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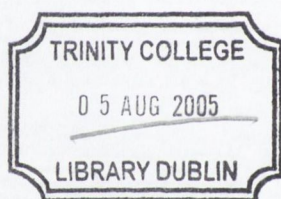
EPIDEMIOLOGY OF LUNG CANCER
IN THE REPUBLIC OF IRELAND

Submitted for the degree of Doctor of Philosophy
(PhD)

To the University of Dublin (Trinity College)

October 2004

Zubair Kabir MD MSc



THESIS
7680

Dedication

This piece of work is dedicated to my adorable parents

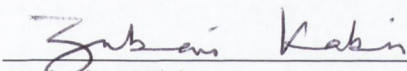
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Declaration

I declare that except where otherwise stated, this thesis is entirely my own work and has not been submitted to this or any other University as an exercise for any other degree award.

I declare this work was carried out by myself in the Department of Respiratory Medicine located in St. James's Hospital (Dublin) under the supervision of Professor Luke Clancy.

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SUMMARY

The study aimed at investigating the epidemiology of overall lung cancer pattern in the Republic of Ireland across different time-periods. The study also examined the lung cancer incidence pattern across major cell-types (adenocarcinoma, small cell carcinoma, large cell carcinoma, and squamous cell carcinoma), with special emphasis on Dublin City populations. Finally, the study addressed the temporal association between lung cancer deaths and urban air pollution levels using black smoke (BS) as the indicator variable for urban air pollution mixture in Dublin City, ten years before and after the introduction of the Coal Ban in 1990 across Dublin City. The overall aim of the study is also to provide with robust epidemiological evidence surrounding the hypothesis that there may be a gender difference in the susceptibility to developing lung cancer.

The study is an ecological analysis, but different methods have been employed pertinent to specific study objectives. The study made the best use of data available to date from various sources, using appropriate statistical modelling techniques to address the issues, together with different statistical software packages. Simple age-cohort modelling (Poisson regression) for lung cancer risk estimation across different birth-cohorts (1888-1967), Joinpoint regression modelling for estimating the annual-percent-changes in lung cancer death rates from 1970 to 1999, multivariable logistic regression modelling for risk assessment of lung cancer incidence (1994-2001) across cell-types, and age-period modelling (Poisson regression) for lung cancer-air pollution association. Attributable risk and population attributable risk have been estimated where appropriate. All the lung cancer estimates (rates, risks, ratios) are adjusted for age and smoking, and also standardised to the Irish Population Standard.

From 1990 onwards, lung cancer death rates are declining annually among males (-2.4%), while females have shown a deceleration in their annual death rates (0.1%). However, the 85+ year-old females are still showing a significant annual rise (6.7%). Those born before the World War II have a three-fold increased lung cancer risk relative to those born in 1963-1967 (the youngest birth-cohorts in the study) across both sexes. Lung adenocarcinoma (AC) is increasing significantly (8% annual rise) from 1994 onwards in females across the Republic. Also lung AC has a modest increased risk for Dublin City populations across both sexes compared to the rest of the Republic. Assuming a cause-effect relation, 2-5% (n=74-177) excess lung cancer deaths are attributable to high BS levels in the pre-coal ban period (1981-1990), while only 1% (n=34) excess lung cancer deaths are attributable to very low BS levels in the post-coal ban period (1991-2000). Overall, the study does not support the hypothesis that females have a greater susceptibility to developing lung cancer.

Assuming no changing risk profile of the youngest birth-cohorts, the overall lung cancer trend over the coming years is expected to be encouraging in the Republic of Ireland based on the observed declining lung cancer risk pattern for those born after 1935. The study demonstrated an age-cohort phenomenon for lung cancer, consistent with the changing smoking pattern across successive generations. The underlying geographical variations in lung cancer cell-types imply some emerging 'urban' environmental risk factors contributing in part to the observed variations, together with the residual confounding effect of active smoking acting differentially on certain cell-types. In conclusion, further identification and quantification of putative risk factors for lung cancer (AC among females in particular) is necessary, integrating traditional epidemiological approaches with modern molecular techniques.

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ABBREVIATIONS

AC	Adenocarcinoma of lung
APHEA	Air Pollution and Health
AR	Attributable Risk
ASIR	Age-Standardised Incidence Rate
ASIRR	Age-Standardised Incidence Rate Ratio
BMI	Body Mass Index
BS	Black Smoke
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSO	Central Statistics Office
DNA	Deoxyribonucleic Acid
EAPC	Estimated-Annual-Percent-Changes
EPA	Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer
EU	European Union
ETS	Environmental Tobacco Smoke
FCTC	Framework Convention on Tobacco Control
FTC	Federal Trade Commission
GST	Glutathione-S-Transferase
HIPE	Hospital In-Patient Enquiry Scheme
HRT	Hormone Replacement Therapy
ICD-O	International Classification of Diseases (Oncology)
ISAAC	International Study of Asthma, Allergies in Childhood
LC	Lung Cancer
LCC	Large Cell Carcinoma of lung
LET	Linear Energy Transfer
NNK	Nitrosamines (4-Methylnitrosamino-1-3-Pyridil-1-butatone)
NRT	Nicotine Replacement Therapy
NSCLC	Non-Small Cell Lung Carcinoma
OC	Oral Contraceptive
OR	Odds Ratio
PAH	Polycyclic Aromatic Hydrocarbons
PAR	Population Attributable Risk
ROI	Republic of Ireland
RR	Relative Risk/Rate Ratio
SAS	Statistical Analysis System
SEER	Surveillance, Epidemiology, and End Results
SMCC	Small Cell Carcinoma of lung
SQCC	Squamous Cell Carcinoma of lung
TRO	Tumour Registration Officer
TTNA	Trans-Thoracic Needle Aspiration
US	United States
UK	United Kingdom
WHO	World Health Organization

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Epidemiology of Lung Cancer in the Republic of Ireland

INTRODUCTION AND STRUCTURE OF THESIS

This thesis is a detailed epidemiological study of lung cancer pattern in the Republic of Ireland over thirty years from 1970 to 1999. It also examines the potential temporal association between lung cancer death pattern and urban air pollution mixture levels in Dublin City from 1981 to 2000. This study tests the hypothesis that the introduction of Coal Ban across Dublin City in 1990 has had an impact on the temporal pattern of lung cancer deaths. In addition, the study investigates the epidemiological pattern of lung cancer incidence by major histological sub-types (adenocarcinoma, squamous-cell carcinoma, small cell carcinoma, large cell carcinoma) in the Republic of Ireland from 1994 to 2001. The study also examines a possible gender susceptibility to developing lung cancer in the Republic of Ireland.

STRUCTURE OF THESIS

This study is structured into ten distinct chapters, with emphasis on the impact of urbanization and geographical variations in identifying any potential emerging risk factors for lung cancer in the Republic of Ireland. Chapter one gives a background to the present study, an overview of the global epidemiological pattern of lung cancer, and the reasons for conducting the study in the Republic of Ireland. A summary of the aim and objectives of the study are also provided in chapter one.

Chapters two, three, four and five critically appraise the research findings published to date on the epidemiological pattern of lung cancer, and each of these

chapters focuses on specific issues. Chapter two deals with the global pattern of lung cancer epidemiology, with special emphasis on underlying geographical variations and urbanization patterns across various geographical regions. Chapter three critically discusses the major risk factors for lung cancer, and other potential risk factors for lung cancer. Chapter four looks separately at the epidemiological pattern of lung cancer histological sub-types across the globe together with the potential risk factors and biases for the rising lung adenocarcinoma incidence worldwide. Chapter five brings all the evidence together to support a lung cancer pandemic.

The results are presented in chapters six, seven, eight, and nine, which address the four study objectives separately. Each chapter is separated into methods, results, and discussion. Chapter six examines lung cancer death patterns in the Republic of Ireland across gender over a thirty-year period (from 1970 to 1999). Chapter seven deals with lung cancer incidence pattern in the Republic of Ireland by major histological sub-types across gender from 1994 to 2001 together with other study covariates. Chapter eight looks at lung cancer death patterns in Dublin City from 1981 to 2000. Chapter nine addresses the issue of lung cancer death patterns with regard to urban air pollution levels in Dublin City from 1981 to 2000, using black smoke levels as the indicator variable for urban air pollution mixture.

Chapter ten summarises the study findings, draws conclusions on the study findings, and also provides an insight into the future directions of epidemiological research in general within the Republic of Ireland.

Chapter One

BACKGROUND TO THE STUDY

1.1 Introduction

The opening chapter leads us through the salient features for undertaking the present project on lung cancer epidemiological patterns in the Republic of Ireland. This chapter has two distinct sections. The first section provides a background into the history, as well as the public-health implications of both traditional and modern epidemiological approaches to lung cancer across the globe. The same section briefly spells out the important risk factors for lung cancer development, and also the possible areas of active research on lung cancer epidemiology from a global perspective. The second section focuses on two specific populations, comparing and contrasting the lung cancer epidemiological patterns on this island of Ireland. The same section also outlines the strengths and limitations of conducting such epidemiological studies in the Republic of Ireland.

1.2 Lung cancer epidemiological patterns: a global overview

Epidemiological evidence is the foundation for primary and secondary disease prevention. Epidemiological approaches are used to track the occurrence of disease, to characterize natural history, and to identify determinants of disease. For lung cancer, routine mortality statistics have confirmed that the disease became more frequent during the first half of the 20th century. Today, lung cancer is the most common cancer worldwide. In males, the highest incidence rates are seen in Eastern Europe and North America.¹ In females, high incidence rates are found in Northern and Western Europe, as well as in North America. In 2000, it was estimated that there

were about 375,000 cases of lung cancer in Europe: 303,000 in males and 72,000 in females.¹ In 2000, the number of lung cancer deaths was about 347,000 (280,000 in males and 67,000 in females) in Europe.¹ This suggests the overall poor survival rates of lung cancer even in the 21st century. Epidemiologically, this also indicates that lung cancer mortality rates may closely correspond to incidence rates.

Case-control and cohort studies, the epidemiological study designs that are used to evaluate exposure in disease association, causally linked smoking to lung cancer in investigations reported from the 1950 onwards. Around 90% of lung cancer cases among males are attributed to smoking alone, especially in the developed countries, as opposed to 40-60% among females.² However, follow-up studies on lung cancer incidence and mortality rates have shown that their rise and decline parallel the trends of past smoking habits, more consistently observed across the male populations. The epidemiological evidence, and the complementary biological understanding of respiratory carcinogenesis have convincingly supported the conclusion that smoking is the most dominant risk factor for lung cancer.

At the end of the 20th century, lung cancer had become one of the world's leading causes of preventable death. It was a rare disease at the start of that century, but exposures to new aetiological agents and an increasing lifespan combine to dub lung cancer as a scourge of the 20th century. While tobacco had been widely used throughout the world for centuries, the present pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties that resulted in a new pattern of sustained exposure of the lung to inhaled carcinogens.

German scientists in Nazi Germany conducted some of the earliest research on the links between smoking and lung cancer.³ By the early 1950s, epidemiological studies in Britain and the United States using the case-control method had shown that cigarettes were strongly associated with the risk of lung cancer.⁴⁻⁶ This association was corroborated by the pioneering cohort studies of British physicians, US veterans of the armed forces, and volunteers recruited by the American Cancer Society. By 1964, the evidence was sufficient to support a conclusion by the US Surgeon General that cigarette smoking caused lung cancer.⁷ The Royal College of Physicians had reached the same conclusion two years earlier.⁸ Passive smoking, the involuntary inhalation of tobacco smoke by non-smokers, also contributes to 25-30% excess lung cancer cases.⁹ This reported strength of population attributable risk (25-30%) for passive smoking causing lung cancer has been questioned in a recent study.¹⁰

While the predominant cause of lung cancer is now well known (namely, tobacco smoking), there are other causes, some acting in concert with smoking to synergistically increase risk. The suspicion that radon was a cause of lung cancer in underground miners was raised early in the 20th century and led to what was probably the first occupational respiratory carcinogen to be identified.¹¹ Radon in indoor environments is now considered to be a significant cause of lung cancer.

The list of human occupational causes of lung cancer also includes arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons (PAH), and other agents.¹² Outdoor air pollution, which includes combustion-generated carcinogens, is also considered to contribute to the lung cancer burden in 'urban' dwellers.¹³ Indoor air contains several respiratory carcinogens, including

radon, asbestos, and cigarette smoke. In some developing countries, exposure to cooking fumes from cooking stoves and fires is associated with lung cancer risk.¹⁴ Beginning in the 1980s, associations of diet with lung cancer risk have been vigorously investigated anticipating that dietary micronutrients might be found that modify the high lung cancer risk, especially among smoking populations.¹⁵

Even though the epidemiology of lung cancer has been extensively investigated for more than 50 years, there are still active areas of research, some quite relevant to prevention. It is interesting to note that the majority of the wealthy nations across the globe did undergo rapid urbanization in the 1960s and 1970s. This might have compounded the contemporaneous lifestyle patterns gradually changing across these wealthy nations, probably giving rise to a paradoxical effect of the growing affluence on populations in the form of less healthful dietary habits and increased physical inactivity.

No single study has yet investigated a potential underlying geographical pattern for lung cancer death trends across the wealthy nations representing defined geographical regions to address such lifestyle issues. An aetiologically distinct geographical pattern alone may also suggest the emergence of a common environmental risk factor for lung cancer. This potential local environmental factor can also be modified by behavioural and cultural patterns across such populations, as an age-cohort phenomenon, in addition to residual confounding by past smoking habits. This can be demonstrated in Japanese men with the highest smoking prevalence in the 1970s, but the corresponding lung cancer death rates were far lower than the majority of the Western nations.¹⁶ This apparent heterogeneity may suggest a

local ‘smoking paradox’,¹⁷ and also the influence of potential effect modifiers on lung cancer risk. The Japanese men also use a distinct cigarette type (activated-charcoal filtered).¹⁷

Lung cancer is reported to be associated with lifestyle factors other than tobacco smoking alone. This is demonstrated in the apparent association between lung cancer risk and inadequate physical activity levels.¹⁸ Recent epidemiological investigations for lifestyle factors as that of the association between lung cancer and diet are encouraging. However, epidemiological studies on lung cancer linking to changing dietary habits over successive generations are limited.

The European Prospective Investigation into Cancer and Nutrition (EPIC) project that includes ten European countries is a valuable resource in the future.¹⁹ The Republic of Ireland, however, is not a collaborator of this EPIC project. The apparent lack of data accessibility to a few of the large historical birth-cohort databases, which are owned and operated by a few of the European and the US scientists alone, may also be a limitation for the research community. Such historical cohorts identify serial changes of dietary intake levels over time across successive birth-cohorts, and also help in addressing other lifestyle risk factors, such as adult weight gain or physical inactivity levels.

There is still concern about specific ‘urban’ risk factors. These are indoor and outdoor pollutants, and also radon and diesel emissions, particularly across the industrialised nations. There also has been a need for research to track the risks of smoking over time, as the cigarette has evolved in its design characteristics and yields

of tar and nicotine. This was previously assessed by standard protocols using a machine since the 1950s.²⁰ Such lifestyle factors could be addressed through large historical cohorts within or across the nations.

There is emerging evidence on the genetic determinants of lung cancer risk. A current research approach, termed molecular epidemiology, integrates the traditional epidemiological approaches with modern molecular techniques to assess the possibility of any gene-environment interactions. While the evidence from the traditional epidemiological approaches conclusively established the carcinogenicity of tobacco smoke, molecular epidemiology should characterize the sequence of molecular and cellular changes as a non-malignant becomes malignant, and also the factors determining susceptibility to tobacco smoke. Biomarkers of exposure, dose, susceptibility, and genetic damage may allow epidemiological investigations to uncover specific pathways of human lung carcinogenesis. However, such modern molecular techniques are both highly localised and specialised, which may not have a wide application across the globe, especially in the developing nations.

Descriptive epidemiological studies on temporal patterns for lung cancer still remain important tools for investigating the 'changing face' of lung cancer epidemiology across any populations. Such approaches are still applied to European populations for risk assessment, despite the explosion of molecular techniques.²¹ Such approaches are particularly worth considering in countries where no temporal pattern for lung cancer has yet been delineated that is potentially aetiological, and may be recently emerging. Temporal patterns reinforce the existing causal relationship, and also generate new hypothesis. This has been demonstrated in the

notable epidemiological shift in the incidence of lung cancer cell-types across the globe, especially in the wealthy nations.

After a steady increase in incidence from 1973 to 1987 across the industrialised nations in particular, lung adenocarcinoma has supplanted lung squamous-cell carcinoma as the most frequent form of lung cancer across these populations.²² Lung adenocarcinoma increased markedly in all race-sex subgroups. This has been attributed to changing smoking habits alone, but new aetiological patterns across different epidemiological settings may be responsible for such an underlying biological phenomenon. Such phenomena are essentially important for the wealthy nations, because they have been undergoing rapid urbanization compounded with a changing lifestyle, and this can have a gender differential impact on a few of the potential lifestyle factors for lung cancer risk.

Temporal patterns for lung cancer mortality data could be presented and interpreted both in traditional methods and by adopting a relatively modern approach of a probabilistic modelling technique.²³ The traditional estimation of trends by age-adjusted mortality rates alone may not be appropriate for elucidating temporal variations due to purely secular (period) influences, or due to purely generational (cohort) influences. Such estimates are both confounded by a changing age structure. Temporal variations in lung cancer suggest an evolution of the disease due to changes in the known predominant risk factor (smoking), and this may preclude the immediate need for investigating other causes for lung cancer. If lung cancer incidence rates are increasing and cannot be adequately explained by changes over time in active smoking alone, then the search for new risk factors is necessary.

As cigarette consumption contributes to 90% of lung cancer cases, and the consumption pattern has changed over successive generations, lung cancer temporal patterns are more likely to suggest an age-cohort phenomenon. Such cohort hypothesis could better be explained through an age-cohort modelling technique, as adopted in lung cancer epidemiological studies over the years.²⁴

An age-period model, on the other hand, is more applicable to identify a period effect in populations where any intervention programmes (for example, national tobacco cessation activities) have been undertaken. Such period effects can also occur if there is any sudden change in an environmental risk factor (namely, changing urban air pollution levels) following a national legislation similar to the Clean Air Act in Britain in the 1950s.²⁴ Nevertheless, the overwhelming association of lung cancer risk with tobacco smoking makes it difficult to identify other potential lifestyle risk factors, especially among male populations. This implies the effect of residual confounding by past smoking habits on any epidemiological study findings examining potential new aetiological factors for lung cancer risk.

1.3 Lung cancer epidemiology in the Republic of Ireland

The Republic of Ireland, a small Western European nation with a population of about four million people, has one of the highest lung cancer incidence rates across Europe in recent years, female rates are particularly higher than the European average.²⁵ This may suggest the introduction of a relatively new changing lifestyle across the female populations of the Republic. Unfortunately, lung cancer incidence data for the whole of the Republic is only available for a short duration (1994-2002), which is insufficient to give any robust temporal pattern.²⁵ However, lung cancer

mortality data of the National Central Statistics Office is of longer duration to give an insight into the lung cancer epidemiological pattern across the Republic. No comprehensive information exists in the Republic on an underlying temporal pattern for lung cancer deaths. In addition, risk estimations for lung cancer development using an age-cohort model, and simultaneously adjusting for cumulative tobacco consumption across the birth-cohorts, have specifically received little attention.

In 2000, the Republic of Ireland reported 922 and 515 lung cancer deaths in males and in females, respectively.¹ The corresponding age-standardised (world population standard) death rates per 100,000 person-years were 38.3 and 17.3, respectively.¹ In the 1960s, a study in Northern Ireland reported higher lung cancer mortality rates in Belfast, the capital city of Northern Ireland.²⁶ The author speculated that the observed excess lung cancer deaths in urban areas, especially among non-smokers might be due to the industrialisation in the 1960s, and probably giving rise to a poor urban air quality. A similar hypothesis was generated in the 1960s across three other capital cities (Dublin, Helsinki and Oslo).²⁷ Various estimates computed for lung cancer attributing to ambient air pollution in the 1980s were 1-2% of all lung cancer cases,²⁸ an 'urban effect' of 12% for lung cancer risk,²⁹ and less than 10 lung cancer cases per 100,000 persons annually attributable to air pollution.³⁰

In the 1950s and 1960s, Northern Ireland had already established a strong industrial base, unlike the agrarian economy in the Republic of Ireland.³¹ The two neighbouring countries shared a common lifestyle, and probably a similar smoking habit across the general populations. Relative to the Northern Ireland lung cancer mortality rates, the rate ratios in the Republic of Ireland were consistently lower for

both males and females since the beginning of the 1920s, but had started to increase among females from the 1960s onwards.³¹ This period (in the 1960s) mirrors the urbanization peak in Northern Ireland, and the beginning of a rapid urbanization phase in the Republic of Ireland. The 1960s also experienced an underlying changing lifestyle pattern across these two populations.

The apparent inconsistency in lung cancer mortality risk on this island across the two populations with similar behavioural patterns, however, is unclear. This might suggest a gender differential of potential lifestyle factors on lung cancer risk across two apparently different epidemiological settings. The settings are different probably due to the relative difference in urbanization from 1960 onwards. Such an important epidemiological transition in the 1960s might have had also modified the future course of lung cancer incidence pattern across these two population-groups, especially among females. This transition in lung cancer pattern cannot be observed until the late 1990s, considering the long latency period of lung cancer.

Dublin City, the capital of the Republic of Ireland, has documented evidence of excess overall mortality in the 1970s and 1980s that could be due to poor air quality in Dublin City. Dublin City also had episodes of smog in the 1980s.³² A recent study concluded that the observed excess respiratory and cardiovascular deaths in Dublin City between 1984 and 1996 were attributed to poor air quality, using black smoke as an indicator variable for urban air pollution mixture.³³ In addition, an intervention in the form of ban on the marketing, sale, and distributing bituminous coal, which primarily was used for domestic heating, was introduced across Dublin City in 1990. The same study reported a statistically significant decline in overall

mortality in Dublin City, and in particular a marked and sustained decrease in all-respiratory deaths following the introduction of the Coal Ban in 1990.³³ However, no such temporal association has been documented for lung cancer death patterns before and after the Coal Ban in 1990 across Dublin City. As outlined earlier, an age-period modelling technique instead of an age-cohort modelling technique is helpful to give an insight into such a temporal pattern in Dublin City, following the introduction of the Coal Ban in 1990.

There is also no documented evidence of a potentially changing pattern for lung cancer incidence by major histological sub-types (adenocarcinoma, squamous-cell carcinoma, small-cell carcinoma and large-cell carcinoma) in the Republic of Ireland. It is, however, unclear whether lung adenocarcinoma incidence is increasing across the whole of the Republic, or in specific 'urban' areas, such as Dublin City. Such an observation may help in identifying a potentially high-risk population to target future health-care interventions, and also to provide significant leads to further investigations, integrating traditional with modern epidemiological approaches.

There is consistent epidemiological evidence suggesting that lung adenocarcinoma is relatively more frequent among non-smokers, in young individuals, and across female populations.³⁴ This provides clues to an underlying biological mechanism for lung adenocarcinoma, and also the differential impact of potential lifestyle factors on the new generation female smokers. The fact that smoking prevalence across the Republic is declining since the 1970s,³⁵ more rapidly among males, provides further opportunities for investigating putative risk factors for lung cancer development, particularly across the female population.

1.4 Conclusion

In conclusion, the epidemiology of lung cancer consistently reinforces one major theme: the preventable nature of the disease. The apparent pandemic of lung cancer can be reduced through well-targeted health prevention programmes, both locally and globally. Unfortunately, the existing anti-smoking activities are yet to have a significant impact at the population level. The changing face of lung cancer epidemiology also needs an in-depth analysis across different epidemiological settings for seeking a means to ensure an early greater annual decline in lung cancer rates, and also for investigating new hypothesis/risk factors. This can be achieved through traditional descriptive epidemiological study designs in specific populations where long-term high-quality data are available, or through modern epidemiological approach trans-nationally if multi-centred studies exist. However, in populations where neither of the above conditions is currently favourable, such as the Republic of Ireland, any baseline information on lung cancer epidemiological pattern will have a significant public-health implication, and will also provide future directions for exploratory research, risk assessment, and policy-making.

