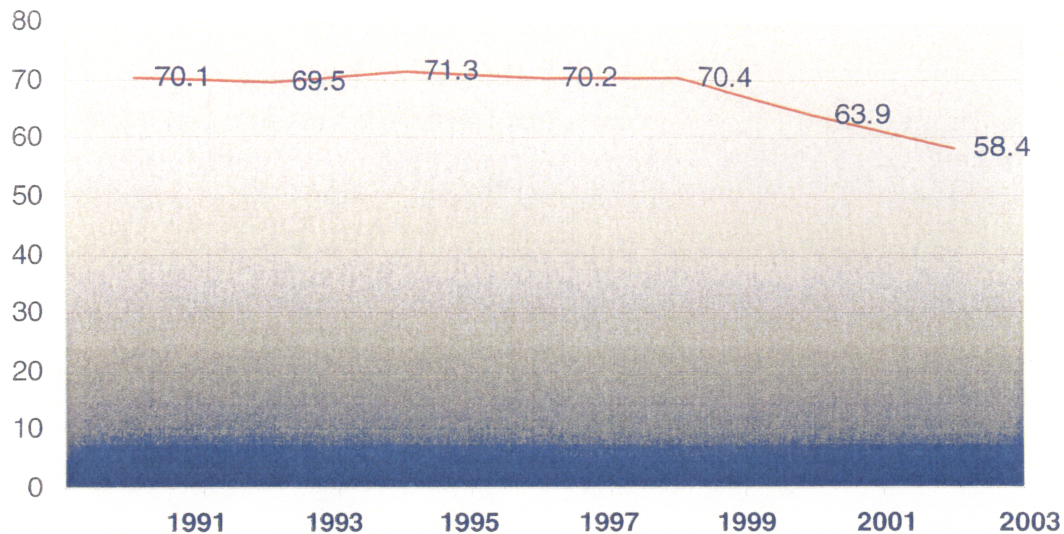


Figure 21-Percentage of High School Students Reporting Cigarette Use (Ever tried smoking, even 1 or 2 puffs) Adapted from CDC Data¹⁹⁰

What is missing from this success story is a universal acceptance of the paradigm shift from a treatment-focused to a prevention-focused lung cancer avoidance strategy. Huge market forces in both cigarette manufacturing and healthcare promote maintenance of the status quo. These influences are further reflected in government policy. A worldwide anti-tobacco treaty that was completed in 2003 and implemented this year has yet to be ratified in this country¹⁹¹. Sustaining the reduction in smoking prevalence will require continued changes in attitudes among Americans (particularly in states and regions where smoking has the greatest cultural acceptance) and a return to the pre-modern concept that primary prevention is a legitimate and powerful approach to health and wellness.

¹⁹⁰ Cigarette Use Among High School Students-United States, 1991-2001. MMWR 53(23); 499-502. 2004.

¹⁹¹ Worldwide Anti-Tobacco Treaty Takes Effect. *The New York Times*. A8. February 28, 2005.