1.5 Aim and objectives of this study

As outlined earlier, there is limited information on the epidemiological pattern for lung cancer in the Republic of Ireland, and also for the major lung cancer histological subtypes. Any geographical variation in lung cancer pattern within the Republic of Ireland is also important for identifying high-risk populations across the country. Public-health intervention in the form of Coal Ban was introduced across Dublin City in 1990, and this intervention may also have had a potential impact on the temporal pattern of lung cancer deaths in Dublin City.

Therefore, the overall aim of this study is to describe the epidemiology of lung cancer pattern in the Republic of Ireland, with the following primary objectives to:

- Describe temporal patterns for lung cancer deaths in the Republic of Ireland from 1970 to 1999 by age, gender, and smoking prevalence, together with the estimation of the strength of temporal association between lung cancer death rates and cumulative tobacco consumption (in pack-years) across different birth-cohorts (1888-1967).
- Examine the epidemiological patterns for lung cancer incidence across major histological sub-types (adenocarcinoma; squamous-cell carcinoma; small-cell carcinoma; large-cell carcinoma), with special emphasis on the annual incidence rates of these cell-types (adjusting for smoking and age across gender) in the Republic of Ireland from 1994 to 2001.
- Describe the epidemiological pattern of lung cancer deaths in Dublin City populations from 1981 to 2000 across different time-periods and birth-cohorts, with a gender-breakdown.
- Investigate a temporal association between lung cancer deaths and urban air pollution levels in Dublin City (1981-2000), using black smoke as an indicator variable for urban air pollution mixture, ten years before and after the introduction of the Coal Ban in 1990 across Dublin City.

Chapter Two

LUNG CANCER EPIDEMIOLOGY: A LITERATURE REVIEW

2.1 Introduction

This chapter reviews the overall lung cancer epidemiological patterns from a global perspective, and outlines the temporal patterns for lung cancer across defined geographical regions (North America; Europe; Asia). The public-health implications of any underlying geographical variations are discussed. The potential contribution of urbanization to the underlying geographical variations is also emphasised.

2.2 Patterns of lung cancer occurrence

Because of the high case-fatality rate for lung cancer, the incidence and mortality rates are nearly equivalent. Consequently, routinely collected mortality data provides a long record of the occurrence of lung cancer. We are presently amid an epidemic of lung cancer that dates to the mid-20th century. Lung cancer was rare until the disease began a sharp rise around 1930 that culminated by mid-century with lung cancer becoming the leading cause of cancer death among males.³⁶ The epidemic among females followed that among males, with a sharp rise in rates from the 1960s to the present, pushing forward lung cancer to become the most frequent cause of female cancer mortality.³⁶

2.3 Temporal trends (geographic patterns)

Lung cancer is the most commonly diagnosed cancer worldwide,³⁷ but its geographical distribution shows marked regional variations.³⁸ The global variation in

age-standardised incidence rates is greater than four-fold among males, and five-fold among females.³⁹ Because of differences in cancer registration between countries, caution is needed in interpreting these data. However, this marked variation in rates cannot be explained on the basis of diagnostic practices and data quality alone.

Lung cancer tends to be most common in developed countries, wealthy nations in particular, and less common in developing countries, particularly in Africa and South America.⁴⁰ The low rates of lung cancer in Africa are comparable to the United States (US) rates in 1930, when rates of lung cancer were under 5 cases per 100,000 for both sexes.^{41, 42} In contrast, African-Americans in the US, an epicentre of the disease, now experience lung cancer incidence rates that are among the highest in the world. As the lung cancer epidemic begins to subside in the developed countries, it is on the rise in the developing world.⁴³

2.3.1 The North American experience

In the US, it was estimated around 160,000 people would die from lung cancer in 2000.⁴⁴ An examination of the time trends of age-specific lung cancer mortality rates in the US further highlights the differing epidemic patterns in males compared to females. In the older age groups, the rates continue to increase in both sexes, but the rates of increase are decelerating more significantly in males than in females.⁴⁵ The rates of lung cancer are now decreasing in the younger age groups, where decreases that are more pronounced for males are now becoming evident in females.^{45, 46}

As the younger birth cohorts age, their reduced risk of lung cancer should thus translate into substantial reductions in the overall occurrence of lung cancer. These

future reductions may probably be more favourable for males than for females. In a recent analysis of lung cancer mortality in the US from 1970 to 1997, Jemal *et al* found that the rates of decrease in younger males and females (namely, those born after 1950) were moderating, even though the decline continues.⁴⁵ These investigators suggested that the moderation could reflect patterns of smoking initiation.

2.3.2 The European experience

In Europe, lung cancer is also the most commonly diagnosed cancer. There were an estimated 375,000 cases (303,000 in males and 72,000 in females) of lung cancer in Europe in 2000.¹ The number of lung cancer deaths in Europe is only slightly less in the same year: 347,000 (280,000 in males and 67,000 in females),¹ further suggesting the poor survival rates, and the equivalence of lung cancer mortality rates with incidence rates. So lung cancer mortality rates correspond closely to incidence rates. There are also substantial differences in incidence and mortality in the different regions and populations within Europe. In males, incidence and cumulative risk is highest in Eastern Europe. In females, the highest incidence of lung cancer is in Northern Europe, which is almost twice as high as Western Europe. A similar pattern also follows in lung cancer mortality.

A recent analysis⁴⁷ of lung cancer mortality trends in the 15 member states of the European Union (EU) has shown declining trends in males in 11 member states (the earliest occurring in Finland and the United Kingdom in the early 1970s), stable trends in France and Greece, but rising trends in Portugal and Spain. Although tobacco control in Europe has been highly effective in males, there has been almost 'complete failure' in females.⁴⁷ Lung cancer mortality in females have been rising

since the 1950s in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, the Netherlands, and Sweden. In the case of the Netherlands this increase has been very steep. The rising trends have slowed in Greece, Ireland, Portugal and Spain. In the United Kingdom (UK), the overall trend has begun to turn downward, however, large differences exist in the levels and trends between males and females, with very high mortality rates in Scotland.⁴⁸

2.3.3 The Asian experience

Although male lung cancer has declined since the 1970s in the US and several European countries, one of the wealthy East Asian countries (namely, Japan) has shown a continuous increase since the 1950s.⁴⁹ In general, lung cancer rates in Asian countries are low, ranging from 9 to 14 for males in India compared to 30 to 40 in Japan.⁵⁰ However, much higher rates are seen among male Chinese of Singapore (69.7), in Hong Kong (78.7) and in Shanghai (53.0).⁵⁰ Chinese females have relatively high rates, for example, 33.2 in Tianjin compared to 44.5 for males, and 21.9 among the Chinese of Singapore.⁵⁰ Lung cancer has gradually increased across both sexes in China (1980-1989).⁵⁰

In Japan, the peak age in both sexes has gradually shifted to more than 85 years old.⁴⁹ In 1995, the average age of lung cancer death was 71.6 years for males and 73.0 years for females in Japan.⁴⁹ In Korea, these were in the 60s for both sexes.⁵¹ Such differences may be explained by differences in life expectancy, and Japanese have the highest life expectancy, therefore this alone may account for the age difference at death for lung cancers.

2.4 Future implications of underlying geographical variations

International variations, as well as sex differences in lung cancer incidence, are largely attributable to different smoking patterns; the high rates in Western countries reflect the increase in cigarette consumption after World War II. It will be sometime before rates rise in those populations that have begun to smoke recently. Japanese men had the highest smoking prevalence in the 1970s in the world with very low cancer rates in the 1990s.¹⁶ This also suggests a lesser toxic cigarette (activated charcoal-filtered) consumption in Japanese men compared to the Americans.¹⁷

Studies investigating temporal trends have revealed significant ‘birth-cohort’ effects. Lee and colleagues showed that in the UK, cohort-specific incidence of lung cancer is related to the smoking patterns of that same generation.⁵² Similar observations were reported in the US.⁴⁵ In males, the countries that were first to experience the smoking epidemic were also the first to show a decrease in smoking prevalence, with subsequent declines in risk of lung cancer.² This phenomenon was first observed in the UK and Finland in the 1970s and 1980s.² It is also suggested that the aetiology of lung cancer may be different in young versus older age groups.

Looking at incidence by birth cohort can also assess the future evolution of lung cancer burden. Predictions for the year 2010 show that, in the majority of EU countries (with the exception of Spain, Greece, France and Portugal) there will be a decline in mortality from lung cancer in males, but an increase in females.² The falls now observed among males in several populations were heralded by decreases in younger birth cohorts, even at a time when the disease was increasing in older males. Lung cancer in females illustrates the ‘birth cohort paradox’: overall rates continue to

rise, while rates are falling among young females. In Japan, lung cancer deaths are predicted to double by 2029, because of ageing of the baby-boomer generation (those born between 1947 and 1951),⁵³ although a ‘local smoking paradox’⁵⁴ might be worth considering in any future lung cancer patterns in Japan.

2.5 Geographical variations: hypothesis generation?

Substantial geographical variation in lung cancer mortality rates has been observed within countries. For instance, in the US lung cancer death rates were the lowest in Utah, the state with the lowest adult smoking prevalence, and were highest in Kentucky, the state with the highest adult smoking prevalence.⁵⁵ Lung cancer trends in the regional distribution can provide clues about the determinants of lung cancer. In the past, rates tended to be highest in urban areas, which led to ‘conjecture’ that air pollution might be a cause of the lung cancer epidemic.⁵⁶

Several hypotheses^{57, 58} were prompted by patterns observed in a systematic review of US lung cancer mortality rates for the period 1950 to 1969,⁵⁹ particularly the rates among males. High lung cancer rates in coastal areas were postulated to reflect employment in shipyards with attendant asbestos exposure. This hypothesis then was tested in a series of population-based, case-control studies, showing that employment in the shipbuilding industry was indeed associated with an excess risk of lung cancer development.⁶⁰

Another shift then took place in the distribution of lung cancer in the US, with lung cancer mortality rates among white males becoming highest in the South and lower in the Northeast.⁶¹ This fluidity in the geographical variation underscores the

value of regularly monitoring lung cancer mortality patterns. Therefore, a distinct geographical pattern may be potentially aetiological, and may provide significant leads to generating a new hypothesis, or confirming the existing hypothesis.

2.6 Urban-rural differences within countries

A basic and almost universal observation has been that urban residents have an increased occurrence of developing lung cancer. The urban-rural difference in death rates from lung cancer has been demonstrated by a number of investigators using contrasting methods of study. Stocks in Great Britain used population density as the reference line for lung cancer rates.⁶² Lew demonstrated urban-rural differences in lung cancer, as a part of the comparative study of deaths rates in male industrial policy-holders and of males holding ordinary insurance policies.⁶³ He correlated a 30-50% higher rate in the group with urban residence, low economic level and industrial or manufacturing occupational environment. By contrast, ordinary policyholders belonged to the higher income groups with significantly fewer opportunities for protracted exposure to industrial hazards.

Eastcott⁶⁴ in an analysis of native New Zealanders and immigrants studied the effect of urbanisation on death rates for cancer of various body sites. Of all visceral cancers, those of the lung and bronchus exclusively showed variations attributable to exposure of the host to environment. The effect was directly related to the intensity of antecedent exposure. The exclusive factor in the former environment capable of incrimination was urban residence. Mancuso *et al*⁶⁵ in a study limited to a single, highly populated and industrialised state (Ohio), correlated urban residence with the liability to lung cancer by showing that the observed death rate was greater than

expected in the eight industrialised urban counties, and one-third less than expected in the remainder of the state. While it is unlikely that occupational exposure to a specific carcinogenic atmospheric environment can materially affect nation-wide incidence figures, there is little question that the increased liability to lung cancer is consistent with the increased industrialisation.

An ecological study in Iowa⁶⁶ reported lung cancer rates to be significantly increased in urban counties, even after holding smoking status constant. An observational study⁶⁷ among different sub-groups of professional drivers in urban and rural areas of Sweden showed the increased risks of lung cancer in some categories of drivers in urban areas, as opposed to no increased risk for any categories of drivers in rural areas. An autopsy-based study in Athens⁶⁸ showed a higher Reid Index (ratio of gland and thickness of broncho-aleveolar epithelium) among subjects with mainly urban residence in comparison with those with mainly rural residence.

2.7 Urbanization: a potential risk factor?

All these observations may suggest an “urban” risk factor for any excess lung cancer rates. The mostly likely ‘urban’ factor is urban air pollution. However, the so-called ‘urban’ factor may reflect other influences instead of, or in addition to, outdoor air pollution: these could include indoor air pollution, patterns of migration, or factors related to population density.

Contemporaneously, the majority of the urban cities across the industrialised nations were undergoing rapid urbanization in the 1960s and the 1970s with a changing lifestyle pattern. The ‘urban’ factor in such populations may be the

paradoxical effect of rising affluence compounded with a changing lifestyle in the form of less healthful eating habits, increased mechanization and less physical activity.⁶⁹ Such effects occur throughout the life course of a population in a cohort-wise fashion, and thus urbanization and life course may have an integral part to play in future epidemiological studies on chronic diseases.⁷⁰ So urbanization may have an independent effect, but it is difficult to disentangle from other temporal factors influencing the lung cancer death pattern. Epidemiologically, urbanization may be an intermediate variable, an effect modifier, or a potential confounder for the changing temporal pattern of lung cancer across a defined population.²³

2.8 Race and ethnicity

The patterns of occurrence of lung cancer by race and ethnicity make lung cancer a relevant disease for those concerned with the health of females and minorities. In the US, lung cancer incidence rates are similar among African-American and white females, but lung cancer occurs about 50% more frequently among African-American and white males.⁷¹ The marked reduction in cigarette smoking that has occurred among African-American youths forecasts a possible reversal of this trend, and, if this trend persists, declines in the incidence of lung cancer among African-American can be expected.⁷² In addition, lung cancer mortality rates among Hispanics, Native Americans, and Asians/Pacific Islanders are significantly lower than rates among African-American and non-Hispanic whites.³⁷ However, such huge variations across race and ethnicity are not reported from other European or Asian countries, probably due to the lack of adequate data, or may be due to relatively low ethno-cultural mixed population.

2.9 Socio-economic and religious patterns

An inverse association between lung cancer and socio-economic status, particularly among males, has been observed. A two-fold difference in mortality between low and high social class, as measured primarily by occupation, is seen in British mortality data, with similar results in other surveys measuring income or education.⁵⁰ Smoking habits account for at least part of the socio-economic differentials, with rates of smoking considerably higher among blue-than white-collar workers and among those with lower levels of education.

In several surveys in the US, a 20% to 50% lowered rate of lung cancer was found among Jewish males, although some excess risk has been noted among Jewish females, which remains unexplained.⁵⁰ At even lower risk are Mormons and Seventh-Day Adventists, whose religious dictates proscribe the use of tobacco products.⁵⁰ For similar reasons, lung cancer incidence is expected to be lower in the majority of the Arab countries, although data are not currently available.

In conclusion, it is quite evident that lung cancer 'epidemic' is still very much on the radar screen, and there are distinct geographical variations in lung cancer pattern across the globe. The fact that urbanization compounded with a changing life style pattern could in part have contributed to the changing face of lung cancer epidemiology, changing smoking habits over successive generations is still the predominant contributor to such geographical variations. Nonetheless, it is equally important to identify putative risk factors for lung cancer recently emerging, particularly in areas where smoking prevalence has declined substantially. The next chapter (three) focuses on the major risk factors for lung cancer development.

Chapter Three

RISK FACTORS FOR LUNG CANCER:

A LITERATURE REVIEW

3.1 Introduction

This chapter critically reviews the published evidence of the major risk factors for lung cancer. Although the causes of lung cancer are almost exclusively environmental, evidence also suggests that there is substantial individual variation in the susceptibility to respiratory carcinogens. Given the multifactorial aetiology of lung cancer, synergistic interactions among risk factors also have substantial consequences for lung cancer risk. The emerging understanding of cancer genetics indicates the additional relevance of gene-environment interactions. Given that many risk factors have been identified for lung cancer, a practical question is the relative contribution of these factors to the overall burden of lung cancer.

The population attributable risk (PAR) estimates for lung cancer indicate that in the US, active smoking is responsible for 90% of lung cancer cases, especially among males.¹ Females have a lower PAR of 40-60% for lung cancer risk caused by active smoking.¹ Nevertheless, such an overwhelming association makes it difficult to recognize other lifestyle risk factors for lung cancer. So an apparent association between lung cancer risk and other potential lifestyle risk factor may be due to the residual confounding by past smoking habits.

Outdoor air pollution accounts for 1-2% of all lung cancer cases,⁷³ and dietary factors have been hypothesized to account for approximately 20% of the lung cancer burden.⁷⁴ Passive smoking (environmental tobacco exposure) is also responsible for 25-30% of lung cancer cases.⁹ Last but not the least, occupational exposures (9-15%), and radon (10%) are other risk factors for lung cancer.⁷⁵

3.2 Smoking: an overview

A single aetiological agent, cigarette smoking, is by far the leading cause of lung cancer, accounting for approximately 90% of lung cancer, especially among males and in countries where cigarette smoking is common.⁷⁶ Compared to never-smokers, smokers have a 20-fold increased lung cancer risk. In general, trends of lung cancer occurrence closely reflect patterns of smoking, but rates of occurrence lag smoking rates by about 20 years. Analyses using statistical modelling techniques showed a tight association between national mortality rates and smoking.⁷⁷ The unequivocal causal association of cigarette smoking with lung cancer is one of the most thoroughly documented causal relationships, using traditional epidemiological approaches.⁷⁸ Peto *et al* have quantified the burden of smoking-related deaths from lung cancer in the major developed countries.⁷⁶ They also forecasted a staggering future burden for China, which now has one-third of the world's smokers.

Cigar smoking is also an established cause of lung cancer,⁷⁹ but lung cancer risks may be less due to differences in smoking frequency and depth of inhalation. The same pattern holds true for pipe smoking.⁷⁹ It has been suggested that cigarette smoke is less irritating and thus more easily inhaled than pipe or cigar smoke. In some Scandinavian countries where pipe and cigar smoking is nearly as common as

cigarette smoking, risks from pipe/cigars have been almost as high as for cigarettes.⁸⁰ In certain populations, such as India, where ‘smokeless’ products and *bidis* are used, and in Chinese populations where water pipes are common, increased lung cancer risks have been reported.⁸⁰ Limited data suggest an increased cancer risk following consumption of other tobacco products, such as *narghile* in western Asia and northern Africa, *toombak* in Sudan, and also *hooka* in India.⁸⁰

3.2.1 Quantitative risks

The risk of lung cancer among cigarette smokers increases with the duration of smoking, as well as with the number of cigarettes smoked per day.⁸¹ This observation has been made repeatedly in cohort and case-control studies. Doll and Peto⁸¹ proposed a quantitative model for lung cancer risk that predicted a stronger effect of duration of smoking than of amount smoked per day (intensity). They report that excess risks of lung cancer rose in proportion to the square of the intensity of smoking, but to the 4th or 5th power of the duration of smoking. However, studies have shown clear independent effects of intensity and duration.^{82, 83}

These observations have public-health implications. Those who initiate smoking earlier in life are most likely to become heavier smokers and remaining smokers, thus developing lung cancer at younger ages. Prevention strategies preventing teenage smoking or at least delaying the age of onset of smoking can have a wide impact at the population level. Hence, clinicians should focus more on the duration rather than on the actual age of smoking. Epidemiological investigations have not shown consistent associations between depth of inhalation of tobacco smoke

and lung cancer, although risks were higher among moderate/deep versus none/slight inhalers in a large cohort study,⁸⁴ and also in a large case-control study.⁸⁵

3.2.2 Smoking cessation

Cigarette smokers can benefit at any age by quitting smoking. The likelihood of developing lung cancer decreases among those who quit smoking compared to those who continue to smoke.⁸⁶ As the period of abstinence from smoking cigarettes increases, the risk of lung cancer decreases. However, even for periods of abstinence of more than 40 years, the risk of lung cancer among former smokers remains elevated compared to never-smokers. In general, studies have shown comparable reductions in risk following smoking cessation, regardless of sex, type of tobacco smoked, and age of initiation.⁸⁷ Since periods of temporary quitting tend to be short, there is a strong relationship between all the temporal variables (age, age at start of smoking, duration of smoking, time since quitting), which makes it difficult to assess the independent effect of each of these temporal variables.⁸⁰

3.2.3 The Changing Cigarette

The composition of cigarettes has evolved considerably since the 1950s. The global market shifted from mainly ‘unfiltered’ cigarettes to predominantly ‘filtered’ cigarettes. For example, the percentage of all cigarettes smoked in the US that were filter-tipped was 19% in 1955, 51% in 1960, 80% in 1970, 92% in 1980, and more than 97% in 1992.¹⁶ The filters in use in the US are predominantly cellulose acetate, while charcoal filters are common in Japan and some other countries.⁸⁸ In the mid-1960s, ventilation holes were added to the filter, but they were technically flawed.

Reconstituted tobacco has been used increasingly since the 1960s, and there have been changes to the cigarette papers and additives used.⁸⁸

A concomitant shift toward lowered levels of tar and nicotine has also occurred in the 1960s from about 38 and 2.7 mg to 13.5 and 1.0 mg, respectively.¹⁶ Tar is a complex mixture that includes many chemicals that are cancer initiators and/or promoters. Tar and nicotine yields were measured with a smoking machine using the Federal Trade Commission (FTC) standardized protocol.²⁰ Such protocol did fail to account for any compensatory changes (blocking of the ventilation holes, more frequent and deeper puffs, and an increase in the number of cigarettes smoked) in smoking patterns for those switching from higher yield to 'lower' yield products. Although the risk of lung cancer is reported to be 40-50% lower among smokers of low-tar and low-nicotine cigarettes than among other smokers, consistent evidence is lacking.⁸⁵ A similar effect has been observed among long-term smokers of filtered cigarettes compared to smokers of unfiltered cigarettes, but with controversies.⁸⁹

These observations are primarily derived from either case-control or cohort studies, but epidemiological data do not provide insights into the consequences of smoking one product or another across the full time period of smoking. Consequently, researchers cannot compare the risks of smoking one type of cigarette across decades with that of smoking another. Because of these methodological issues, the epidemiological data need to be interpreted with caution. Further insights into the potential 'beneficial' effects of 'lower yield' cigarettes were investigated through a series of cohorts (the American Cancer Society Cancer Prevention Study I and II, and the British physician cohort study of Doll and colleagues). Finally, the Institute of

Medicine report by Stratton and colleagues concluded that changes in cigarette design and manufacturing over the last 50 years had not benefited public health.⁹⁰

3.2.4 Passive Smoking (Environmental Tobacco Smoke)

Passive smokers inhale a complex mixture of smoke that is now widely referred to as environmental tobacco smoke (ETS). In 1981, two nearly simultaneous publications indicated that lung cancer risks were increased among non-smoking females married to smokers.^{91, 92} Since then, the collective epidemiological evidence in the US (National Research Council, ⁹ 1980; Surgeon General, ⁹³ 1986; Environmental Protection Agency, ⁹⁴ 1992) suggests that risk of lung cancer was elevated by about 30% among female non-smokers whose husbands smoked. Estimates indicate that passive smoking, classified as a class A human carcinogen, accounts for almost 3000 lung cancer deaths per year in the US.⁹³ However, the reported risk estimates for ETS are constantly being challenged for confounding, small sample sizes, and exposure misclassification bias for using spouse smoking habits as a proxy measure for ETS.¹⁰

The recent studies^{95, 96, 97} have taken all the above limitations into account and reported fairly similar results. A comprehensive review⁹⁸ also argued the confounding effect of poor diets and less healthful lifestyles on a cross-cultural basis, which may be strongly correlated with having a smoking husband, especially in affluent urban societies. Also, 'sidestream' smoke contains higher concentrations of toxic agents (mainly nitrosamines) than the 'mainstream' smoke.⁹⁹ The association of lung cancer and second-hand smoke provides further evidence of the dose-response relationship of cigarette smoke and lung cancer, and also suggests that there may not be a threshold

level for tobacco carcinogenesis.⁹³ Importantly, epidemiological studies alone can provide such dose-response evidences.

3.2.5 Smoking prevalence and tobacco consumption patterns

The World Health Organization (WHO) has identified the use of tobacco as the major preventable cause of death for mankind.⁹⁹ Worldwide, cigarettes represent the most important tobacco product. World production of tobacco is approximately seven million tonnes annually.⁹⁹ China accounts for almost a third of the total. The people most immediately exposed to the products of tobacco combustion are the users, that is, the active smokers. The prevalence of smoking varies throughout the world and is subject to change. The proportion of smokers is decreasing among males in industrialized countries. More than 70% of males born in Europe and North America during the first decades of the 20th century were smoking during some time of their life, but this proportion has decreased in males born in the latter decades of the 20th century. There are also increasing proportions of former smokers in many countries, particularly among the older age groups.⁹⁹

A different pattern is seen in females. Smoking by females only became prevalent in the second half of the 20th century. While some countries, such as the UK, the proportion of females who smoke has started to decrease in recent years, in most industrialized countries this proportion is still increasing. In developing countries, less comprehensive data are available. It is clear, however, that a great increase in smoking has taken place during the last decade in many countries. This increase is particularly dramatic in China, where more than 60% are estimated to smoke. Smoking prevalence among females in most developing countries is still low,

although in many countries young females are taking up the habit. In India and its neighbouring countries, smokeless tobacco is widely used and '*bidi*' smoking is also common, this being the cheapest form of smoking available.⁹⁹

In the US, the prevalence of adult smoking decreased from 24.7% to 22.5% between 1997 and 2000 alone.¹⁰⁰ Smoking among adults is a less sensitive indicator of trends in smoking initiation than is smoking among adolescents, but it does reflect the combined overall effect of changes in both smoking initiation and cessation.⁵⁵ No state in the US has reached the objective of Healthy People 2010 to reduce the percentage of adults who smoke to 12%.¹⁰¹

In Europe, substantial changes have taken place with regard to smoking prevalence and the volume of tobacco smoked per capita, although not all tobacco products 'consumed' in a particular country will actually be smoked there.¹ The regional temporal variation in the annual per-capita tobacco consumption is very large: from big declines in the UK (39%), Sweden (33%), and Finland (28%) to a great increase in Portugal (64%). In addition, there is regional variation in the total per-capita tobacco consumption: Ireland, for example, had one of the highest per-capita consumption in 1994 (2550 grams), with lowest in Sweden (870 grams).¹ Despite inadequate data, a declining smoking prevalence in males is observed, with a few countries also reporting a decline in female smoking prevalence (UK, Ireland, the Netherlands and Belgium).^{1,16}

Japan had the highest smoking prevalence in the world among males in the 1960s and 1970s, but is also showing a decline more recently.¹⁶

Appendix one shows a model describing the stages of tobacco epidemic based on data from developed countries. There is a time lag between increase in consumption and the manifestation of lung cancer.

3.2.6 Effectiveness of anti-smoking measures: an overview

Since the release of the seminal report of the first US Surgeon General in 1964,⁷ knowledge about tobacco use, addiction, and tobacco-related disease has increased dramatically. With this knowledge have come major public health improvements. The prevalence of tobacco use has been cut in half, the number of former smokers nearly equals the number of current smokers, and some gains have been achieved in reducing lung cancer incidence and mortality rates.¹⁰² However, it is clear that we have not solved the problems associated with tobacco use, as evident from our previous discussion.

The first point of the recently revised 1985's European Code Against Cancer (ECAC) is "Do not smoke. If you smoke, stop. If you fail to stop, do not smoke in presence of non-smokers".¹⁰³ The risk of cancer rapidly decreases upon stopping smoking, and the benefit progressively increases over time.¹⁰⁴ Large proportions of adult smokers want to quit smoking. Marked reductions in future lung cancer mortality could be achieved if more money and resources were devoted to smoking cessation programmes, which has the potential to be one of the most cost-effective public health interventions.

It has been estimated that about half of the population of 'ever' smokers in the US have already stopped smoking, but cessation is nevertheless very difficult for most

smokers as cigarette smoking in particular is recognised, as been an addictive habit. From a public-health point of view, persuading adult smokers to give up rather than focusing on smoking prevention in adolescents can gain more benefit in terms of an immediate impact on number of deaths from lung cancer. Adolescent smoking prevalence is also a better indicator for future lung cancer mortality trends.⁵⁵ Sadly, smoking prevalence among adolescents is increasing in the industrialised nations.¹⁶

Two broad approaches are used to decrease the prevalence of smoking: the ‘individual’ approach and the ‘community’ intervention strategies.^{1, 99} The individual approach requires use of proven cessation techniques, availability of appropriate medications (such as nicotine replacement or psychotropic medications), and, more importantly, the involvement of physicians in cessation and patient education. However, the success of this individual approach is limited by the effectiveness of medication and the physicians’ knowledge of the available options.

On the other hand, community interventions are useful tools for reducing the smoking prevalence. In many countries, including the UK, Finland and Poland, a substantial reduction in the number of smokers has been achieved by changing public attitudes to tobacco.¹ Such strategies are very difficult to implement especially without social pressure not to smoke, and a legislative framework to make smoking expensive. There are huge political conflicts, involving interest groups, such as agricultural and finance ministries, tobacco growers, and the tobacco industries. It has been shown that a 10% increase in cigarette price could have a 4% reduction in adult tobacco consumption in high-income countries,⁹⁹ and a 20% reduction in teenage

smoking.¹⁰⁵ In summary, such policy changes have effects on the population that impact both smoking uptake and decisions to quit.

Many countries have smoking cessation programmes in some form or other. For example, banning smoking in public places in major cities, such as New York, San Francisco, as well as the recent nationwide Smoking Ban in the workplaces in the Republic of Ireland.¹⁰⁶ However, very few countries across the globe have a comprehensive tobacco cessation programme. Singapore is one such a country, which not only has a comprehensive anti-tobacco programme, but it is also stringently enforced.¹⁰⁷ Now that tobacco use and second-hand tobacco smoke exposure have been shown to be causal factors for an expanding list of cancers and other diseases, it is essential to implement whenever and wherever possible the approaches and interventions that have shown to be effective. The recent WHO Framework Convention on Tobacco Control (FCTC) is an important step in this direction.

Although we know that smoking cessation will reduce future cancer risk, we know little about smoking reduction or transition to other tobacco products (such as smokeless tobacco use by the US adults) as methods for reducing cancer risk. Do smokers who use nicotine replacement products (gum, patch, inhaler, or lozenge) to reduce but not quit smoking decrease their intake of potent carcinogens, and thus reduce future cancer risk?

A recent study¹⁰⁸ addressed that question and concluded that although reduced smoking and concomitant reductions in biomarkers of cancer risk can occur with behavioural and pharmacological support, reduced smoking is of 'limited value' as a

means of reducing the potent tobacco-specific carcinogen, NNK (nitrosamines). The authors speculated that smokers compensate for the reduced smoking by becoming more efficient smokers: i.e. exerting more from a cigarette, thus, even a large reduction in smoking is often led to only a modest reduction in levels of NNK metabolites. Although this observation is consistent with other studies,^{109,110} it is yet another reminder that standardized methods for assessing tobacco constituent exposure, such as machine-measured protocols of the US FTC, cannot adequately account for variations in human smoking behaviour. Consequently, sceptics suggest that now is the time to implement 'harm reduction' approaches, because so many smokers cannot or will not quit smoking.¹¹¹

Nonetheless, there have been advances in our understanding of the epidemiology, and the genetics of nicotine addiction. These findings have opened new areas of smoking prevention and cessation research using pharmacological interventions both with pharmacological agents and nicotine replacement therapy (NRT). As health professionals, however, we must vigorously support smoking prevention and cessation programmes. We must also champion efforts to make tobacco use a socially and culturally unacceptable habit, and support all government actions to eliminate tobacco as an environmental carcinogen. The so-called 'reduced yield' cigarettes lack consistent evidence for the attenuation of lung cancer risk, and the evidence base for 'novel' products (NRT) is also limited.¹¹² Thus, the publicity and marketing of such products must not distract attention away from interventions proven to reduce the prevalence, intensity, and duration of smoking.

3.3 Air Pollution

During a typical day, the average adult inhales about 10,000 litres of air.¹¹³ Consequently, even the carcinogens that are present in the air at low concentrations are of concern as a risk factor for lung cancer. The relationship of acute and chronic non-malignant respiratory disease with ambient air pollution is well-established, but the evidence for an effect of community air quality on cancer risk is far less conclusive, although an association of air pollution with lung cancer has been observed for at least 40 years.¹¹⁴ This association has received only sporadic attention, because of the predominate role played by cigarette smoking in the vast majority of lung cancers in Western industrialized nations. Nonetheless, there have been persistent concerns that air pollution may cause lung cancer and other cancers. These concerns have been prompted by the release of carcinogens into outdoor air from industrial sources, power plants and motor vehicles, and the recognition that these outdoor carcinogens also contaminate indoor air.

Three major obstacles lie in the path of establishing a causal connection between ambient air pollution and lung cancer risk: the latency between exposure and cancer occurrence combined with pronounced temporal changes in air quality; the difficulty in estimating cumulative personal exposure to ambient air pollution; and confounding of cancer risk by other personal exposures, especially active smoking and ETS.¹¹⁵ These obstacles have not been adequately addressed in the body of epidemiological evidence on cancer and air pollution. However, there is sufficient convergence of evidence from many population-based studies that ambient air pollution has contributed to the human cancer burden, lung cancer in particular. These are as follows:¹¹⁵

- Known and probable human carcinogens are present in the ambient air environment, for example, organic products of incomplete combustion (benzo-a-pyrene in particular), arsenic, asbestos, etc.
- Urban residents show a consistent lung cancer excess compared to rural inhabitants, even when estimates are appropriately adjusted for tobacco smoking and occupational exposures.
- Among urban residents, gradients of community air pollution levels correspond with area differences in lung cancer risk.
- Communities adjacent to certain large point sources of carcinogenic air pollutants, such as arsenic smelters, show an excess of lung cancer in proportion to the nearness of the household to the point source, following adjustment for tobacco and occupational exposure levels.

3.3.1 Urban air pollution (ambient air)

Several migrant and ecological studies provided support for the general hypothesis that ambient air pollution is associated with lung cancer risk. There is abundant evidence that lung cancer rates are higher in cities than in rural settings.^{58, 65-}

⁶⁷ Although urbanization and lung cancer mortality is linked, this association could arise from differences in the distributions of other lung cancer risk factors, such as smoking and occupational exposures, by degree of urbanization. Adjustment for these factors may considerably attenuate the effect of urban location, but an “urban” effect persists in a few studies.⁷³

Cohort and case-control studies are limited by difficulties in assessing past exposure to the relevant air pollutants. The exposure to air pollution has been assessed on the basis of proxy indicators or on the basis of actual data on pollutant levels. These data, however, reflect mainly present levels or levels in the recent past and refer to total suspended particulates, sulphur dioxides, and nitrogen oxides, which are not likely to be the agents responsible for the carcinogenic effect, if any, of air pollution. In addition, the majority of the nations may not have good quality data from monitoring stations, which are usually fixed. Furthermore, the sources of data might cover quite a wide area, masking small-scale differences in exposure levels, and thus giving rise to exposure ascertainment bias.

The quantification of relative risk estimates for lung cancer on both the urban and rural dwellers is generally on the order of 1.2 to 1.5, following adjustment for smoking.¹¹⁶ In several of these studies, the joint effect of air pollution and smoking appeared to be greater than the addition of individual risks.¹¹⁶ In addition, none of these studies considered personal exposure to ETS, and few took into account lifetime residence. These two factors exert opposite effects on air pollution-lung cancer risk estimates. Thus, the major limitations of urban-rural comparisons are the absence of quantitative measures of exposure to ambient air pollution, and the urban-rural difference in indoor environments caused by ETS. If these studies were the only sources of evidence, it would be difficult to determine whether the 'urban effect' is due to indoor or outdoor exposures.

The potential confounding effect of differences in urban-rural indoor exposures should be diminished in studies comparing two or more similarly urbanized

areas, if appropriate care is given to the consideration of socio-demographic and occupational variables. Some took advantage of the low prevalence of smoking in the Seventh Day Adventists.¹¹⁷ However, the Harvard Six Cities Study¹¹⁸ provides one of the most complete characterizations of air pollution exposures to date. Although not statistically significant based on 120 lung cancers, the study reported 1.4 times higher lung cancer risk in the most polluted compared to that in the least polluted city, suggesting a 14-20% increase in lung cancer mortality for every 10 microgram/ m³ increase in long-term exposure to fine particulate. This finding was recently confirmed in a long-term follow-up study of the American Cancer Society CPS II,¹¹⁹ but an increased risk of 8% for every 10-microgram/m³ rise was observed.

The magnitude of the lung cancer effect per each 10µgm⁻³ increase of particulate air pollution in the Six Cities Study may have been biased upward by the convergence of two factors. Firstly, if particulate air pollution exerts its carcinogenic effect relatively early in the multistage process, it results in a lag of 20 or more years between effective exposure and disease. Secondly, if differences in the concentrations of particulate air pollution between the least and the most polluted cities of the Six Cities Study were greater in the 1950s and 1960s than during the follow-up period when air monitoring data were being generated for this study.

A few studies have used exposure biomarkers offering a new approach to quantifying the lung cancer risk associated with air pollution. One of the studies uses carcinogen-DNA adduct levels, and found that their levels are markedly elevated in residents of a highly industrialized region (in Poland) in comparison with controls

from a less polluted region.¹²⁰ Such levels of biomarkers could be used to predict cancer risks, following validation.

Studies have also taken advantage of ‘natural experiments’. Stevens and Moolgavkar²⁴ observed declines in lung cancer incidences among non-smoking males in England and Wales coincident with substantial declines in levels of particulate and sulphur dioxide pollution that resulted from the implementation of nation-wide air pollution control measures. Observing that the rates of lung cancer began their decline within a few years of the reduction in air pollution, critics have challenged the authors’ interpretation of the data. However, the authors argued that reductions in lung cancer risk in former smokers have also been observed within two years of quitting smoking.³⁰ Dublin City experienced a Coal Ban in 1990,³³ which might also provide a unique opportunity for a ‘natural experiment’ over the next decade, considering a long latency period of at least 20 years.

In summary, the reported estimates of PAR for lung cancer due to urban air pollution have been based on markedly different methods. In 1981, Doll and Peto²⁸ estimated that perhaps 1-2% of lung cancer cases were related to air pollution. Even in light of recent findings, this appears to remain a reasonable estimate. Karch and Shneiderman²⁹ in the same year estimated that the ‘urban factor’ accounted for 12% of lung cancer cases. It has also been argued that cigarette smoke has little impact on outdoor pollution concentrations. Outdoor combustion-source particulate air pollution penetrates indoors and, for persons from non-smoking homes, the indoor, outdoor, and personal exposures are similar and highly correlated.¹²¹ In 1990, the US EPA estimated that less than 1% of lung cancers could be attributed to the effects of current

levels of air pollution.¹²² So, the extent that air pollution may contribute to lung cancer, and that the overall epidemiological evidence is equivocal, its contribution is minimal relative to cigarette smoking.

3.3.2 Indoor air pollution

An individual's total exposure to air pollution depends on indoor, as well as outdoor exposures. Indoor air quality has large potential health implications because people may spend substantial amounts of time indoors. Indoor air pollution may stem from incoming outdoor air or may originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking.¹²³ A trade-off exists between energy efficiency and indoor air quality, as ventilation allows heated/cooled air to escape but improves air quality.¹²⁴

In more developed countries, the two most important indoor pollutants that influence lung cancer risk in never-smokers are passive smoking and radon.⁷⁵ Asbestos exposure may pose a risk to building occupants, but its environmental influence is estimated to be minimal.¹²⁵ Of major concern in the developing world, however, is the indoor air contamination from the use of unprocessed solid fuels, notably coal, for cooking and space heating.

Mumford and colleagues¹⁴ inferred that smoky coal was a major determinant of the geographical distribution of lung cancer in China. Case-control studies conducted elsewhere in mainland China¹²⁶ and Taiwan¹²⁷ further implicated coal use as a risk factor for lung cancer. Another case-control study in Shanghai, where most homes are unheated, reported no association between the use of coal and lung cancer

risk.⁸² Exposure to coal burning in the pre-adult years, however, was associated with lung cancer risk in a study of females in Los Angeles County.¹²⁸ More recently, investigators have argued that the apparent association between air pollution and lung cancer among Chinese females in Hong Kong is mediated through dietary habits, because some of the major indoor pollutants (ETS, incense, and cooking fumes) are associated with dietary habits.¹²⁹

3.3.3 Future directions

Current knowledge about ambient air pollution and lung cancer is based largely on the experience of Western industrialised nations. The populations of the developing countries are exposed to levels of air pollution from combustion sources in both ambient and indoor environments that rival or exceed those commonly observed in the industrialised West. There has been relatively little research on ambient air pollution and lung cancer among urban residents of the developing countries.⁷³ As a greater proportion of the world's population moves from rural communities to the rapidly expanding and highly polluted cities of Asia and the Southern Hemisphere, there is a clear need to address the large gap in epidemiological research. Such research could guide global policies for public health safety. Nonetheless, direct epidemiological observation of exposed populations provides the best information for evaluating the magnitude of outdoor air pollution-related excess lung cancer.

In conclusion, large-scale epidemiological studies of air pollution and lung cancer are needed if we are to obtain sufficiently informative data. Large numbers of cases will be necessary to measure the effects of air pollution and other factors, such

as occupation and smoking. Without improved epidemiological methods, however, even large studies may fail to inform.

Current developments in biological markers of exposure represent one approach to improving epidemiological methods. In addition, methods for retrospective estimation of lifetime exposure to air pollution should be developed and tested, so that large case-control and retrospective cohort studies can be feasible. If possible, retrospective characterization of levels of certain physical and chemical constituents could aid greatly to the interpretation of between-city patterns of lung cancer occurrence. Finally, new designs and statistical methods (such as hybrid studies combining ecological-level contrasts for air pollution effects between cities with individual-level data)¹³⁰ may provide additional insights.

3.4 Dietary habits: an overview

Diet is considered to be a principal environmental factor for determining the incidence of many major cancer sites, including lung cancer. Much of the epidemiological research on diet and lung cancer has been motivated by the hypothesis that diets high in anti-oxidant nutrients may protect against oxidative DNA damage, and thereby protect against cancer.¹⁵

The overwhelming contribution of cigarette smoking as a cause of lung cancer imposes challenges to detecting the role that other lifestyle factors, such as diet, in the aetiology of lung cancer. Cigarette smoking is so closely associated with less healthful lifestyles, such as less healthful diets,¹³¹ that it is often difficult to discern whether the dietary factors of interest have truly been disentangled from the effects of

smoking. Compounding this problem, even associations between dietary factors and lung cancer that truly exist are likely to be very weak in relation to smoking. In many instances, the potential residual confounding effects of smoking could thus plausibly be strong enough to explain the observed associations between lung cancer and dietary factors.¹³² In the future, studies that control for cigarette smoking in the design are best suited to address the persistent concern about residual confounding by cigarette smoking.

3.4.1 Fruit and vegetable consumption

The most consistent finding on diet as a determinant of cancer risk is the association between consumption of vegetables and fruit, and reduced risk of several cancers.¹³³ However, observational studies (case-control and cohort)^{134,135} showed mixed results for a protective effect of fruits on lung cancer risk. The evidence favouring a protective association for lung cancer is more consistent with vegetable consumption.¹³⁶ Overall, studies indicated that subjects in the highest consumption categories of vegetables and fruits experience 10-50% less risk for lung cancer compared to the lowest consumption categories, irrespective of smoking status.¹³⁷

3.4.2 Micronutrients

Research on vitamins and lung cancer in humans has focused mainly on carotenoids (total and beta-carotene), vitamins A (retinol), C, and E. Two different strategies are usually adopted. First, using data from food-frequency-questionnaires (FFQ), which provides a better average measure of micronutrient 'exposure'. Second, using blood measurements, which have the advantage of measuring concentrations closer to the cellular level where the postulated biological effect occurs. Mixed results

have been observed with both dietary intake of retinol and circulating retinal concentrations with regard to lung cancer risk.^{135, 138} By contrast, total carotenoids, beta-carotene, and vitamin C are more supportive of a reduction in lung cancer risk, using both the above approaches for measurements.^{137, 138} The preponderance of evidence from observational studies has thus demonstrated a ‘protective’ association between carotene (specifically, beta-carotene) and lung cancer.

3.4.3 Chemoprevention Trials

Observational studies indicated that the protective effect of beta-carotene provided a 30-80% reduction in the risk of lung cancer between the highest and lower intake categories.¹³³ However, this overwhelming evidence of a protective effect from observational studies, especially beta-carotene, has been challenged by the results of four randomised, double-blind, placebo-controlled chemoprevention trials. In fact, the CARET (Carotene and Retinol Efficacy Trial)¹³⁹ in the US and the ATBC (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study)¹⁴⁰ in Finland showed an increased risk of lung cancer with beta-carotene supplementation, especially among ‘heavy’ smokers. However, the Finland study most recently hypothesized that a combination of dietary antioxidants reduces lung cancer risk in male smokers.¹⁴¹

A difference in results between observational studies and preventive trials would arise if fruits and vegetables were protective due to constituents other than beta-carotene (confounding).¹⁴¹ Alternatively, at very high non-physiological doses, beta-carotene might have a paradoxical adverse effect,¹⁴² in particular among smokers. The chemoprevention trials clearly suggest a more complex role than researchers had previously thought. These trials also emphasize that we do not know

whether the associations present in observational studies are specific to the micronutrients, or whether the micronutrient measurements are merely serving as a marker of the intake of other protective substances or even of more healthful dietary habits in general.

3.5 Asbestos exposure

Asbestos, a well-established occupational carcinogen, refers to several forms of fibrous naturally occurring silicate minerals (chrysotile, crocidolite, amosite, and tremolite).¹²⁵ The epidemiological evidence dates to the 1950s, although clinical case series had previously led to the hypothesis that asbestos causes lung cancer.¹⁴³ In a retrospective cohort study in 1955, Doll observed that asbestos textile workers at a factory in the UK had a 10-fold elevation in lung cancer risk and that the risk was most heavily concentrated during the time frame before the regulatory limitations were imposed.¹⁴⁴ A 7-fold excess risk for lung cancer development was subsequently observed among insulation workers in the US.¹⁴⁵ The peak incidence occurred 30 to 35 years after the initial exposure. This suggests the very long latency period of carcinogenesis.¹⁴⁶

It is uncertain whether asbestos acts directly as a carcinogen, or indirectly by causing chronic inflammation. Asbestos and cigarette smoking are both independent causes of lung cancer, but in combinations they act synergistically to increase lung cancer risk multiplicatively.¹⁴⁷ Cigarette smoking may increase the lung cancer risk associated with asbestos exposure by enhancing the retention of asbestos fibres.¹⁴⁸

3.6 Radiation

Epidemiological studies of populations that have been exposed to high doses of radiation show that lung cancer is one of the cancers associated with exposure to ionising radiation. However, the risks of low-dose radiation, which are more relevant to contemporary workers and the general population, have proven difficult to characterize.¹⁴⁹ Two types of radiation based on the rate of energy transfer to tissue are relevant to lung cancer: low linear energy transfer (LET) radiation (for example, x-rays and gamma rays); and high-LET radiations (neutrons and radon).

3.6.1 High-LET radiation (Radon)

Radon is an inert gas that is produced naturally from radium in the decay series of uranium. Underground miners exposed to radioactive radon and its decay products, which emit alpha particles, have been consistently found to be at increased risk of lung cancer.⁷ A pooled analysis estimated an apparently linear, approximately 6% increased risk per working-level year of exposure.¹⁵⁰ Cigarette smoking and radon decay products synergistically influence lung cancer risk in a manner that is supra additive but sub-multiplicative.⁷⁵

Today the main concern about lung cancer risk from radon and its decay products comes from residential rather than occupational exposure, because it is a ubiquitous indoor air pollutant, entering buildings in soil gas. Studies of highly exposed underground miners have been used as a basis for extrapolation of the risk at the typically lower residential doses.¹⁵¹ Even the lowest historical radon concentration in a uranium mine is roughly 50 to 100 times higher than in the average home.¹⁵²

A meta-analysis¹⁵³ resulted in a pooled relative risk of 1.14 at 150 Bq/m³ of exposure, which was similar in smokers and non-smokers, consistent with the extrapolation based on underground miners. The US EPA and the National Research Council have estimated that approximately 15,000 to 20,000 lung cancer deaths per year in the US are caused by radon.¹⁵⁴ This is also quantitatively comparable with risk models derived from underground miners.¹⁵⁵ Such coherence lends support to using extrapolation of the miner data to estimate the risk of indoor radon, which has been substantiated in recent studies across residential settings.¹⁵⁶

3.6.2 Low-LET radiation (X-Rays and Gamma Rays)

Epidemiological data of low-LET radiation to lung cancer are derived from three principal sources: the atomic bomb survivors in Japan,¹⁵⁷ patients with disease such as ankylosing spondylitis receiving multiple radiotherapy,¹⁵⁸ and occupational groups in professions exposed to radiation.¹⁵⁹ Taken together, low-LET radiation is associated with higher lung cancer risk when exposure occurs at a higher dose rate (atomic bomb survivors, for example) as opposed to those for high-LET radiation, suggesting that the two types of radiation have different dose-rate relationships.¹⁶⁰

3.7 Host factors (genetic/molecular basis of Lung Cancer)

Genetic susceptibility to lung cancer has long been postulated. Environmental agents, even cigarette smoking, cause lung cancer in only a minority of exposed persons (less than 10% of the smokers),¹⁶¹ leading to the hypothesis that susceptibility is inherently determined. Epidemiological evidence showing that a family history of lung cancer predicts increased risk also supports a genetic basis for

lung cancer susceptibility.¹⁶² This long-postulated hypothesis is now being actively addressed using the approach of molecular epidemiology.

Familial aggregation of lung cancer has been demonstrated primarily in case-control studies.¹⁶³ In these studies, a positive family history of lung cancer has been found to be a risk factor. Although shared smoking patterns within families may explain a large part of the association with family history, increased related risks were found even after adjustment for smoking.

3.7.1 High-penetrance genes

Segregation analyses suggest inheritance of a major gene that, in conjunction with tobacco smoking, might account for 50% to 80% of cases diagnosed below age 60.¹⁶⁴ On the other hand, the largest study of lung cancer in twins reported to date did not provide evidence indicating a genetic basis for susceptibility.¹⁶⁵ This follow-up study of 15,924 male twin pairs in the US did not show greater concordance in monozygotic compared with dizygotic twins, and death rates from lung cancer were similar by zygosity group in surviving twins whose siblings died of lung cancer.

3.7.2 Genetic polymorphisms

With the application of the new and powerful tools of modern molecular and cell biology, a framework for understanding the genetic basis of lung cancer risk is emerging. Figure offers a general schema for the process of carcinogenesis by tobacco smoking (**Appendix two**). This framework indicates multiple points at which genetically determined host characteristics might be important (for example, carcinogen metabolism and activation, and DNA repair capacity).

Some of the metabolising enzymes (phase I of the cytochrome p450 system) have been investigated in regard to lung cancer risk (CYP1A1 and CYP2D6), with variations across the populations.¹⁶⁶ Among the detoxifying enzymes (phase II), there are at least four genetically distinct classes of the glutathione S-transferases (GST),¹⁶⁷ which detoxify reactive metabolites of polycyclic aromatic hydrocarbons (PAH) contained in tobacco smoke. A few studies suggest that individuals with high activity of a particular GST polymorphism have lower risk of lung cancer.^{167, 168}

3.7.3 Somatic cells and genetic events

There are other candidates for determinants of susceptibility to lung cancer in smokers, including oncogenes and suppressor genes, and DNA repair capacity.¹⁶⁹ Much research remains to be done to clarify the association between variations in DNA repair capacity and lung cancer risk. Individuals with a less proficient DNA repair capacity phenotype have been shown to have an increased risk of lung cancer.¹⁷⁰ Mutations in the p53 tumour-suppressor gene are also frequent events in lung cancer. Among lung cancer cases, the proportion of p53 mutation increases with the duration and amount of tobacco smoking.¹⁷¹ Point mutations of certain oncogenes have also been reported in lung cancer.¹⁷²

A recent communication revisited an earlier 'hypothesis' that female smokers may be more susceptible than male smokers to the carcinogenic properties of cigarette smoke.¹⁷³ Differences in the biology of lung cancer do exist between the two sexes: higher levels of DNA adduct formation and increased *CYP1A1* expression among females,¹⁷⁴ as well as decreased DNA repair capacity,¹⁷⁰ and increased incidence of *K-ras* gene mutations in females.¹⁷⁵ A novel oestrogen receptor β has also been

detected in lung tumours.¹⁷⁶ This suggests that oestrogen signalling may have a biological role in tumorigenesis.

In summary, gender-specific lung cancer studies should be given a priority to address this controversial issue of greater susceptibility of females to lung cancer in terms of hormonal, genetic or metabolic factors. Nonetheless, a recent study found no gender susceptibility to developing lung cancer, and thus suggested that the search for biological mechanisms for female-male differences in rates of smoking-induced lung cancer might not be necessary.¹⁷⁷

3.8 Presence of acquired lung disease

In addition to hereditary factors, increased host susceptibility to lung cancer may result from previously incurred lung damage. Such acquired lung diseases assume the two major forms: those that obstruct airflow, such as COPD (Chronic Obstructive Pulmonary Disease); and fibrotic disorders that restrict lung capacity, such as pneumoconiosis. However, an apparent association between these disorders and lung cancer have been controversial for more than sixty years.¹⁷⁸

Cigarette smoking is the principal cause of both COPD and lung cancer.¹⁷⁹ Thus, clarifying the relevance of COPD to the development of lung cancer awaits further proof that this association is not accounted for by cigarette smoking. Regardless of any mechanism, the presence of COPD is a clinically useful risk indicator for lung cancer progress.

Clarifying the possible relationship between various types of pneumoconiosis (asbestosis, silicosis, etc) and lung cancer also poses particularly vexing challenges. Any underlying differences in the pattern of associations between the various types of pneumoconiosis and lung cancer emphasize that fibrosis is not a homogenous exposure, but one that is dependent on the properties of the specific mineral fibre, such as its size, shape, and durability.¹⁸⁰

In conclusion, lung cancer risk is multifactorial, and active smoking is the predominant risk factor. Other environmental risk factors are also worth considering, especially in areas with significant declines in smoking prevalence.

Chapter Four

LUNG CANCER HISTOLOGICAL PATTERNS:

A LITERATURE REVIEW

4.1 Introduction

This chapter critically reviews the published literature to date on the epidemiological pattern of lung cancer by major histological sub-types (adenocarcinoma; squamous cell carcinoma; small cell carcinoma; large cell carcinoma) from a global perspective. This chapter reviews and outlines the potential risk factors for the rising lung adenocarcinoma incidence, together with the possible biases contributing to such an increase in lung adenocarcinoma incidence.

4.2 Major histological sub-types of lung cancer

Lung cancer occurs in multiple histological types, as classified by conventional light microscopy. The four major types include squamous cell carcinoma (SQCC), adenocarcinoma (AC), large cell carcinoma (LCC), and small cell carcinoma (SMCC). Together, these four types of lung cancer account for >90% of lung cancer cases in the US.¹⁸¹ Despite extensive research, the mechanisms leading to these different types of lung cancer remain uncertain. Over recent decades there have been both geographical and temporal changes in the distribution of histological subtypes of lung cancer. Knowledge of these modifications, the steady increase in the incidence of lung AC across the wealthy nations in particular, may help recognize the potential aetiological and pathological mechanisms in lung cancer.

Lung AC has become the leading lung cancer subtype in North America,²² and in Europe,¹⁸² as well as in Asia.⁴⁹ This increase may be partly ‘artefactual’ and involve several ‘biases’, or may be a ‘real’ change.³⁴ Hypotheses have focused on the cells of origin of lung cancers, and on the pathways of differentiation of malignant cells.¹⁸¹ Smoking has been shown to cause each of the major histological subtypes of lung cancer, although there is substantial variation in the dose-response relationship between smoking status and the histological subtypes by gender.¹

4.3 Temporal patterns and geographical variations: an overview

General changes in the lung cancer epidemic have been taking place over the last decade, but to different degrees around the world. In the 1960s, the most frequent histological subtype in the US and Europe was SQCC.⁵⁰ During the mid-eighties, the incidence rate of AC surpassed that of SQCC in the US.²² In parts of Europe, SQCC still remains the most frequent subtype,¹⁸³ but is swiftly changing patterns. Consistent upward trends in AC incidence were reported in the US in the 1960s and 1970s.¹⁸⁴ During the same period upward trend in the incidence of AC was observed in the Netherlands,¹⁸⁵ Switzerland,¹⁸² and in Asian countries, such as Japan,⁴⁹ Korea¹⁸⁶ and Hong Kong.¹⁸⁷

A few of the earlier studies in the 1960s and 1970s were either hospital-based or were autopsy cases, however, more recent population-based studies have confirmed the upward trend in AC.^{188, 189, 190} Similar results have been published using the SEER (Surveillance, Epidemiology, and End Results) programme of the National Cancer Institute (US) showing that AC had become the most frequent subtype leading to a differential shift from SQCC to AC in the beginning of the 1980s.^{22, 191} In summary,

this period of 1960-1970 also seems to correspond well with the rapid urbanization phase in many wealthy nations across the globe.

4.3.1 Temporal and geographical patterns across gender

Geographical and temporal trends also differ in males and females. The hospital-based studies in the 1960s and the 1970s showed that AC was the most frequent subtype in males.¹⁸⁴ However, this predominance of AC in males was not confirmed in the subsequent population-based studies. For example, from 1969 to 1971 and from 1984 to 1986, the incidence of AC in the US increased by 110% in white men and by 151% in black men, while SQCC rates increased by only 25% and 50%, respectively. By contrast, the rates for both AC and SQCC increased by similar percentages (220% and 209%, respectively) over the same time period among females in the US.¹⁹²

In the US, using the 1960-1989 data from the Connecticut Tumour Registry, the oldest population-based registry in the world, Zheng *et al*¹⁸⁸ showed that the overall age-adjusted incidence rates for SQCC and SMCC have stabilised in males, but still increasing in females. The incidence of AC has been increasing in both sexes, but there has been a sharper increase among females since the mid-1970s.¹⁸⁸ However, the same study reported that the recent birth-cohorts had a decline in SQCC and SMCC, as well as in AC across both sexes.

In 1974-1991 data from the SEER programme, Travis *et al*¹⁹³ showed that the age-adjusted lung cancer rates among white and black females continued to increase for all histological subtypes, with the exception of LCC among whites. A recent birth-

cohort study in the US showed that lung cancer incidence rates for white males and females converged rapidly for AC, SMCC and LCC, but less so for SQCC among those individuals born after 1960s.¹⁹⁴ The authors also concluded that their findings might suggest that males and females may be 'equally' susceptible to developing lung cancer from a given amount of cigarette smoking, rather than supporting the hypothesis that females are more susceptible to developing lung cancer.¹⁹⁴

In Japan, Tanaka¹⁹⁵ reviewed 282 autopsy cases from 1950 to 1983 and showed an increasing number of AC, which surpassed SQCC in the 1980s. Watanabe *et al*¹⁹⁶ reported that the proportion of AC also increased from 52% to 69% between the 1960s and the 1980s in females. Recently, Morita⁴⁹ confirmed the same finding in a larger study using autopsy cases from 1958 to 1997. Also, the more recent Osaka Cancer Registry (Japan) analysis¹⁹⁰ showed that AC, as well as SQCC and SMCC incidence is increasing among younger adults, and the authors suggested a possible change in lifestyle as an explanation.

In a Korean clinical study,¹⁸⁶ SQCC accounted for 54% and AC was 18% among males, while in females AC and SQCC were 45% and 28%, respectively. The same study reported that SQCC started to decline after 1987, but AC increased since the 1990s. In Hong Kong,¹⁸⁷ the proportion of AC in females increased from 34% to 59% from the 1960s to 1980s, and a decrease in the proportion of other subtypes. China, however, is showing a different pattern altogether where SQCC decreased from 68% to 53%, and AC increased from 14% to 27% among males between 1980 and 1989, while in females AC decreased from 64% to 39%, but SQCC increased from 22% to 32% between 1980 and 1989.¹⁹⁷

In Europe, SQCC predominated in almost all countries around 1985 (45% of lung cancers in the overall, ranging from 36% in Denmark to 56% in Slovakia).¹⁹⁸ The proportion of AC varied greatly between the countries within Europe.¹⁹⁸ In males, AC represented 10% (Poland, Slovakia) to 23% (Denmark) of all lung cancers. In females, AC was the most frequent cell-type in Denmark (38%), France (36%), Italy (37%), Spain (55%) and Switzerland (42%). By contrast, SQCC predominated in females in the Netherlands, Poland and the UK, representing 30-35% of lung cancers.

In a few of the longitudinal studies done in Europe, one of them showed an increase in the incidence of AC in the Netherlands.¹⁸⁵ In Switzerland,¹⁸² a birth-cohort analysis showed that AC incidence increased in both sexes by approximately 2.5 fold between 1974 and 1994; and during the period 1990-1994, it was more than 3-fold higher than the incidence of SQCC in young adults of both sexes. In summary, there is a changing epidemiology of lung cancer in European countries with an increasing AC among females since the 1980s and the early 1990s.

In Israel,¹⁹⁹ an interesting study was conducted between the Jewish and the Arab populations. The study showed that from 1981 to 1995, SQCC decreased from 30% to 24% in Jewish males and from 17% to 13% in Jewish females. In Arab male populations, the opposite occurred and the percentage rose from 24% to 29%. In the Jewish males, AC increased from 12% to 16%, and from 20% to 23% in females. In the Arab male population, the percentage also rose from 12% to 15%. Regarding age-adjusted incidence rates, SQCC rates and AC rates decreased and increased, respectively, among Jewish population, whereas in the Arab population the incidence rates of both AC and SQCC had increased.

4.3.2 Temporal variations in the ratio of Adenocarcinoma/Squamous Cell Carcinoma (AC/SQCC) by age and gender

A few important temporal changes were also noted in the distribution of histological sub-types of lung cancer across the geographical regions, such as the changing ratio of AC over SQCC by gender and by age groups. In North America and in Asia,^{186,187, 200} adenocarcinoma of the lung was the most common subtype in younger males (age < 55 years). In all these series, the ratio AC/SQCC decreased with age and SQCC became the most common among older males. In females, AC was the most common sub-type across all age groups, but a few studies showed a reverse ratio of AC/SQCC after the age of 55.^{186,200} These findings suggest the importance of age-specific incidence rates of major histological subtypes of lung cancer over time.

In the US, Dodds study¹⁹¹ over the 1974-1981 period showed that in males aged <65 years the incidence of AC increased with time, whereas the incidence of SQCC decreased. However, the number of both subtypes rose with time in males >65 years old. This suggested that in 1981 AC was becoming the predominant cell type in younger populations, whereas older adults were more likely to have other subtypes. In females, the incidence of AC increased roughly in the same proportion in the age groups over or under 65 years. The incidence of SQCC has been increasing with time in successive cohorts of females >65 years. However, in females <65 years there has been no dramatic reduction in the incidence of SQCC. All these differences between age groups suggest that increasing incidence of AC is 'not' just an artefact.³⁴

Similar results were observed in other parts of the US.¹⁸⁸ The incidence of SQCC peaked for males born around 1920-1925, 10-20 years before AC incidence,

which peaked for males born around 1940. Cohort peaks have been reached 10-20 years earlier for males than for females. In summary, the ratio AC/SQCC in the US has markedly decreased to 1.9 (1990-1991) since the 1960s, especially among males.

²⁰¹ This ratio was similar to that observed in Montreal, which was 2.0 in 1993.¹⁸³

In Europe, the ratio of AC/SQCC is still high: 12 in Strasbourg (1993), and 10 in Bohemia (1981-1985).¹⁸³ However, other European countries have lower ratios, for example, 1.6 in Denmark (1993-94).²⁰² The ratio in Asia is low. The ratios were: 2.6 in the Philippines (1990-91),²⁰³ 2.1 in China (1979),¹⁹⁷ 2.7 in Japan (1997).⁴⁹

In conclusion, the male-to-female ratios of lung cancer by histological subtypes could be classified into three distinct types: North American type (ratio being around 2.0), European type (ratio between 8 and 10), and Asian type (the ratio being around 3.0).⁴⁹ These patterns may closely correspond with the smoking patterns across these populations, especially among females, in addition to anti-smoking policies, changing cigarette designs, and other changing lifestyle patterns, together with adverse changes in smoking behaviour among younger adults.

4.4 Potential risk factors for the rising lung adenocarcinoma incidence

Geographical differences and temporal trends lung adenocarcinoma (AC) incidence lead to the question of changes in risk factors with time. Such variations may also help identifying any putative risk factors for lung adenocarcinoma.

4.4.1 Tobacco consumption patterns

The increase in incidence of AC could be partly explained by an increase in tobacco smoking. Several authors have found a dose-response relationship between AC and smoking.¹ This risk increased with both number of cigarettes per day, and the duration of smoking.²⁰⁴ Reduction of tobacco consumption in the 1960s, males in particular, has been followed by a declining incidence of SQCC in the 1980s, but not by a decrease in AC incidence. Other environmental factors could partly explain these differences in temporal trends between the histological subtypes.

Relative risk for AC has been found to decrease more slowly after smoking cessation than that for SQCC.²⁰⁵ Variations in composition of cigarette tobacco with time could have played an important role. These variations could have favoured the development of AC at the expense of SQCC. This could explain too why differences in incidence patterns between SQCC and AC are less pronounced in females, who started smoking 10-20 years later than males.

The introduction of filter cigarettes in the 1950s has been incriminated in the increase in incidence of AC, which occurred 20 years later.¹⁸⁸ Filters remove larger particles in cigarette smoke, thus reducing deposition of those particles in central airways where SQCC develop preferentially. This could lead to a reduction in SQCC incidence.²⁰⁶ AC occurs in the peripheral areas of lung that lacks the defences present in the major bronchi (ciliated epithelium and mucus-secreting cells).⁵⁰ Peripheral lung of the smoker of 'low-yield' filter cigarettes is exposed to relatively higher doses of smoke, including PAHs and NNK, which is an organ tobacco-specific systemic carcinogen mainly inducing AC in laboratory animals.²⁰⁷ Furthermore, the tobacco

blend (for example, in the US) has increased the nitrate content from about 0.5 to 1.3-1.5%, which enhances the combustion of tobacco resulting in increased tobacco smoke.¹⁹² While more 'complete' combustion decreases the concentrations of PAHs, the increased production of nitrogen oxides contributes to the increased formation of NNKs. Such biological phenomenon constitutes the 'systemic carcinogen hypothesis,'¹⁹² which may be responsible for the increasing AC incidence.

An alternative or additional explanation for the rising AC incidence is the 'airborne carcinogen hypothesis'.²⁰⁸ This suggests that the significant reduction in cigarette tar/nicotine content has caused smokers, especially females, to increase the number of cigarettes smoked per day, and also to draw greater puff volumes, as well as inhale more deeply than smokers of plain cigarettes (5 puffs/min with puff volumes up to 55 ml).¹⁹² With increasing puff volume, smoke particles are inhaled into the lung with greater velocity. This forced inhalation of the smoke aerosol opens the alveoli widely and facilitates the rapid saturation with nicotine. Consequently, an increased deposition of smoking particles in the small airways could result in an increased risk of AC.

The idea that deeper inhalation causes primarily AC in the distant parts of the lung is also supported by data showing that most lung neoplasms among smokers of pipes and cigars are SQCC arising from the major bronchi.²⁰⁹ In addition, cigars and pipes generate alkaline smoke with significant amounts of unprotonated nicotine that are rapidly absorbed through the oral mucosa. This also quickly satisfies any craving for nicotine.²⁰⁹

4.4.2 Adenocarcinoma in Non-Smokers

The influence of tobacco smoke on the risk of AC is not considered as great as that of other two histological types is supported by reports that more never smokers and fewer heavy smokers were observed among patients with AC than among those with SQCC or SMCC.²¹⁰ However, nearly all of the reports were from case-control studies,²¹¹ and these studies generally had very few never-smokers available for analysis.²¹⁰ Furthermore, investigations have focused on relative risk rather than other measures of public-health significance, including excess risk and population attributable risk (PAR).

A recent prospective Iowa Women's Health Study group reported that AC is more strongly associated with tobacco smoke exposure than previously recognized, especially in postmenopausal Caucasian females.²¹² The same study reported a PAR of 60% for smoking in AC cases, and the excess risk for heavy smokers compared with never-smokers was highest for AC (n=206), compared to SQCC (n=122) or SMCC (n=104).

Nevertheless, lung AC is relatively the most common histological subtype among never-smokers, and the underlying explanation is yet to be resolved in both sexes across the developed and the developing countries. In North American males alone, AC accounts for 31-54% of all lung cancers in non-smokers, as compared to 25-33% in smokers.²¹³ In China, AC represents 64-80% of lung cancers in non-smoking females.²¹⁴

4.4.3 Lung adenocarcinoma and ETS

Although the risk due to passive smoking (ETS) is probably small, there has been a large population exposed to passive smoking in the past. In Wu's study,¹²⁸ the risk of AC increased with increasing years of passive smoking in non-smokers, but this did not reach statistical significance. In another study,²¹⁵ after adjustment for age and active cigarette smoking, a statistically significant risk for AC was found for females. But after further adjustment for occupation and income, the risk was no longer increased.

In a multi-centre population-based case-control study,²¹⁶ Fontham found that tobacco use by spouse was associated with 30% excess risk of lung cancer in non-smoking females. However, there was no statistical difference between the odds ratio (OR) for AC (OR=1.29), and the OR for other primary lung carcinoma (OR=1.37), suggesting an alternative explanation for the changing distribution by histological subtype. Also, if 'sidestream' smoke contains mainly gaseous components penetrating deeper into the lung than 'mainstream' smoke with higher particulate matter, more adenocarcinomas would be expected in passive smokers.⁸⁹

The apparent weak association of ETS is likely to be affected by confounding and other sources of bias. In addition, most of the studies considered ETS exposure from the spouse only and not from other sources, such as ETS at the workplace, during transportation, or in social settings.

A recent population-based case-control study in Germany²¹⁷ took the above limitations into account, and showed an increased OR (1.56) with AC in high ETS

exposure at all sources among females that increased to 1.83 when ETS exposure sources other than home were considered, compared to no or low ETS exposure across both the settings. Although the results were not statistically significant, they suggest that females may be at an excess risk of developing AC due to workplace ETS exposure rather than residential ETS exposure. Kabat *et al*²¹⁸ also noted an elevated lung cancer risk due to ETS exposure in vehicles among females. These findings suggest the underlying impact of urbanization on increased lung cancer risk, particularly AC among working female populations.

A recent study²¹⁹ in the US concluded that 76% of never-smokers and 92% of ever smokers are exposed to ETS through household contacts, as well as 58% and 67% of never-smokers had ETS exposure during childhood and adulthood, respectively. They argued the importance of quantifying the lifetime ETS exposure in former and never-smokers. In addition, a Polish study²²⁰ observed that ETS exposure during childhood (before the age of 18), significantly increased the risk of SQCC and SMCC, but was not statistically significant for AC. The Mayo Clinic Study²¹⁹ also showed that never-smokers without ETS exposure had a significantly higher proportion of AC (76%) compared to never-smokers with ETS exposure (66%).

In summary, all these observations reinforce the importance of assessing the cumulative amount of ETS exposure other than from household/personal history taking. This is important for understanding the increased risk for AC among female never-smokers in particular.

4.4.4 Other Environmental Factors

An excess of AC has been described after exposure to asbestos mainly.²²¹ However, because of methodological issues (small sample size, lack of non-exposed controls, inadequate source of pathological material) in such studies, no definitive conclusion can be given about the relationship between a carcinogen and a particular lung cancer histological subtype.

The authors who tried to evaluate the relationship between occupational categories and AC found no or slight increased relative risk of AC.²¹⁵ These series have small numbers of subjects in each occupational category. A study in Finland²²² showed a high risk of AC in the miners and quarries groups, compared to all other economically active men. Radon, an important occupational carcinogen, is apparently associated with a higher risk for SMCC, and a lesser risk for other non-small cell lung cancers (NSCLC).²²³

Outdoor air pollution may also play a role. Katsouyanni²²⁴ studied a small series of females in Athens and described an interaction between smoking and air pollution only in Non-Small-Cell Lung Cancers (NSCLC) other than AC. There was no effect of air pollution on non-smokers. In Italy,²²⁵ the risk of AC increased in the industrial area (RR=2.1), especially in the proximity of the shipyard (asbestos exposure) but not in the city centre areas.

In China, the effect of indoor pollution, primarily due to coal burning, was stronger for SQCC than for AC in one study, but similar in another.^{126, 226} Using ETS, incense, and cooking fumes as examples of major indoor air pollutants among

Chinese females in Hong Kong, investigators have recently concluded that dietary habits might be a confounder for such an apparent association, and needs to be controlled for such associations.¹²⁹

Association between dietary habits and histological subtypes is generally a weak inverse relationship. A few case-control studies showed a relatively weak inverse relationship between beta-carotene intake and AC than with SQCC,²²⁷ and a stronger inverse relationship between fruit intake and AC, as well as with SQCC.²²⁸ In China, non-smoking females showed a stronger inverse dose-response relationship between fresh fruit or fresh fish consumption and AC than with SQCC or SMCC.²²⁹ Such observations may suggest the influence of other protective nutrients.

4.4.5 Specific Lifestyle Factors

Gender differences in the histological distribution of lung cancer and a possible greater susceptibility of females than males to tobacco carcinogens,^{173,230,231} suggest the influence of sex-specific hormones. Siegfried²³² first hypothesised that oestrogens may possibly influence lung cancer development, and subsequently a positive synergism between smoking and oestrogen replacement therapy was also reported.²³³ In the 1960s and 1970s, oral contraceptive pills (OC) with high oestrogen content were introduced into the global market, and consequently, an increase in OC users.⁵⁰ Hormone replacement therapy (HRT) was also introduced during the same period.⁵⁰ Thus, changing reproductive behaviours among females across successive generations might also influence the histological subtype patterns over time.

A recent case-control study in Germany²³⁴ showed that for all major histological subtypes, a reduction in risk was observed with OC users, which was least pronounced for AC across all types of users (both ever and long-term users for more than 12 years), and was not statistically significant. This was, however, significant in another study.²³⁵ The German study²³⁴ also indicated a lowered lung cancer risk with HRT, particularly among long-term users, and was independent of cell subtypes. Taioli and colleagues,²³¹ however, showed a 70% significant excess risk of AC for HRT users versus non-users. Incidentally, exogenous oestrogens have been classified as a human carcinogen.²³⁶

Despite its inherent limitation, BMI (body-mass-index) has been used in epidemiological studies as a proxy measure for obesity, and has also been positively associated with the risk of a variety of cancers, including the hormone-dependent cancers (postmenopausal breast cancer, endometrial cancer, prostate cancer), which are predominantly adenocarcinomas.⁵⁰ BMI is also a potential risk factor for oesophageal adenocarcinoma, colon adenomas and adenocarcinomas.⁵⁰

There may be a temporal association between the increasing adenocarcinoma incidence of these major cancer sites, and the rising obesity prevalence across the wealthy nations in particular.²³⁷ However, the issue of whether obesity is protective for lung cancer remains unresolved. A major reason is that most studies have been conducted in populations that smoke, where the strong impact of smoking on both BMI and lung cancer risk may obscure the true relation between BMI and lung cancer risk. In addition, none of the studies have examined a potential relationship between histological subtypes of lung cancer and BMI,²³⁸ except one.²³⁹

The lone prospective study²³⁹ that examined a relationship between obesity and histological subtypes of lung cancer concluded that waist circumference might be differentially associated with the histological subtypes, after adjusting for active smoking only. Although females in the upper BMI quintile were at decreased risk of all lung cancer subtypes, especially SQCC, the highest quintile of waist circumference (a better indicator for central adiposity than waist/hip ratio) was positively associated with SMCC and SQCC, after adjusting for BMI, but not with AC. This study,²³⁹ however, did not support the hypothesis that AC is most likely to be associated with a high level of abdominal fat.

It is possible that a higher waist circumference in a smoker is a marker for greater levels of active and passive smoking, as well as other poor lifestyle habits, such as poor levels of physical activity, or poor diet. A recent case-control study,²³⁸ however, showed a positive relation between BMI and overall lung cancer risk for both never-smokers and former smokers, after adjusting for lifetime ETS exposure and dietary habits. This study could not adjust for baseline or changing weight patterns because of the nature of case-control studies in general, but commented on the possibility of an ‘even stronger positive association.’

The observed positive obesity-lung cancer association may have a biological plausibility. Obese persons tend to have higher levels of oestrogens, converted from androgens in fat tissue.²⁴⁰ In combination with lower levels of steroid hormone-binding globulin (SHBG),²⁴⁰ there may be more circulating unbound oestrogen, able to bind to its receptor in lung and other tissues. Oestrogen may act as a promoter,²⁴¹ with high oestrogen levels acting as a growth factor on cancer cells. Obese persons

are also known to have higher circulating levels of insulin, which also may promote cancer cells by acting as a growth factor.²⁴² So, an underlying endogenous hormone metabolism associated with adiposity can stimulate cell proliferation, inhibit apoptosis and enhance angiogenesis.²⁴³

All the above biological mechanisms are consistent with the obesity-cancer associations observed in other major cancer sites.⁵⁰ The association between ‘leanness’ and lung cancer mortality may not be causal, but rather an artefact of the effects of smoking and pre-existing disease,²⁴⁴ possibly suggesting a ‘reverse causality bias’.²⁴⁵ Such methodological issues could be better addressed through long-term follow-ups of large historical cohorts. Innovative epidemiological study designs involving biochemical-molecular techniques to exclude a genetic predisposition or any gene-environment interactions in the metabolism of tobacco carcinogens is worth considering.

4.5 Rising incidence of adenocarcinoma: possible biases

Despite the above possibilities contributing to the apparent rising incidence of adenocarcinoma across the wealthy nations, and among female populations in particular, there might be potential biases contributing to such an interesting phenomenon. Such biases are discussed in the following sections.

4.5.1 Detection bias

Investigations for a diagnosis of lung cancer tend to be made in smokers, particularly males with pulmonary symptoms. McFarlane²⁴⁶ in an autopsy series found that 43 of 153 lung cancers (28%) had not been diagnosed ante mortem. The

proportion of non-smokers was higher in the undiagnosed group than in those patients having an ante mortem diagnosis of lung cancer (30% versus 8%). This study also revealed a predominance of females in the undiagnosed group. A case-control study²⁴⁷ showed that sputum cytology was ordered in patients with chronic cough, recent cough, male sex and smokers. This leads to a detection bias in non-smokers, asymptomatic individuals and in females. As adenocarcinoma is the most common subtype in these groups, its incidence may have been previously underestimated. Correction of this detection bias might lead to the conclusion that the incidence of lung cancer in general and adenocarcinoma in particular is increasing with time.

The distribution by histological subtypes in various countries should be compared with caution, because the proportion of specified histology can vary greatly. In a country such as the Netherlands or Switzerland more than 90% of lung cancers have a pathological diagnosis, while in Poland and Hong Kong only 40-50% of histological subtypes are specified.¹⁹⁸ Historically in Europe, the origin of adenocarcinoma in the lung was debated, and adenocarcinomas were often considered as metastatic from an unknown primary. The proportion of patients with adenocarcinoma of unknown primary rather than a primary adenocarcinoma of the lung may vary between institutions or countries.²⁴⁸ So, the degree of change in this diagnostic classification contributing to an increase in the incidence of adenocarcinoma has not been evaluated yet.

4.5.2 Changes in diagnostic techniques

Adenocarcinoma often is not bronchogenic but develops in the peripheral parenchyma of the lung. Because early stage adenocarcinomas do not cause ulceration

or obstruction of the major bronchi, the first manifestations of these tumours in almost half of all patients are signs of metastasis. Some peripheral adenocarcinomas may invade and obliterate bronchi before diagnosis, leading to a misdiagnosis of bronchial carcinoma. Because the clinical presentation differs from one histological type to another, the distribution by cell type in series of patients diagnosed by bronchoscopy, trans-thoracic needle aspirate (TTNA), trans-bronchial needle biopsy, autopsy or surgery may vary significantly.

In radiological series, 52-75% of adenocarcinomas present as a peripheral nodule.²⁴⁹ This explains why there might be an underestimate of the proportion of adenocarcinomas in bronchoscopy series. However, the introduction of the flexible bronchoscope in the late 1960s and the increased use of TTNA since the 1980s²⁰¹ have both improved access to the lung periphery; this may have also led to an increase in the proportion of adenocarcinoma detected. However, using data from the Connecticut Tumour Registry, Thun *et al*²⁰¹ showed that the rise in adenocarcinoma ‘antedated’ these diagnostic innovations.

A continuing decline in the incidence rates for lung cancers of unspecified histology among males has been observed, since the 1970s.¹⁸⁸ This might partially explain the observed time trend. Adenocarcinoma might also be expected to constitute a high proportion of surgical cases. Nevertheless, the rate of adenocarcinoma is often lower than expected.²⁵⁰ This could be explained by the significantly greater incidence of unresectability due to the late staging of adenocarcinoma disease compared to squamous cell carcinoma for an equivalent size of tumour.²⁵¹

4.5.3 Change in the criteria for histopathological classification

Several authors have evaluated the impact of changing classification on distribution of cell types by rereading the slides of patients previously diagnosed using the original classification. There was a 6% increase in rate of adenocarcinoma when using the first WHO classification, at the expense of the other histological types.¹⁸⁴ The first WHO classification of lung tumours was published in 1967 and revised in 1981.²⁵² In the initial classification, solid tumours with mucin production were classified as large cell carcinoma, whereas in the current classification they are categorized as adenocarcinoma.

The influence of the second change in classification has been evaluated by Kung¹⁸⁷ who found an increase in the proportion of adenocarcinoma from 34% to 41% after having reviewed the slides using the second WHO classification. However, using the SEER data, Travis *et al*²² examined the age-adjusted rates of large cell carcinoma and mucinous adenocarcinoma between 1977 and 1989, and showed that large cell carcinoma grew steadily, whereas mucinous adenocarcinoma rose during the 1970s and plateaued during the 1980s. This suggested no major shifts in classification from large cell carcinoma to mucinous adenocarcinoma in 1981.

Some authors have also suggested that the observed increase in adenocarcinoma incidence may reflect differences in the classification of scar cancer cases,²⁵³ because the histological type of scar cancer is usually adenocarcinoma, and scar cancer has the same clinical features, as well as a similar prognosis to any adenocarcinoma of the lung.²⁵⁴ If scar cancer is, indeed, responsible for the observed increase, then factors that cause scar formation also must be increasing. Some

investigators, however, have suggested that the origin of the scar is a tissue response to the tumour itself and, therefore, the result of that growth rather than its precursor.²⁵⁵

Lung cancers that were reported to be associated with scars also vary widely from 6.9% to 29%. Auerbach *et al*²⁵³ studied 505 cases of patients with lung cancer and found that the percentage of scars in those cases has nearly doubled (from 6.9% in 1955-1975 to 11.7% in 1986-1989), although there were a smaller percentage of peripheral cases with scar cancer in the recent period (33%) than in the previous period (44.8%).

4.5.4 Change in pathological techniques

Since the 1980s, Periodic Acid Schiff (PAS), PAS-diastase, mucicarmin have routinely been used to stain histological specimens for presence of mucin or alcian blue stains. Valaitis reviewed the impact of staining using mucicarmin and PAS and/or PAS-diastase in 219 cases of lung cancer.²⁵⁶ He noted a reduction in number of undifferentiated carcinomas with an increase of adenocarcinomas. Between 40% and 47% of cancers initially categorized as undifferentiated carcinomas were reclassified as adenocarcinomas. Similarly, in another study,²⁵⁷ the proportion of adenocarcinomas increased from 11% to 29% after slides were reviewed using special stains for mucin. However, Thun *et al*²⁰¹ showed that the rise in adenocarcinoma 'antedated' these diagnostic innovations.

4.5.5 Inter-reader variability

There is an inter-reader difference in pathological diagnosis, even when using the same classification. A study where five pathologists reviewed 50 lung cancers, inter-reader variability ranged from 2% for well-differentiated squamous cell

carcinoma, 5% for well-differentiated adenocarcinoma to 42% for poorly differentiated adenocarcinoma.²⁵⁸ In another study,²⁵⁹ all the pathologists agreed on a classification of 67% of 476 lung cancers, and two agreed in 94% of cases. The rates of agreement were 86% for squamous cell carcinoma, 89% for small cell carcinoma, 76% for adenocarcinoma, and only 40% for large cell carcinoma. Campobasso²⁶⁰ also reported similar results: a high agreement for SQCC, SMCC and AC (kappa statistic=0.87, 0.89, 0.85, respectively) in contrast to that for LCC (kappa statistic=0.71). Weiss,²⁶¹ however, reported a 47% agreement rate for AC; the lower the degree of differentiation, the lower was the degree of agreement.

Such differences in interpretation might potentially apply to a hospital-based study with a small number of pathologists interpreting the results. In population-based studies, the large number of pathologists might dilute individual differences in interpretation. Whether the differences are in diagnosis between pathologists from different countries, however, remains unknown. Interestingly, studies have shown that non-smokers have a higher proportion of well-differentiated adenocarcinoma than smokers across both genders.²⁰³ It has also been argued that female adenocarcinoma in the US is predominantly more poorly differentiated subtype,⁴⁹ whereas the Asian female non-smokers have predominantly well-differentiated adenocarcinoma.²⁰³ The reasons for such variations are unknown.

4.5.6 Prognosis and survival rates of adenocarcinoma

In general, the overall survival of lung cancer patients is poor. The survival patterns for all the major histological sub-types have not changed significantly over the past two decades. There is variation in survival rates by gender and race. The five-

year survival rate for overall lung cancer is 12% for white males and 16% for white females, but the corresponding percentage for blacks are slightly lower.⁵⁰ Variation in survival by cell type is limited, with the poorest survival (about 5%) for small cell carcinoma.⁵⁰ Five-year survival rates reach 46% for localised tumours, but these account for only 16% of all lung cancers.⁵⁰ As adenocarcinoma predominantly manifests late, because of its peripheral location, as well as the metastatic nature of presentation, the survival rate is generally poor. Females with adenocarcinoma have a longer survival when treated with ‘gefitinib.’²⁶² This implies the role of endogenous oestrogens on lung pathogenesis.

4.6 Summary and Conclusions

In summary, there is not much significant change in clinical practice, and in survival rates of the major histological sub-types of lung cancer to contribute to a rising adenocarcinoma incidence over the past two decades, together with the fact that the rise in adenocarcinoma ‘antedated’ any of the diagnostic innovations. Lung adenocarcinoma incidence rates are consistently increasing worldwide, especially across the wealthy populations, and much sharper among females, as evident from the declining male-to-female ratios of AC/SQCC.

These distinct patterns began in the 1960s across a few nations, but were ubiquitous in the 1980s. Although smoking patterns were changing across the wealthy nations in the 1960s and 1970s, they were not convincingly consistent with the underlying temporal and regional variations in lung cancer incidence by major histological subtypes. The changing patterns may also reflect the exacerbating effects of diet, reductions in occupational exposures, or reductions in air pollution from coal

burning that could potentiate the risks from smoking. Other potentially important parameters that are not directly considered in any temporal and geographical variations, apparently due to lack of consistent data, include differences in cigarette composition across countries, and variations in the age of initiation, intensity of smoking at various ages, and age at cessation, both within and across countries.

Furthermore, the majority of the wealthy nations were undergoing a rapid urbanization phase in the 1960s and 1970s with a changing lifestyle, and this phase might be an important epidemiological transition for many chronic diseases, including lung cancer. The incidence rate of lung adenocarcinoma also peaked around the 1980s, and particularly among female populations. The dose-response relationship between smoking and lung adenocarcinoma among females is also lower compared to that in males with lung adenocarcinoma. Lung adenocarcinoma is also relatively more common among younger individuals (less than 55 years of age). Such consistent temporal and geographical patterns may suggest the emergence of a major environmental risk factor. This emerging pattern may be compounded with rapid urbanization and a changing lifestyle, in addition to the residual confounding by changing smoking habits. More importantly, such distinct emerging geographical patterns are aetiologically significant, offering rich opportunities for exploratory research across such populations.

In conclusion, the recent lung adenocarcinoma rise across the industrialised nations in particular is real and is less likely to be attributed to all the potential biases discussed earlier. The fact that such a real increase in lung adenocarcinoma has been particularly observed since the late 1970s and the early 1980s, it is equally important

to note that a shift in industrialisation together with a changing life style pattern were contemporaneous events. The recent rise in lung adenocarcinoma is a complex issue of host of environmental factors that needs novel epidemiological approaches to address such issues. Therefore, life course epidemiology and urbanization may have an integral part to play in future epidemiological studies on chronic diseases,⁷⁰ including lung cancer. In summary, the recent pattern of lung adenocarcinoma is a cohort effect of any changing environmental risk factors in the 1960s and 1970s.

Chapter Five

LUNG CANCER 'PANDEMIC': GOING UP OR DOWN?

So far it has been clear that there is a lung cancer pandemic. This chapter, however, gives an insight into the changing pattern of such a lung cancer pandemic over the next few years, as well as outlines a few of the general approaches to address such a pandemic.

Worldwide, lung cancer is the most common preventable cancer death as 90% of lung cancer cases are attributed to smoking alone, but there are huge regional variations in their epidemiological patterns.⁹⁹ In the US, lung cancer incidence and mortality among white males has been declining since 1991, and among black males since 1993.⁵⁵ This reflects earlier smoking behavioural changes among males following the publication of the seminal report in 1964.⁷

The recent stabilization in lung cancer incidence and slowing rate of increase in death rates among white and black females in the US also suggest that a reversal in the trends among females may be occurring.⁵⁵ This may be consistent with the rising adenocarcinoma incidence among females. There is also evidence that the recent birth-cohorts are showing a convergence of lung cancer death rates among both males and females born after 1960,¹⁹⁴ suggesting an encouraging trend. The fact that the annual adult smoking prevalence is either increasing or have remained stable between 1991 and 2000,²⁶³ together with an overall 600% increase in female lung cancer death rate from 1930 to 1997 in the US,¹⁷³ are issues of concern.

In Europe, lung cancer mortality rates are declining for males in 11 of the current 15 member states, with stable trends in two, but rising trends in Portugal and Spain.^{47, 264} However, majority of the Eastern European countries are showing an increasing trend.²⁶⁵ For example, Hungary has the highest current male lung cancer mortality rate, and is also projected to increase further in the short term. Except the UK and Ireland, where recent female lung cancer death rates have begun to fall, the remaining European countries are projected to show a rising death rate over the next few years.^{264, 265} This rise may also be consistent with the rising incidence of adenocarcinoma among females in European populations.²⁶⁶ The Russian Federation shows a recent downtrend in death rates from lung cancer, which is expected to reverse soon with a second peak around 2003.²⁶⁷ In Europe, large increases in smoking prevalence among adolescents are equally disturbing.

In Japan, the number of deaths due to lung cancer would double for both males and females during the next three decades due to the ageing of the baby-boomer generation (individuals born between 1947-1951).⁵⁴ In addition, Japan female populations are showing a rising adenocarcinoma incidence, although there is a declining male: female ratio.⁴⁹ The fact that lung cancer incidence rates among younger adults (45-49 age groups) are increasing in Japan is worrying, and also needs to be monitored closely for possible emerging risk factors. The smoking prevalence among Chinese and Indian populations, the two most populous countries, is increasing among the younger generations,⁵⁰ thus, the possibility of global lung cancer burden being mainly concentrated in the developing countries by 2020.⁹⁹

In conclusion, the 'changing face' of lung cancer epidemiology mirrors the changing cigarette epidemic, although the rising lung adenocarcinoma incidence remains mostly unresolved, especially among female populations. In addition, rising teenage smoking prevalence may offset the current encouraging trend in the majority of the wealthy nations.

Therefore, countries with lower rates of smoking prevalence need to act quickly to prevent smoking prevalence from rising, and to reduce it further. In the absence of a truly comprehensive national tobacco control programme, and in the absence of significant social pressures, this epidemiological transition would eventually result in the tens of millions of premature deaths, including lung cancer deaths. Global and local initiatives, such as the WHO Framework Convention on Tobacco Control (FCTC), ²⁶⁸ and the recent nationwide Smoking Ban in the workplace across the Republic of Ireland, ¹⁰⁶ are certainly bold steps in the right direction to stop the 'pandemic' of lung cancer.

The geographical and regional variations in lung cancer, together with the gender differences in lung adenocarcinoma 'epidemic' are to be actively pursued in future epidemiological studies integrating traditional with modern molecular epidemiological approaches. Such analyses would help developing a molecular-epidemiological risk assessment model for a specific population, and also help early detection and prevention of clinical lung cancer cases. Sound epidemiological evidence is necessary to carry forward any bold public-health initiatives. It is also important that an inter-disciplinary approach is adopted for lung cancer prevention worldwide, with a strong political commitment.

Chapter Six

LUNG CANCER DEATHS IN THE REPUBLIC OF IRELAND

6.1 INTRODUCTION

This chapter describes the lung cancer deaths in the Republic of Ireland from 1970 to 1999. Methods, results, and discussion are described separately in three different sections. The chapter describes the research methodology employed to examine this particular study objective, and the findings are presented in tables or graphs, with an underlying message following each table or graph. The final section discusses in-depth on the main findings of the epidemiological pattern of lung cancer deaths both from the Irish and the global context.

6.2 METHODS

This section describes in detail the methodology used to examine the epidemiological pattern of lung cancer deaths in the Republic of Ireland from 1970 to 1999. It begins with a description of the sources of various data used in this study then the historical perspective to age-cohort modelling is outlined.

6.2.1 Lung Cancer Mortality Data

The Irish Central Statistics Office (CSO) compiles and collates each death within one calendar year of the date of occurrence of the death. It is a requirement by law that each death in Ireland must be recorded and registered. Every death is registered in the county registrar's district where the death occurred. Because of the fact that a death can be registered up to a year after its actual occurrence, and because

the CSO ensures that they have a complete set of records, the complete file of deaths for any given calendar year is routinely two years behind. For example, 1999 mortality data were only available towards the end of 2001. However, the big advantage of using the routine mortality data in this study is that there is a comprehensive set of computerised information available in the Republic of Ireland from 1970 onwards.

For this study the complete files of mortality data were obtained from the CSO office for the year 1970 to 1999 inclusive. These records were in ASCII format. Information on the age of the deceased, the cause of death, county of residence of deceased, sex, and the date of death was available for each individual death. The coding used for the cause of death was 162 for lung cancer according to the International Classification of Death (ICD-9). The coding for lung cancer in ICD-9 (in 1970) and in ICD-10 (in 1997) had very little variation in contributing to any significant changes to the temporal pattern observed in this study.²⁶⁹ The SAS program was used for the management of the database and imported in Excel for final analysis. The Irish Census data for the years 1981, 1986, 1991, and 1996 were used for standardisation of age-adjusted lung cancer mortality rates. The age-specific population estimates by gender, as outlined by the CSO website (www.cso.ie) between the Censuses were also used for standardisation of lung cancer mortality rates during the intermediate periods.

6.2.2 Cigarette consumption and smoking prevalence data

Comprehensive national smoking prevalence data for the Republic of Ireland do not exist. A number of local and national surveys across specific populations have

been conducted. In 2002 Lee and colleagues¹⁶ compiled international smoking statistics for 30 economically developed countries, including Ireland. For the Republic of Ireland, the authors¹⁶ took data from several sources, including sales and other Irish survey data, which may be an individual survey or a series of surveys repeated over a number of years (**Appendix three**). This study uses the annual per-capita cigarette consumption (excluding pipe/cigar) for the total populations (not by gender) above the age of 15 years from 1920 to 1995, as reported by Lee *et al.*¹⁶ For smoking prevalence data in the Republic, age and gender-specific data are available on an annual basis only from 1971 to 1994, as documented by Lee and colleagues.¹⁶

The lung cancer mortality data were divided into birth-cohorts: a cohort consists of those born in a particular year, which has been derived from the year of death from lung cancer at a specific age. In addition, the lifetime per-capita cigarette consumption in pack-years (one pack-year=20 cigarettes/day for one year) was computed, assuming the minimum age of smoking to be from the age of 15 until 10 years before their reported deaths, as adopted recently in one of the studies.²⁷⁰

A person was born in 1925, and 15 years later (1940) started smoking, died of lung cancer in 1980 at the age of 55. In 1940 the daily per-capita cigarette consumption in adults above 15 years in the Republic of Ireland was reported to be four cigarettes.¹⁶ Hence in the whole year (1940) he would have consumed a total of 1460 cigarettes (4*365 days). However, the following year (1941) the reported annual per-capita cigarette is different.¹⁶ So until 10 years prior to his death (in 1970) the total annual cigarettes consumed by him was computed, and roughly estimates the lifetime cumulative cigarette consumption of this particular individual. This estimate

was again translated into pack-years (one pack-year = smoking 20 cigarettes a day for one complete year). Such computations were carried out for each birth-cohort to estimate their lifetime cumulative cigarette consumption, which was finally incorporated into the age-cohort model (Model III, as given below). As there is no gender-breakdown of cigarette consumption data, the same estimate was used for both sexes introducing some degree of information bias in the analyses.

For trends in annual smoking prevalence in relation to annual lung cancer mortality rates, age-specific smoking prevalence of both males and females across the same calendar period was calculated. This age-specific smoking prevalence was ‘lagged’, assuming a minimum of 10-year lag for the younger age groups (25-45), 20-year lag for those between 45 and 64, and a maximum lag of 30 years for 65 year-olds and above. Such age-specific lagged smoking prevalence has been used elsewhere in similar studies.^{16,112, 271} For age-cohort models, lifetime cumulative cigarette consumption is considered to be a better national indicator than the changing annual smoking prevalence rates at the population level.²⁷⁰

6.2.3 Estimated-Annual-Percent-Changes (EAPC) in Death Rates

Age-adjusted lung cancer death rates were calculated (expressed as rates/100,000 persons) for each year across both genders, standardising to the Irish Census Data. For continuous changes in these death rates over different time-periods, a regression model was utilized to estimate their annual-percent-changes (EAPC). The modelling was done using the recently developed Joinpoint Regression Analysis Program (version 2.7)²⁷² of the United States’ National Cancer Institute’s SEER

statistical software, which has been used successfully in recent studies.^{55, 273}

This Joinpoint²⁷³ analysis fits a series of joined straight lines on a log scale to the age-specific and age-standardised lung cancer death rates (including the overall and truncated: 35-84 year-olds.²⁷³ Line segments are joined at points called joinpoints. Each joinpoint denotes a statistically significant ($p=0.05$) change in trend. In joinpoint analysis, the best-fitting points where the rate changes significantly (increase or decrease) are chosen. The analysis starts with the minimum number of joinpoints, and tests whether one or more joinpoints are statistically significant and should be added to the model (up to three joinpoints). In the final model, each joinpoint indicates a statistically significant change in trend, thus computing the annual percent change (EPAC) for each of those trends by means of generalised linear models assuming a Poisson distribution. Significant changes are considered when there are changes in direction or in the rate of increase or decrease (slope of the line segments). EPAC was also used for the annual age-specific lagged smoking prevalence. An example of the output of Joinpoint Analysis Program is in **Appendix Four**, and the corresponding graph is in **Appendix Five**.

In summary, short-term trends of each line segment were denoted by EPAC, which was estimated by fitting a regression line to the natural logarithm of the rates by using the calendar year as the regressor variable:

$y=mx + b$, where $y= \ln (\text{rate})$ and $x = \text{calendar year}$ (Model I)

Testing the hypothesis that EPAC was equal to zero is equivalent to testing the hypothesis that the slope of the line segment was equal to zero. Statistical significance ($p < 0.05$) was two-sided, and the $EPAC = 100 (e^m - 1)$.

6.2.4 History and implications of age-cohort modelling

By the end of the 19th century, it was realized that disease rates could be strongly influenced by events occurring early in life. Accordingly, statistical models were built on such observations that the incidence of many chronic diseases are strongly influenced by factors that are shared by individuals who are born during the same time (birth cohorts). Frost introduced graphical methods to describe 'cohort analysis'.²³ Since then, graphical techniques have been used to show that mortality from tumours either declined or increased in a cohort-wise fashion. Later on more formal statistical techniques were used to show that temporal trends of female breast cancer in Iceland, and in the prefecture of Osaka in Japan were attributable to increasing risk in successive birth cohorts.²³

No analysis in descriptive cancer epidemiology can ignore age, as the influence of age on the incidence of chronic diseases is usually dramatic. When there are strong temporal trends in disease rates, the effect of age can be seriously distorted in cross-sectional data (data collected during a single period of time). However, examination of the cross-sectional rates would have had lead to a distorted impression that risk declined after a certain age. The cohort analyses can provide significant leads to an aetiological hypothesis, and may also provide aggregated information on disease trends in populations where there is limited individual-level data.

In recent years, advances in statistical theory particularly in the field of log-linear models have led to a re-evaluation of traditional methods of direct and indirect standardisation of analysis of vital statistics rates.²⁷⁴ For example, direct and indirect standardization have been based on the definition of summary indices where mortality for fixed age-specific rates remain constant under changes to the age structure of the population or cohort under study. A more modern approach views such indices as estimates or parameters of a probabilistic model for mortality.²⁷⁴ Such a model is a multiplicative risk model, and when used could detect those temporal variations, which are due to purely secular influences (period effects that affect age groups equally), or when they are attributable to generational influences (cohort effects that affect age groups unequally).²³

The age-cohort model is based on assumption that any temporal evolution of chronic diseases is determined by factors that are shared by birth cohorts. On the other hand, an age-period model would be expected to reflect environmental and other influences at specific periods of time. Such influences might include the effects of environmental pollutants, the introduction of specific interventions at specific periods of time, or changes in medical technology that lead to improved diagnosis. Nonetheless, the age-period-cohort model suffers from an inherent problem of ‘non-identifiability’. Clayton and Schifflers^{274, 275} have suggested an approach to minimise such problems. Such ‘non-identifiability’ could also be alleviated when population-based information on specific risk factors is available,²³ especially when such factors are introduced in a cohort-wise fashion or during specific calendar periods. For example, incorporating cumulative tobacco consumption across birth-cohorts in an age-cohort model, or the inclusion of annual black smoke levels across different time-

periods in an age-period model for lung cancer death rates could both provide a better insight into any temporal variations close to a ‘partially ecologic analysis’.²³

6.2.5 Age-Cohort Analysis for Lung Cancer Risk in this study

In this study a simple age-cohort model was employed to examine the temporal pattern for lung cancer deaths across the Republic of Ireland from 1970 to 1999 by gender. It was assumed that the number of lung cancer deaths in each age group and each birth-cohort was a Poisson random variable that is independent of the lung cancer deaths in all other age groups and birth-cohorts. A ‘synthetic’ birth cohort for each age group was created based on the year and age of death of each individual, using 5-year age and 5-year calendar-period intervals for the simple age-cohort modelling.⁴⁵ Each birth cohort could be identified by the central year in the interval. For example, the 1955 birth cohort would refer to people born between 1951 and 1959, highlighting ‘non-identifiability’. The goodness of fit for the models was judged from the deviance (ratio of the deviance value to its corresponding degrees of freedom).^{274, 275}

In order to test whether temporal trends in lung cancer can be described largely in terms of cohort effects, the following age-cohort model was used:

$$E_{ij} = A_i B_j N_{ij} \text{ (Model II)}$$

E_{ij} = expected number of lung cancer deaths in age group ‘i’ and birth cohort ‘j’

A_i = the effect of age group ‘i’

B_j = the effect of birth cohort ‘j’

N_{ij} = population at risk (year and age-specific population from the Census data)

Because the study objective was to estimate the strength of temporal association between lung cancer and cumulative tobacco consumption across different birth-cohorts by gender, cumulative tobacco consumption in terms of pack-years was incorporated into Model II. So, the next model was:

$$E_{ij} = A_i B_j C_k N_{ij} \text{ (Model III)}$$

C_k = the effect of tobacco consumption units at a particular period on observation ‘k’

The models were fitted by Poisson regression, assuming an idealized experimental condition where successive events occur independently, and at the same rate. In other words, Poisson models are appropriate when the total proportion is fixed, but there is inter-cell variability. This inter-cell variability may lead to over-dispersion,^{274,275} which were taken into account in this study. Estimated risks for each 5-year interval birth-cohort (maximum likelihood estimates) were calculated relative to the youngest birth-cohort, adjusted for age and gender, both for models II and III. All analyses were carried out using *Proc GENMOD* program of SAS software.²⁷⁶ An output of one of the model findings together with the SAS program of the same model has been shown in **Appendix six**.

6.3 RESULTS

This section describes in detail the results of the gender-breakdown of lung cancer death patterns in the Republic of Ireland from 1970 to 1999. All the results are presented in tabular or graphical forms with brief comments outlining the underlying message. EAPCs in death rates and the age-cohort findings are presented in the last two sub-sections of this third section on results.

**6.3.1 Age-Standardised Lung Cancer Death Rates in the Republic of
Ireland: 1970-1999**

Figure 6.1. Male total lung cancer deaths, and corresponding age-standardised lung cancer death rates by year in the Republic of Ireland: 1970-1999.

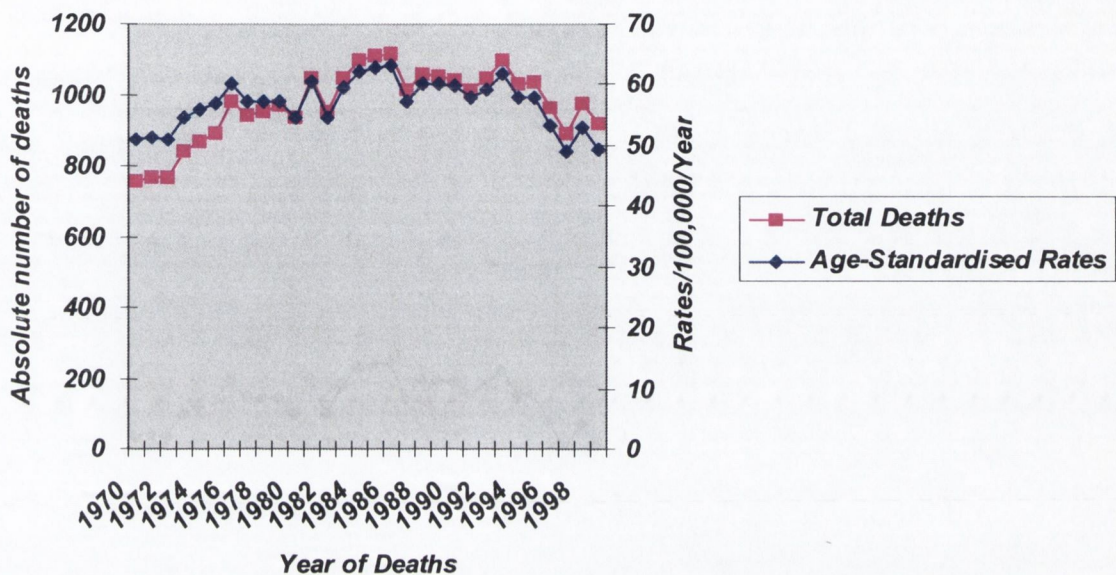
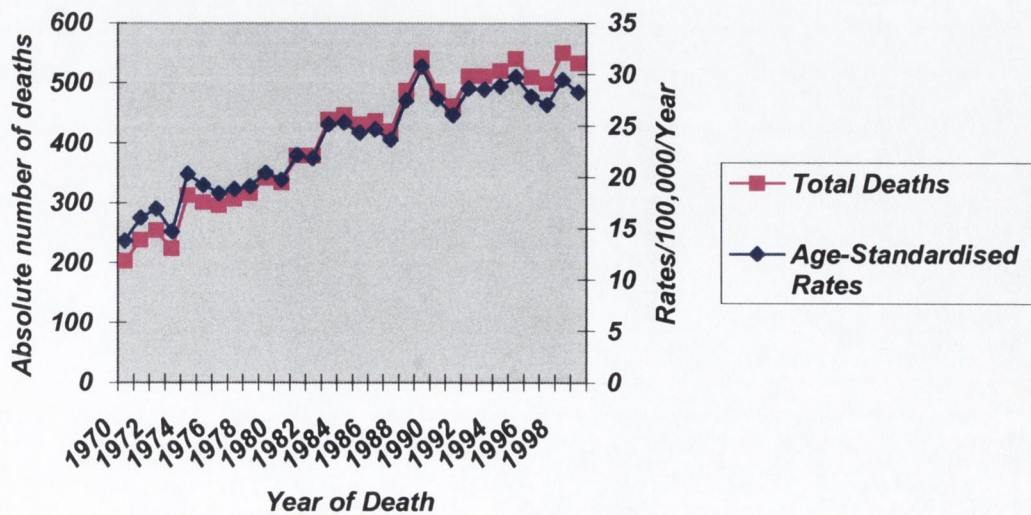


Figure 6.2. Female total lung cancer deaths and their corresponding age-standardised lung cancer death rates by year in the Republic of Ireland: 1970-1999.



Figures 6.1 & 6.2 (male vs. female):

These figures show both the absolute number of lung cancer deaths, and their corresponding standardised rates from 1970 to 1999. In the Republic of Ireland, the lung cancer death rates are higher in males than in females, following age adjustment and standardising to the Irish Standard Population to control for any demographic changes. Male lung cancer age-standardised death rates showed an earlier peak around the mid 1980s followed by a declining death rate, while female lung cancer age-standardised death rates are yet to decline, but have stabilised since the early 1990s. So the declining lung cancer death rates among males, together with a stabilisation in lung cancer death rates among females suggest an overall encouraging trend in lung cancer over the coming years in the Republic of Ireland.

6.3.2 Age-specific lung cancer rates by the year of birth

Figure 6.3. Male age-specific standardised lung cancer rates across different birth-cohorts in the Republic of Ireland (normal scale).

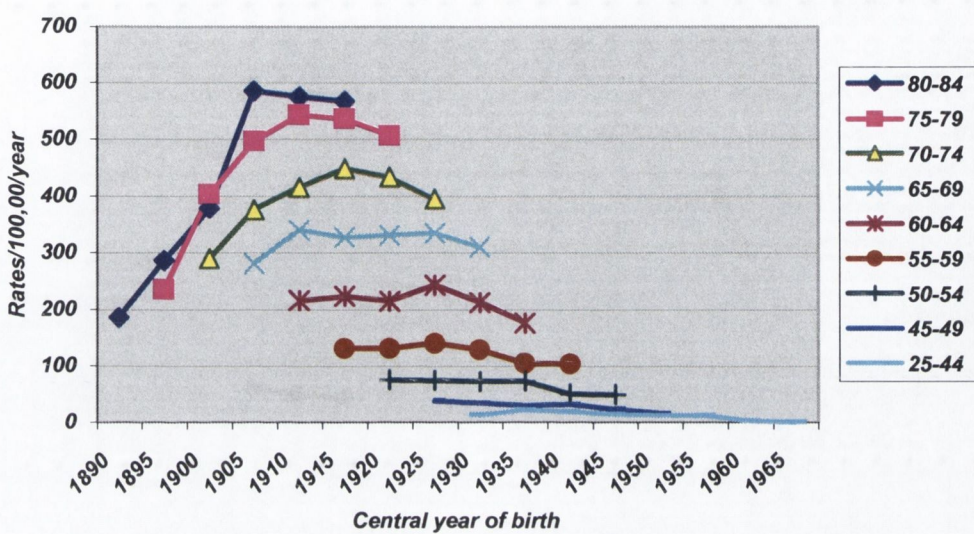


Figure 6.4. Male age-specific standardised lung cancer rates across different birth-cohorts in the Republic of Ireland (log scale).

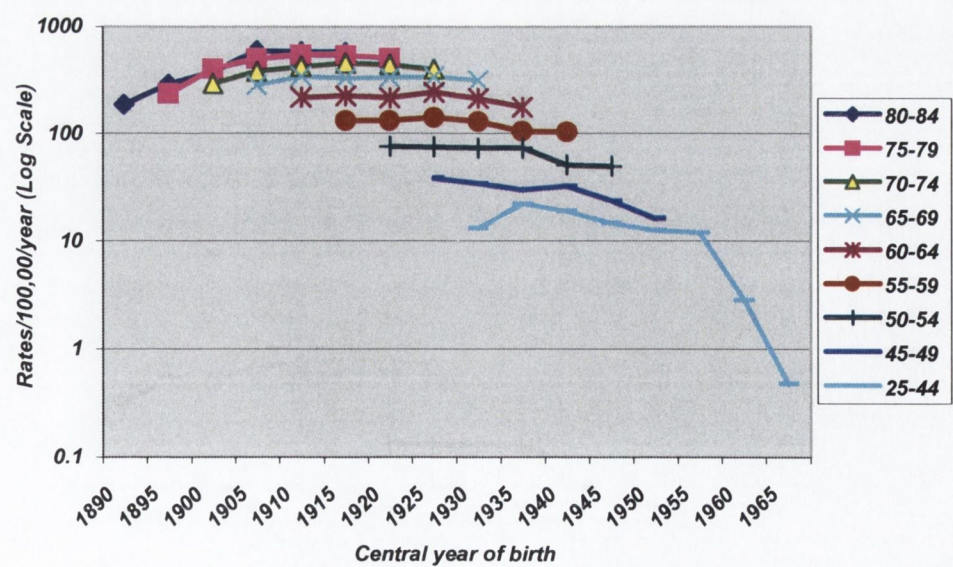


Figure 6.5. Female age-specific standardised lung cancer rates across different birth-cohorts in the Republic of Ireland (normal scale).

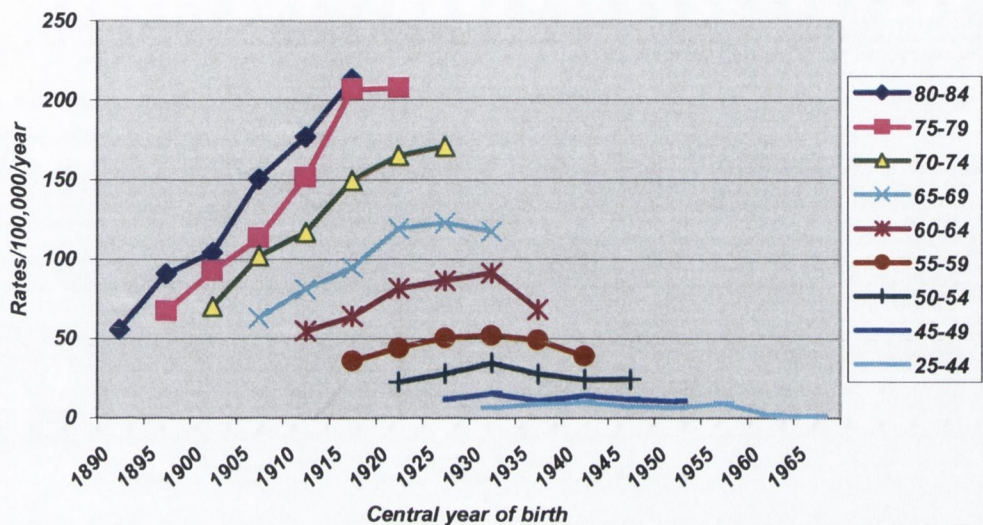
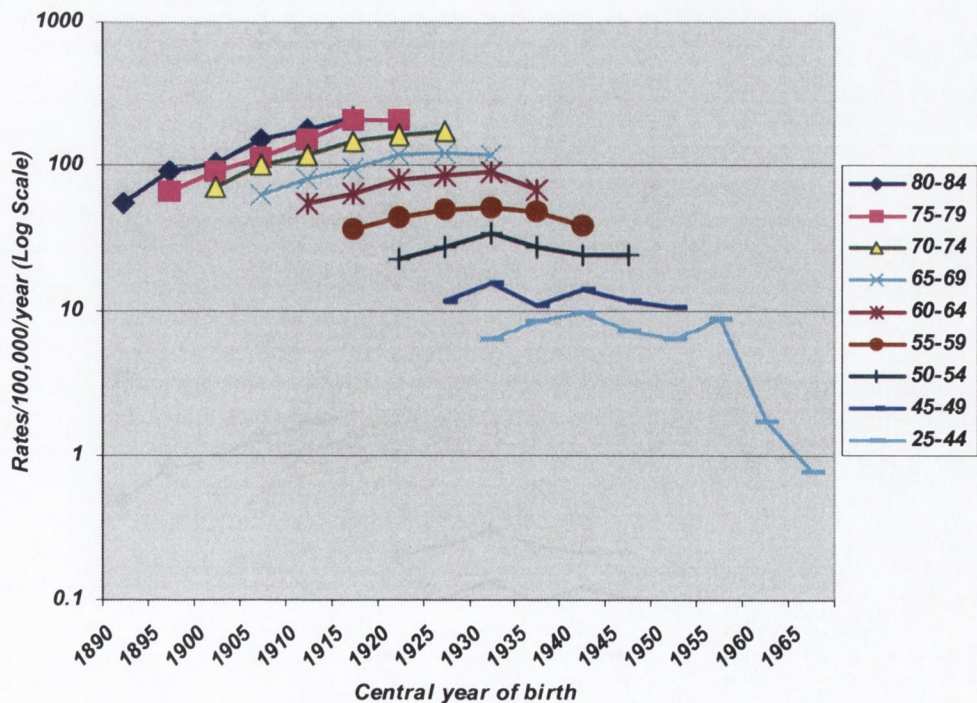


Figure 6.6. Female age-specific standardised lung cancer rates across different birth-cohorts in the Republic of Ireland (log scale).



Figures 6.3-6.6 (age-specific lung cancer rates across birth-cohorts):

In the Republic of Ireland, the age-specific lung cancer death rates were relatively higher among males across all age-cohorts (same age groups across different calendar periods of birth), but were highest among the oldest age-cohorts (80-84 year olds) for both sexes. All the age-specific rates were showing a decline across different age-cohorts for both sexes, except for the oldest age-cohorts in females. Rates in the oldest male age-cohorts decelerated after peaking around 1905, while a stabilisation in rates was observed among the oldest female age-cohorts. Such observations suggest that the future lung cancer death rates in the Republic of Ireland would be strongly influenced by the patterns observed across the oldest age-cohorts of both sexes.

The log scales showed a more realistic picture of the changing lung cancer rates across different age-cohorts, unlike the conventional age-standardised rates on normal scales, especially among the youngest age-cohorts, whose rates were relatively lower. Also, the observed 'parallelism' in the age-specific rates of both sexes across all their age-cohorts signifies minimal interaction (on log scale).

In summary, the figures from 6.3 to 6.6 show the significance of calculating age-specific lung cancer rates by the year of birth on log scales in particular. These are more suggestive of an underlying age-cohort phenomenon in lung cancer rates, as well as reflecting indirectly the future trends in lung cancer rates. So an age-cohort modelling should be the next step to justify an underlying age-cohort phenomenon, rather than presenting age-standardised lung cancer death rates alone.

6.3.3 Estimated-Annual-Percent-Changes (EAPC) in Lung Cancer

Death Rates (Joinpoint Modelling):

Table 6.1. EAPC (Estimated Annual Percent Changes) with 95% CI (Confidence Intervals) of Lung Cancer Death Rates and Joinpoint Analysis among Males: age-specific and age-standardised rates in the Republic of Ireland: 1970-1999.

Age-Specific	EAPC (95% CI) 1970-1999	Trend 1 Years	(First slope) EAPC (95% CI)	Trend 2 Years	(Second slope) EAPC (95% CI)
30-39	-4.0 (-5.0; -3.0)	1970-1977	-7.9 (-14.8; -0.3)	1977-1999	-3.1 (-4.8; -1.4)
40-49	-2.5 (-3.5; -1.4)	1970-1983	-0.7 (-4.2; 2.8)	1983-1999	-3.9 (-6.5; -1.1)
50-54	-2.3 (-2.9; -1.6)	1970-1984	-0.6 (-2.5; 1.3)	1984-1999	-3.9 (-5.6; -2.0)
55-59	-1.5 (-2.1; -0.8)	1970-1982	1.1 (-0.9; 3.2)	1982-1999	-3.2 (-4.5; -1.8)
60-64	-1.1 (-1.7; -0.5)	1970-1988	0.3 (-0.6; 1.2)	1988-1999	-4.2 (-6.2; -2.1)
65-69	-0.04 (-0.4; 0.3)	1970-1985	1.1 (0.3; 2.0)	1985-1999	-1.3 (-2.2; -0.4)
70-74	0.5 (-0.1; 1.1)	1970-1984	3.1 (1.9; 4.3)	1984-1999	-1.6 (-2.5; -0.6)
75-79	1.2 (0.4; 2.0)	1970-1976	14.7 (7.6; 22.2)	1976-1999	0.1 (-0.5; 0.7)
80-84	3.0 (1.9; 4.0)	1970-1985	8.1 (6.3; 9.9)	1985-1999	-0.8 (-2.1; 0.5)
85+	7.7 (6.3; 9.2)	1970-1989	11.0 (8.8; 13.3)	1989-1999	-0.2 (-5.4; 5.3)
Age-Standardised					
Overall (0-85+)	0.05 (-0.3; 0.4)	1970-1990	0.8 (0.4; 1.2)	1990-1999	-2.4 (-3.5; -1.2)
Truncated (30-84)	0.9 (0.3; 1.4)	1970-1985	3.2 (2.5; 3.9)	1985-1999	-1.6 (-2.4; -0.9)

Table 6.2. EAPC (Estimated Annual Percent Changes) with 95% CI (Confidence Intervals) of Lung Cancer Death Rates and Joinpoint Analysis among Females: age-specific and age-standardised rates in the Republic of Ireland: 1970-1999.

Age-Specific	EAPC (95% CI) 1970-1999	Trend 1 Years	(First slope) EAPC (95% CI)	Trend 2 Years	(Second slope) EAPC (95% CI)
30-39	-1.1 (-2.5; 0.3)	1970-1990	-3.3 (-6.0; -0.6)	1990-1999	5.4 (-3.0; 14.4)
40-49	-1.2 (-2.5; 0.1)	1970-1993	-0.7 (-2.7; 1.4)	1993-1999	-4.8 (-17.6; 9.8)
50-54	-0.6 (-1.6; 0.3)	1970-1979	4.1 (-1.2; 9.6)	1979-1999	-1.9 (-3.3; -0.6)
55-59	-0.3 (-1.4; 0.8)	1970-1983	3.6 (0.5; 6.9)	1983-1999	-3.1 (-5.3; -0.8)
60-64	0.5 (-0.4; 1.4)	1970-1988	3.1 (2.0; 4.3)	1988-1999	-4.6 (-6.8; 2.4)
65-69	2.0 (1.2; 2.8)	1970-1983	4.8 (2.0; 7.6)	1983-1999	0.4 (-1.2; 1.9)
70-74	2.3 (1.6; 3.1)	1970-1988	4.0 (2.6; 5.5)	1988-1999	-0.4 (-2.7; 1.9)
75-79	4.0 (3.1; 4.9)	1970-1990	5.8 (4.3; 7.3)	1990-1999	0.3 (-2.7; 3.4)
80-84	4.2 (3.5; 5.0)	1970-1993	5.1 (4.0; 6.3)	1993-1999	0.1 (-5.1; 5.6)
85+	5.6 (3.8; 7.4)	1970-1975	-5.2 (-23.4; 17.1)	1975-1999	6.7 (4.6; 8.8)
Age-Standardised					
<i>Overall (0-85+)</i>	2.4 (2.0; 2.8)	1970-1989	3.3 (2.7; 3.9)	1989-1999	0.1 (-1.3; 1.6)
<i>Truncated (30-84)</i>	2.7 (2.3; 3.2)	1970-1989	3.9 (3.4; 4.6)	1989-1999	-0.3 (-1.9; 1.3)

Tables 6.1 and 6.2 (EAPC)

Both sexes show an annual decline in lung cancer death rates across the relatively younger age groups (less than 64 years), as opposed to the older age groups from 1970 to 1999. The oldest adults (85+ years) have the greatest overall annual rise in lung cancer death rates across both sexes (sharper among males).

On Joinpoint analyses (two slope segments), there are significant changes in the direction of annual death rates in two specific time-periods for both sexes across all age groups. This can be demonstrated in the period 1990-1999. All the age groups of male lung cancer deaths show an annual decline in their lung cancer death rates, including the oldest adults (85+ years). By contrast, the oldest female adults (85+ years) alone show a sharper annual rise in the death rates in the most recent decade.

Likewise, the overall age-standardised lung cancer death rates (0-85+ years) show an annual rise across both sexes from 1970 to 1999 (more significantly among females). On Joinpoint analyses (two slope segments), again there is a significant change in the direction of the overall annual age-standardised lung cancer death rates. This is demonstrated by the deceleration in the annual rise of age-standardised lung cancer death rates in the most recent decade (1990-1999) in females, but a declining trend in the annual age-standardised lung cancer death rates among males in the most recent decade. However, the truncated (30-84 age groups) age-standardised lung cancer death rates among females have begun showing a declining trend in the period of 1990-1999, predicting an overall encouraging trend in lung cancer death rates in the future across the Republic of Ireland.

6.3.4 EAPC and Lagged Age-Specific Annual Smoking Prevalence

Figure 6.7. Male age-standardised lung cancer death rates (25-44 age groups) and lagged (10-year lag) age-specific smoking prevalence in the same period: 1971-1994.

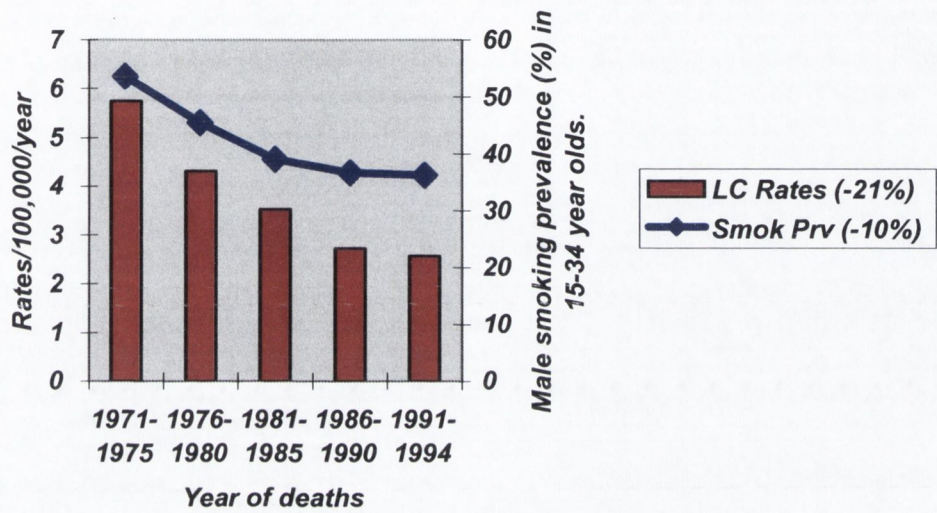
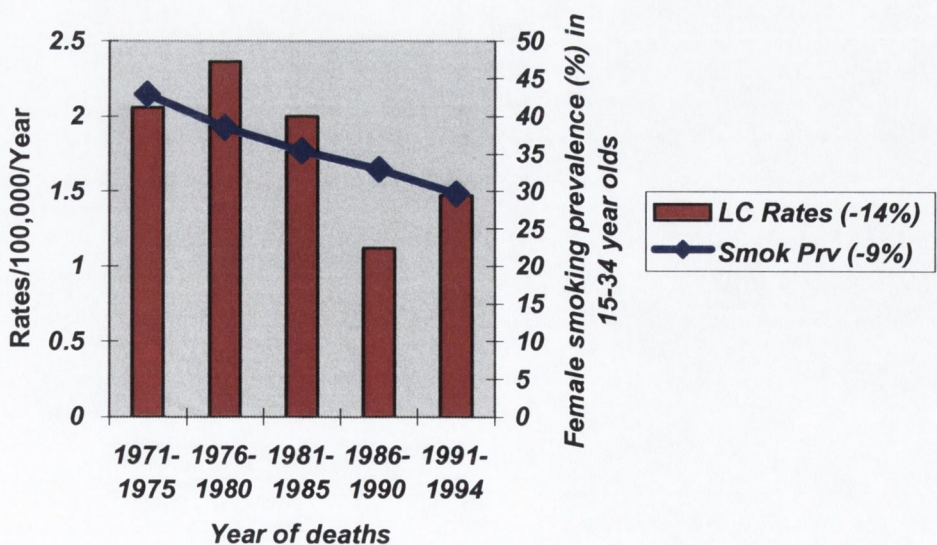


Figure 6.8. Female age-standardised lung cancer death rates (25-44 age groups) and lagged (10-year lag) age-specific smoking prevalence in the same period: 1971-1994.



Figures 6.7 & 6.8 (25-44 age groups across both sexes):

Overall, males had higher age-standardised lung cancer death rates (25-44 age groups), and also greater five-year declining lung cancer death rates compared to their female counterparts. Although the lagged (10-year lag) age-specific smoking prevalence rates were not similar across both sexes, the five-year reduction in smoking prevalence rates was similar (-10%) across both sexes during the same period. Such observations suggest that despite using a lagged age-specific smoking prevalence rate (a better estimate than using the age-specific smoking prevalence rate alone to adjust for the long latency period when historical smoking prevalence data are not available), females show a slower annual decline in lung cancer death rates for the same degree of fall in annual smoking prevalence rates.

Figure 6.9. Male age-standardised lung cancer death rates (45-64 age groups) and lagged (20-year lag) age-specific smoking prevalence in the same period: 1971-1994.

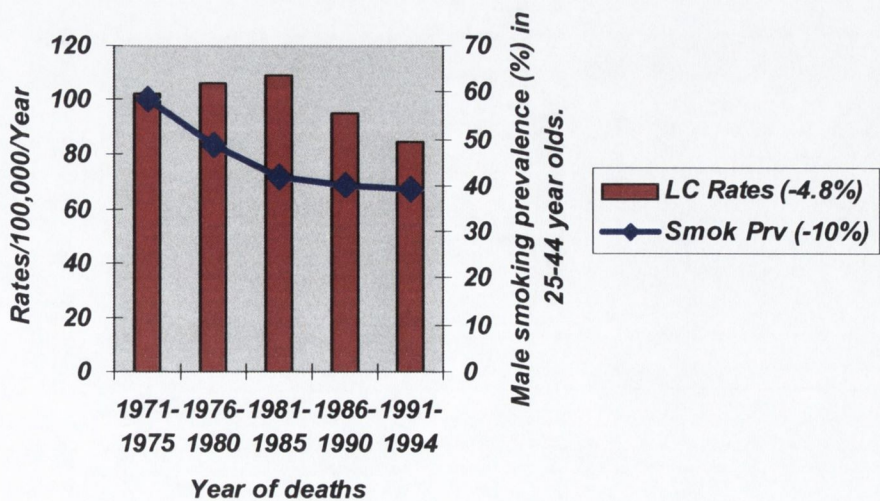
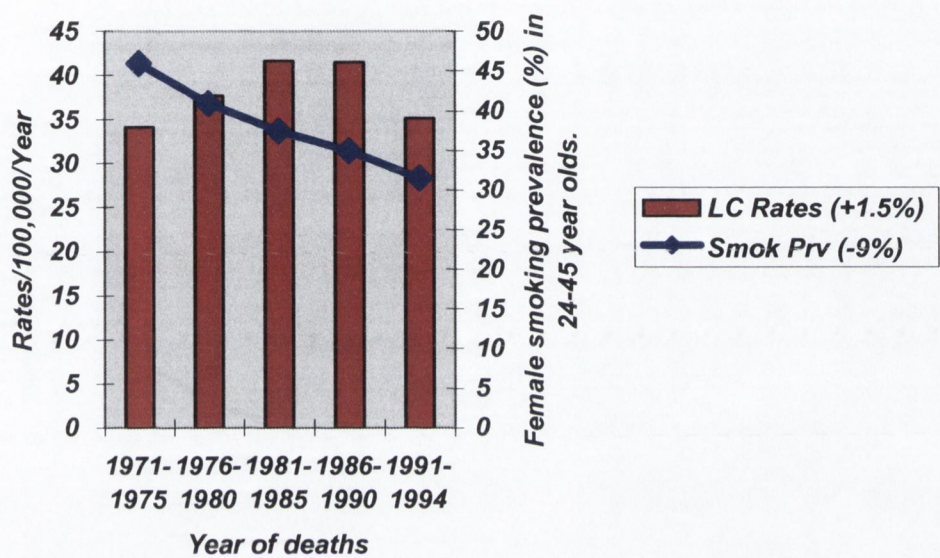


Figure 6.10. Female age-standardised lung cancer death rates (45-64 age groups) and lagged (20-year lag) age-specific smoking prevalence in the same period: 1971-1994.



Figures 6.9 & 6.10 (45-64 age groups across both sexes):

Females had lower age-standardised lung cancer death rates among the relatively young adults (45-64 age groups), but they were rising over the periods studied (1.5%), unlike their male counterparts (-4.8%). Although the lagged (20-year lag) age-specific smoking prevalence rate was relatively higher among males throughout the study period, their five-year declining rate was again broadly similar (-9 to -10%) across both sexes over the same periods. Therefore, the rising lung cancer death rates among the relatively young female adults (45-64 age groups) would not be adequately explained by the differential impact of a changing smoking prevalence across gender alone for the periods studied in the Republic of Ireland.

Figure 6.11. Male age-standardised lung cancer death rates (65-84 age groups) and lagged (30-year lag) age-specific smoking prevalence in the same period: 1971-1994.

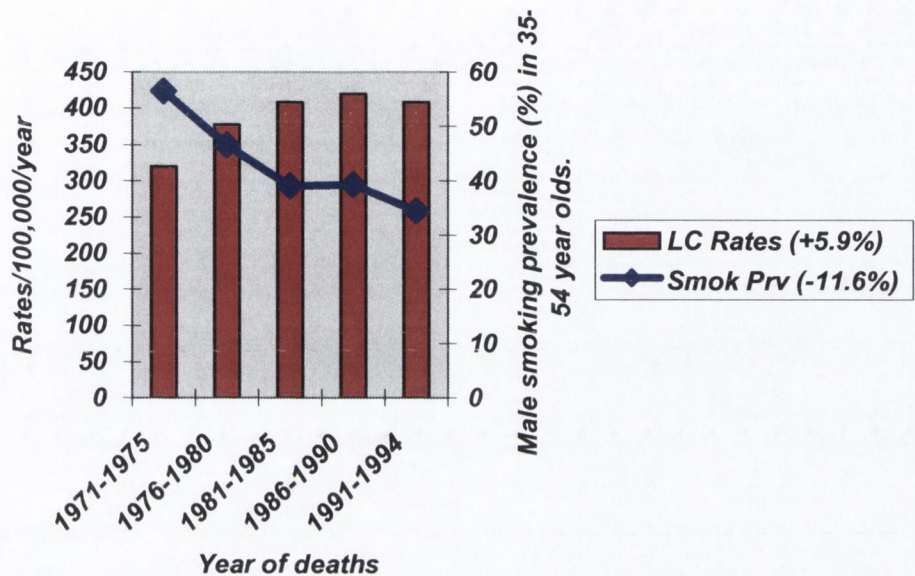
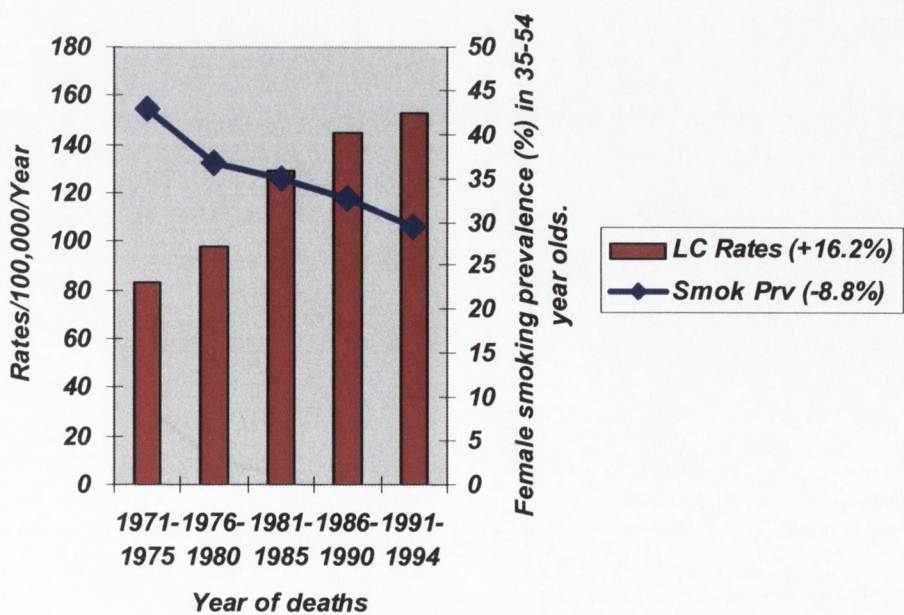


Figure 6.12. Female age-standardised lung cancer death rates (65-84 age groups) and lagged (30-year lag) age-specific smoking prevalence in the same period: 1971-1994.



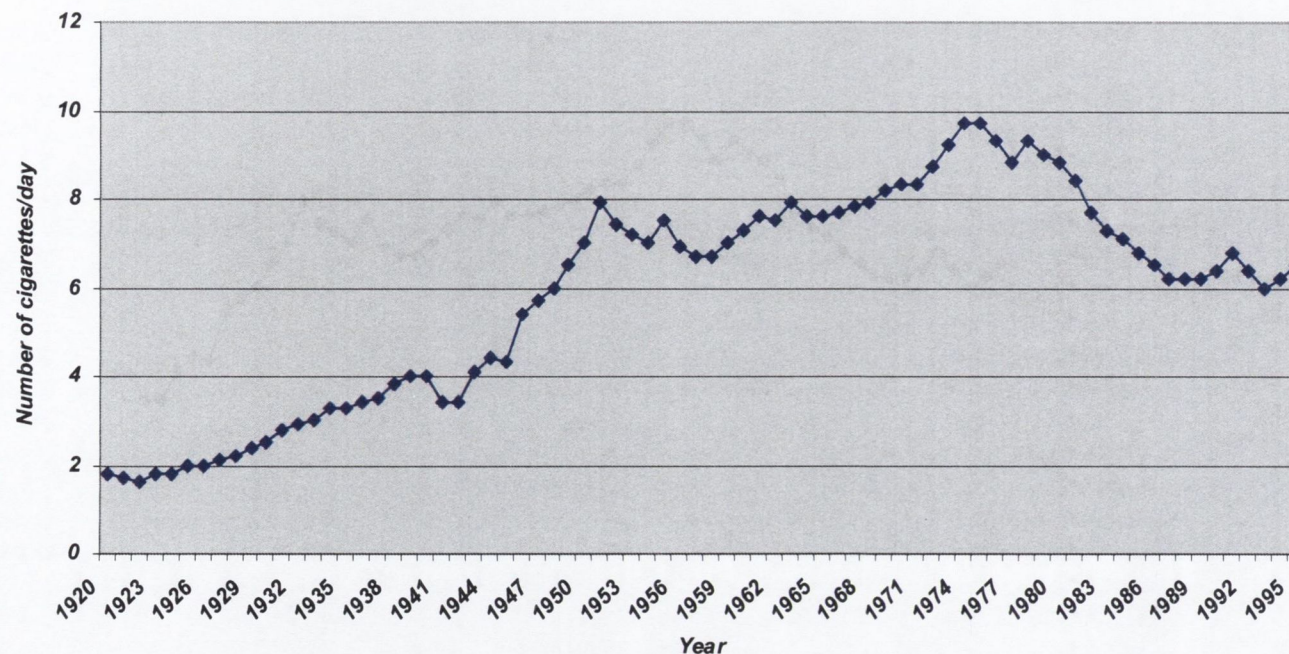
Figures 6.11 & 6.12 (65-84 age groups across both sexes):

The lung cancer death rates among the older female adults (65-84 age groups) were lower, but were increasing at a greater rate (16.2%) than their male counterparts (5.9%). By contrast, the lagged (30-year lag) smoking prevalence rates for the same age groups were higher among males, but there was broadly a similar five-year reduction rate across both sexes (-9 to -11%).

In summary, all the above six figures (6.7-6.12) suggest the apparent inconsistencies in using annual smoking prevalence rates as an indicator for the annual changing pattern of lung cancer death rates across gender for all age groups (especially in those above 65 years) at the national level. Lung cancer death rates change in a cohort-wise fashion across successive generations. This indicates the significance of using lifetime cumulative cigarette consumption across different birth-cohorts, as done in the subsequent analyses.

**6.3.5 Birth-cohort modelling for lung cancer risk estimation by
gender and smoking**

Figure 6.13. Per-capita annual cigarette consumption among adults (15 years and above) in the Republic of Ireland: 1920-1995.¹⁶



¹⁶ Forey B, Hamling J, Lee P, Wald N. In: *International Smoking Statistics: a collection of historical data from 30 economically developed countries* (Second Edition). London: Oxford University Press, 2002.

Figure 6.14. Relative Risks (RR) of total lung cancer deaths in the Republic of Ireland across different birth-cohorts (age and gender-adjusted), before and after controlling for smoking (cumulative cigarette consumption in pack years).

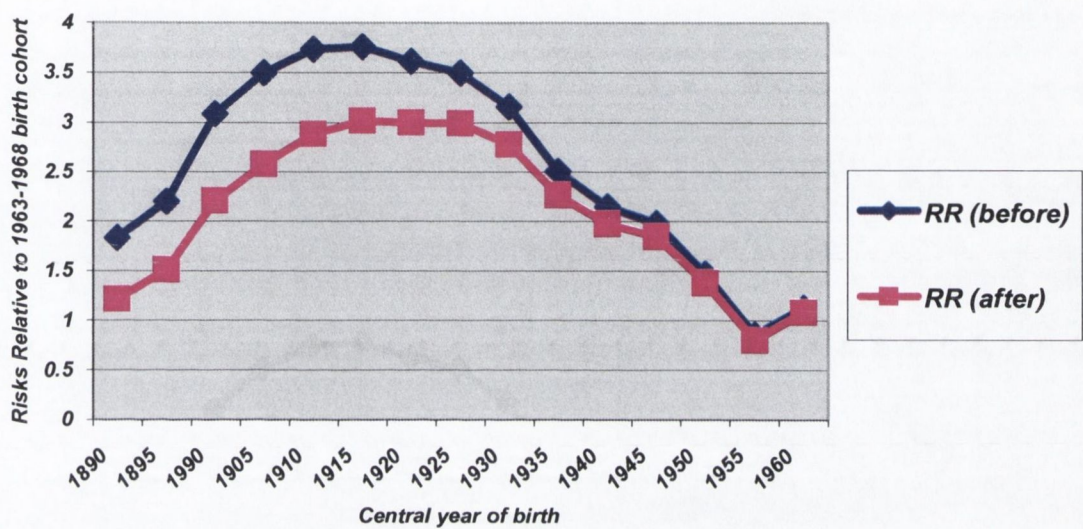


Figure 6.15. Relative Risks (RR) of lung cancer deaths (age-adjusted) in the Republic of Ireland by gender and birth-cohorts, before and after adjusting for cumulative lifetime cigarette consumption.

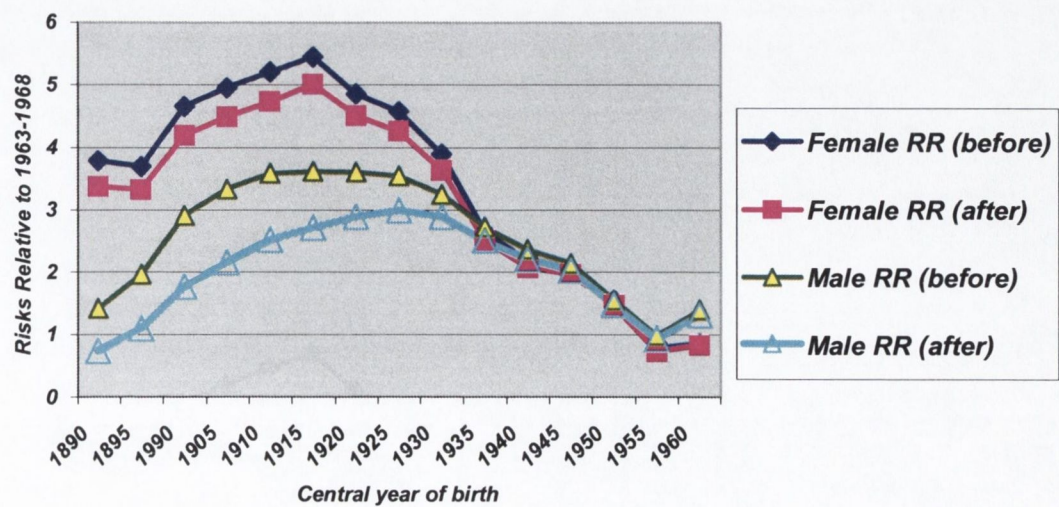


Table 6.3. Relative Risk (RR) estimates with 95% Confidence Intervals (CI) of Total Lung Cancer deaths in the Republic of Ireland across different birth-cohorts, before and after their adjustment for cumulative smoking (adult per-capita annual cigarette consumption units in pack-years).

<i>Birth-Cohorts</i>	<i>Adjusted for Age & gender</i>	<i>Adjusted for age, gender & Smoking</i>
<i>Central year of birth</i>	<i>RR (95% CI)</i>	<i>RR (95%CI)</i>
1888-1892	1.83 (0.93, 3.60) *	1.22 (0.50, 2.98) *
1893-1897	2.20 (1.18, 4.12)	1.52 (0.69, 3.38) *
1898-1902	3.08 (1.71, 5.54)	2.21 (1.09, 4.48)
1903-1907	3.49 (2.02, 6.04)	2.58 (1.36, 4.90)
1908-1912	3.73 (2.23, 6.22)	2.88 (1.65, 5.04)
1913-1917	3.76 (2.33, 6.06)	3.02 (1.83, 4.98)
1918-1922	3.61 (2.31, 5.62)	3.00 (1.92, 4.70)
1923-1927	3.49 (2.31, 5.27)	2.99 (1.99, 4.49)
1928-1932	3.15 (2.15, 4.62)	2.78 (1.92, 4.03)
1933-1937	2.50 (1.76, 3.57)	2.27 (1.61, 3.19)
1938-1942	2.15 (1.55, 2.98)	1.98 (1.44, 2.71)
1943-1947	1.98 (1.45, 2.70)	1.85 (1.37, 2.50)
1948-1952	1.47 (1.09, 1.99)	1.39 (1.03, 1.86)
1953-1957	0.86 (0.58, 1.28) *	0.81 (0.56, 1.19) *
1958-1962	1.13 (0.81, 1.57) *	1.09 (0.79, 1.50) *
1963-1967	Reference (RR=1)	Reference (RR=1)
<i>Deviance (Goodness of Fit)</i>	<i>1.60</i>	<i>1.47</i>
<i>Cohort Effect</i>	<i>p<0.0001</i>	<i>p<0.0001</i>
<i>Smoking Estimate</i>	<i>Not Applicable</i>	<i>-98.5% (p=0.002)</i>

* Not Statistically Significant

Table 6.4. Relative Risk (RR) estimates with 95% Confidence Intervals (CI) of Male Lung Cancer deaths in the Republic of Ireland across different birth-cohorts, before and after their adjustment for cumulative smoking (adult per-capita annual cigarette consumption units in pack-years).

<i>Birth-Cohorts</i>	<i>Adjusted for age alone</i>	<i>Adjusted for age & smoking</i>
<i>Central year of birth</i>	<i>RR (95% CI)</i>	<i>RR (95%CI)</i>
1888-1892	1.42 (0.64, 3.13) *	0.74 (0.27, 2.04) *
1893-1897	1.96 (0.94, 4.09) *	1.10 (0.44, 2.73) *
1898-1902	2.91 (1.47, 5.81)	1.77 (0.78, 3.98) *
1903-1907	3.33 (1.75, 6.37)	2.15 (1.02, 4.51)
1908-1912	3.58 (1.96, 6.58)	2.51 (1.30, 4.84)
1913-1917	3.61 (2.05, 6.38)	2.71 (1.49, 4.91)
1918-1922	3.60 (2.12, 6.13)	2.88 (1.67, 4.94)
1923-1927	3.54 (2.16, 5.81)	2.98 (1.82, 4.89)
1928-1932	3.25 (2.05, 5.16)	2.88 (1.83, 4.53)
1933-1937	2.72 (1.76, 4.19)	2.50 (1.64, 3.81)
1938-1942	2.36 (1.58, 3.53)	2.21 (1.49, 3.26)
1943-1947	2.14 (1.45, 3.15)	2.03 (1.39, 2.96)
1948-1952	1.56 (1.06, 2.28)	1.48 (1.02, 2.15)
1953-1957	0.99 (0.60, 1.60) *	0.93 (0.58, 1.49) *
1958-1962	1.40 (0.93, 2.10) *	1.31 (0.88, 1.95) *
1963-1967	Reference (RR=1)	Reference (RR=1)
Deviance (Goodness of Fit)	1.49	1.38
Cohort Effect	p<0.0001	p<0.0001
Smoking Estimate	NA	-94.6%(p=0.002)

* Not Statistically Significant

Table 6.5. Relative Risk (RR) estimates with 95% Confidence Intervals (CI) of Female Lung Cancer deaths in the Republic of Ireland across different birth-cohorts, before and after their adjustment for cumulative smoking (adult per-capita annual cigarette consumption units in pack-years).

<i>Birth-Cohorts</i>	<i>Adjusted for age alone</i>	<i>Adjusted for age & smoking</i>
<i>Central year of birth</i>	<i>RR (95% CI)</i>	<i>RR (95%CI)</i>
1888-1892	3.78 (1.29, 11.08)	3.37 (0.65, 17.46) *
1893-1897	3.69 (1.37, 9.99)	3.32 (0.77, 14.34) *
1898-1902	4.65 (1.84, 11.76)	4.19 (1.16, 15.12)
1903-1907	4.95 (2.09, 11.75)	4.49 (1.43, 14.10)
1908-1912	5.20 (2.33, 11.61)	4.73 (1.79, 12.52)
1913-1917	5.44 (2.59, 11.43)	5.01 (2.16, 11.65)
1918-1922	4.85 (2.45, 9.63)	4.51 (2.18, 9.34)
1923-1927	4.57 (2.43, 8.57)	4.26 (2.27, 7.99)
1928-1932	3.89 (2.18, 6.92)	3.64 (2.11, 6.29)
1933-1937	2.65 (1.57, 4.49)	2.52 (1.54, 4.11)
1938-1942	2.19 (1.36, 3.54)	2.08 (1.34, 3.24)
1943-1947	2.07 (1.33, 3.23)	1.98 (1.31, 2.99)
1948-1952	1.55 (1.02, 2.37)	1.48 (1.00, 2.21)
1953-1957	0.79 (0.45, 1.38) *	0.74 (0.43, 1.29) *
1958-1962	0.86 (0.54, 1.37) *	0.84 (0.53, 1.32) *
1963-1967	Reference (RR=1)	Reference (RR=1)
Deviance (Goodness of Fit)	1.23	1.19
Cohort Effect	p<0.0001	p<0.0001
Smoking Estimate	NA	0.1%(p=0.07)

*Not Statistically Significant

Birth-Cohort Analysis (lung cancer risks):

In the Republic of Ireland, individuals born in 1913-1917 (around the World War I) had the highest lung cancer risks. These estimates are based on a Poisson distribution of lung cancer death rates from 1970 to 1999. Following adjustment for cigarette consumption, the observed lung cancer risk declined substantially (50% to 90% risk reduction) across both sexes until 1927, while a lesser risk reduction (5-30%) among those born after 1927 has been observed.

The overall lung cancer risk was relatively higher for females compared to their male counterparts across all birth-cohorts relative to their youngest birth-cohorts (born in 1963-1967). Lung cancer risk due to smoking has also reduced significantly (96%) across the male cohorts ($p=0.002$), but a moderate (0.1%) increased smoking risk has been estimated for female cohorts ($p=0.07$). Following adjustment for the cumulative cigarette consumption, females also showed a relatively lower reduction in lung cancer risk than those observed in their corresponding male counterparts.

The lung cancer risks among the relatively young birth-cohorts (especially those born after 1935) had almost a similar risk pattern for both sexes, irrespective of cigarette adjustment. Those individuals with the greatest lung cancer risk were born between 1913-1917 for both sexes, despite assuming a gender variation in smoking habits among the older birth-cohorts. The observed peak of those female birth-cohorts at the highest risk of developing lung cancer (1913-1917) showed no change following adjustment for cigarette consumption compared to their male counterparts. This suggests that factors other than gender variation in annual per-capita cigarette consumption alone would be contributing to such an observation.

6.4 DISCUSSION

This section discusses in-depth the main findings of lung cancer pattern observed in the Republic of Ireland from 1970 to 1999, although brief comments have been outlined following each table or figure in the third section on results.

The approaches employed for examining this particular study objective are both traditional and advanced methods of representing lung cancer death rates. However neither method is without limitations. As outlined in chapter one, the underlying aim of this study is also to describe epidemiologically as to whether there is any gender susceptibility to developing lung cancer in the Irish population. However, the lack of comprehensive information on smoking history in Ireland has meant that concrete conclusions cannot be made on a few aspects of this study. This is demonstrated by the lack of historical information on the gender-breakdown of annual per-capita cigarette consumption. Also, specific smoking topographical factors, such as age at initiation, age at quitting, proportions of smokers and non-smokers across all the birth-cohorts (1888-1967) included in this study population, are not comprehensively available.

Therefore, many of the conclusions drawn are based on epidemiological studies done elsewhere, as discussed in previous chapters (three to five). Such issues are also applicable to the findings discussed in subsequent chapters (seven to nine). Overall, this study design is ecological, with its inherent methodological limitation of ecological fallacy for utilising population-level data, also because individual-level data were not adequately available for this study population.

6.4.1 Lung Cancer Rates

The lung cancer death rate pattern suggests an upward trend in female lung cancer death rates, which may continue rising over the coming years in the Republic of Ireland. Such an observation indicates three possibilities: a demographic change, with longer survival rates in female lung cancer patients; delayed smoking debut for female populations in the Republic leading to an underlying age-cohort phenomenon; a changing lung cancer risk profile across successive generations for female populations in particular. Information on the longer survival rates for female lung cancer patients in the Republic is limited,²⁵ although such changes would have minimal contribution. The observed gender variation in lung cancer death rates by age, year of birth, and in the EAPCs, however, suggests an underlying age-cohort phenomenon in the Republic. Such a phenomenon is most likely attributable to a gender variation in changing smoking behaviour occurring in a cohort-wise fashion over successive generations, as reported elsewhere.^{24, 45, 46}

The study findings also indicate that annual changing smoking prevalence rate is not consistent with the annual lung cancer mortality rates across all age groups, although a lagged age-specific smoking prevalence was taken into account. Also, no gender variation was observed in the annual changing pattern of lagged age-specific smoking prevalence rates over the periods studied. Such findings are consistent with the fact that the changing annual smoking prevalence rate is not a better national indicator at the population level for adequately explaining an underlying age-cohort phenomenon in lung cancer, unlike the cumulative lifetime assessment of cigarette consumption across different birth-cohorts. No such comprehensive information has been produced before in the Republic of Ireland.

6.4.2 Lung Cancer Risks

This section discusses the importance of birth-cohort analyses in estimating lung cancer risks instead of lung cancer rates alone. It also shows the biological implication of incorporating cumulative lifetime cigarette consumption into an age-cohort modelling technique for better explanations.

Based on a simple age-cohort modelling technique, the study findings suggest that the older female birth-cohorts in the Republic of Ireland have experienced a different risk profile not only relative to their younger birth-cohorts, but also when compared with their male counterparts indirectly. Such a gender variation can be explained due to an underlying gender difference in a few of the specific smoking topographical factors. These include: variations in the duration of persistent smoking, gender variation in per-capita cigarette consumption, or even due to different inhalation patterns. Unfortunately, such information is not available for the Irish populations for the periods studied to enable one to draw robust conclusions.

The lung cancer deaths pattern in the Republic of Ireland is very similar to the UK data.²⁴⁵ Consistent with the UK pattern,²⁴⁵ the older birth-cohorts have started smoking in middle age in the Republic. The annual per-capita cigarette consumption substantially increased in the post-Second World War (1950 onwards) and peaked around the early 1970s in the Republic of Ireland, again similar to the UK pattern.¹⁶ The percentage of filter cigarettes across both countries was also similar (50% in the mid 1960s, reaching 90% in the early 1980s).¹⁶ The US pattern was slightly different: the average per-capita consumption was higher for each year; and the observed peak attained in the 1950s was also more sustained until the early 1970s. Unlike Ireland,

50% of the cigarettes were filter-tipped in the 1950s, and by the late 1970s 90% filter-tipped cigarettes were available across the US.¹⁶

The annual cigarette consumption across both sides of the Atlantic has a different temporal pattern.³⁵ The observed variations in their national lung cancer death rates would be due to gender differences in the cumulative consumption of cigarettes (including filter-tipped) throughout a person's lifetime. Consistent with the UK pattern,²⁴⁵ it is less likely that the majority of the older cohorts in the Republic of Ireland had persisted smoking until their death. Similar to the UK cohorts,²⁴⁵ the Irish cohorts born before 1950 would have had started smoking when they were in their mid-30s. If such cohorts had stopped smoking a few years earlier before their deaths, those born before and during the World War I would have had consumed higher amounts of cigarettes annually (figure 6.13). Likewise, those born during and after the World War II would have had consumed lesser amounts of cigarettes.

Therefore, the observed lung cancer risk pattern across different birth-cohorts in the Republic of Ireland is particularly reflective of a variation in the cumulative cigarette consumption throughout a person's lifetime, rather than an overall changing smoking behaviour, consistent with observations elsewhere.²⁷⁰ Although the older birth-cohorts would have smoked both cigars and pipes, whose patterns usually vary across gender,²⁴⁵ this study is restricted to the cumulative cigarette consumption alone, rather than cigars and pipe smoking.

Historically, it is not clear whether the Irish females started smoking 10-15 years later than their male counterparts did, as observed in North America and other

European countries.¹ It is also not clear whether there were any gender variations in the duration of smoking habits among the older generations in the Republic of Ireland. However, this study, and Joinpoint analysis in particular, shows that annual lung cancer rates among the oldest female adults (85+ year olds) are still rising, as opposed to a decline in the corresponding oldest male adults. This suggests that the Irish females did start smoking a few years later compared with their male counterparts.

Birth-cohort analysis (figure 6.15) shows that the peaking of female birth-cohort lung cancer risk pattern did not shift following adjustment for cumulative cigarette smoking. By contrast, there was a shift in peak across male birth-cohorts. As outlined earlier, the average per-capita cigarette consumption among the older female birth-cohorts may be similar, if not higher than their male counterparts, relative to their younger birth-cohorts.

In Glasgow where lung cancer death rate is one of the highest in Europe,²⁷⁷ the extreme rates were observed for women born after 1915 (during World War I), consistent with the birth-cohorts' lung cancer risk pattern in this study. This suggests an earlier smoking debut for older female birth-cohorts in the Republic. The female lung cancer risk estimates across specific birth-cohorts in this study corresponded well with similar birth-cohorts for male lung cancer risk pattern in a British study.²⁴ This again implies that the lung cancer risk pattern for older female birth-cohorts in the Republic is greater. A recent analysis also showed that the rates of all tobacco-attributed deaths (including lung cancer) from 1950 to 2000 in the Republic of Ireland had peaked during the same calendar period (1985) across both sexes for the older age cohorts (70-79 age groups in particular).⁷⁶

All these observations point that the older generations of both sexes in the Republic of Ireland started smoking broadly during the same calendar period. However, the reasons whether the older female birth-cohorts have had a greater lung cancer risk when compared with their male counterparts relative to their respective referent youngest birth-cohorts, are discussed subsequently.

The youngest birth-cohorts (1963-1967) in the Republic of Ireland were born when the average per-capita cigarette consumption was peaking (figure 6.13). The annual smoking prevalence across all age groups in the early 1970s was also at its peak.³⁵ Therefore those born after 1950 in the Republic of Ireland would have had started smoking quite young, probably in their teens, as observed in the UK.²⁴⁵ The Republic of Ireland was beginning to experience a rapid urbanization during the early 1970s, following its inclusion into the European Union in 1973. The country was also undergoing a changing life style pattern in the form of altered nutrition and increased mechanization. Consequently these youngest birth-cohorts (1963-1967) have had a relatively high exposure to environmental pollution in different forms: passive smoking (both in domestic and public settings), urban (ambient) and indoor air pollution, and asbestos exposure from massive building constructions.

Evidence suggests that exposure to passive smoking during childhood predisposes to developing lung cancer later in life, regardless of adult exposure.^{220,278} In addition, the referent youngest birth-cohorts (born in 1963-1967) used in this study analyses would have had started smoking (around 1980s) when the annual smoking prevalence across the general populations was declining in both sexes, with a relatively faster decline among male populations.³⁵

Furthermore, a recent prospective study in a US cohort (both males and females) aged 40-75 years at baseline (1986) showed no significant gender differences in the mean duration of smoking,¹⁷⁷ although evidence suggests that females in general have a lesser duration of smoking.²³⁰ Based on this US prospective study¹⁷⁷ and other studies,²³⁰ the older birth-cohorts in this study would comprise a relatively fewer proportion of female former smokers than in males, and a greater proportion of persistent smokers in females than in males.

Likewise, very few older female and male birth-cohorts in this study would have had started smoking before the age of 15 years, while the proportions of males and females who had stopped smoking for ten or more years would also be equivalent. Taken together, the background risk profile of the referent birth-cohorts (1963-1967) in this study have been relatively high among females in terms of their smoking status that provides an insight into the observed greater relative risk among the older female birth-cohorts when compared with their male counterparts (figure 6.15).

So far it is clear that the observed greater relative risk in lung cancer among the female birth-cohorts (older cohorts in particular) is not due to gender differences in the duration of smoking or due to age at initiation. It is also unlikely to be due to the average per-capita cigarette consumption among females. Gender variation, however, in smoking inhalation patterns is an important contributor to the observed gender differential in lung cancer risk pattern. If this particular condition is also ruled out, it can be confirmed that the observed higher relative lung cancer risk among the older female birth-cohorts (born before 1935) in the Republic of Ireland is due to gender difference in their background risk profile, rather than hypothesising that

females in general have a greater susceptibility to developing lung cancer, as observed elsewhere.^{230, 279} However, a recent prospective study demonstrated no gender variation in lung cancer risk pattern at a given level of cigarette consumption.¹⁷⁷

The smoking inhalation pattern is reported to differ across gender, although no such information is available for the Irish population. In general, females smoked and inhaled greater puff volume when filter cigarettes were introduced into the global market in the late 1950s and the 1960s.¹⁸⁸ Only 50% of the cigarettes were filter-tipped in the late 1960s in the Republic of Ireland,¹⁶ and the tar and nicotine content were also high during such periods, although the nitrate content was declining.

It is very unlikely that the older female birth-cohorts (born before 1935) in the Republic of Ireland have got enough opportunity to smoke filter-tipped cigarettes for a longer duration for the following reasons: delayed age of initiation (mid-30s), poor coverage of filter cigarettes between the two World Wars, filter-tipped cigarettes were relatively expensive, and the older generations were more inclined to remain with their traditional brands. Such anecdotal evidence also suggests that the older female cohorts have used a long cigarette holder device to smoke through, which were popular with female film stars in the 1960s.

The likelihood of changing smoking inhalation pattern due to the introduction of filter-tipped cigarettes alone was most unlikely among the older female birth-cohorts in the Republic of Ireland. In addition, studies have shown no gender difference in lung cancer risk pattern when non-inhalers were excluded.^{279, 280} Conversely, younger birth-cohorts would have had smoked filter-tipped cigarettes for

a longer duration. This may have an impact on the observed lung cancer pattern in the Republic of Ireland, particularly from 1990 onwards.

6.4.3 Summary and Conclusion

In summary, the proportions of persistent smokers among the older female birth-cohorts in the Republic of Ireland is relatively high compared to males, together with a fewer proportion of former smokers in older female birth-cohorts compared with males, as observed elsewhere.¹⁷⁷ This is also consistent with the fact that because historically more of the older male birth-cohorts worked outside the home, their opportunity to smoke was severely reduced compared to their female counterparts who stayed at home and could smoke at will. For similar reasons, older female birth-cohorts who were 'ever smokers' have consumed relatively greater numbers of cigarettes, if not similar to their male counterparts.

Evidence suggests that the older birth-cohorts are long-term smokers, while the youngest birth-cohorts are 'light' smokers and smoke for a shorter duration,²⁰⁵ although no such information is available for the Irish populations. The youngest female birth-cohorts would have had started smoking earlier, and consequently have had relatively fewer proportions of non-smokers, as reflected in their smoking prevalence during the same calendar periods in the Republic of Ireland.³⁵ Taken together, the observed higher relative risk in the older female birth-cohorts is a reflection of the difference in absolute risk in their referent groups, as observed elsewhere in similar epidemiological studies.²³⁰ So, it is unlikely that the observed higher relative risk in the older female birth-cohorts when compared with their male

counterparts is due to a greater female susceptibility to developing lung cancer in the Republic of Ireland.

Any underlying lung cancer pattern from 1990 onwards in the Republic of Ireland is reflective of those born after 1935, considering the long latency period of lung cancer development. However, those born after 1935 in the Republic of Ireland have a lung cancer risk profile that is independent of the adjustment for cumulative cigarette consumption. So the relatively young birth-cohorts (born after 1935), and particularly the youngest birth-cohorts (born in 1963-1967) have a lung cancer risk profile different from their older birth-cohorts in terms of smoking, which is still the predominant risk factor for lung cancer development. The lung cancer risk pattern for the most recent and also for the youngest birth-cohorts of the Republic of Ireland suggests emerging risk factors, in addition to active smoking, acting differentially to modify the lung cancer risk pattern across different age groups in a cohort-wise fashion within the Irish populations.

Furthermore, the older female birth-cohorts in the Republic of Ireland do not have a greater lung cancer risk compared with their male counterparts, because of an underlying gender difference in their background risk profile. Changing smoking habits as the predominant risk factor for lung cancer development have less influence on the relatively young birth-cohorts in the Republic of Ireland. Thus, it is worth considering any putative risk factors for lung cancer and also for cell-types in particular across populations where changing lifestyle pattern is compounded with rapid urbanization (Dublin City populations, for example).

Despite the inherent limitations of ecological analyses, the study findings helped to generate a new hypothesis for the younger birth-cohorts in the Republic of Ireland, i.e. they are less likely to develop lung cancer due to active smoking alone, although smoking is a strong residual confounder for such observations. The study findings also showed that the observed risks for the younger birth-cohorts are lower relative to their older birth-cohorts across both sexes. This suggests an overall declining lung cancer death pattern over the coming years in the Republic of Ireland, assuming no change in the current risk profile of the youngest birth-cohorts.

In conclusion, female lung cancer death rates would continue rising over the coming years across the Republic of Ireland because of the continual annual rise in rates among the older female adults in a cohort-wise fashion, until the rates level off and then begin to decline. A declining lung cancer risk pattern in the youngest birth cohorts in the Republic is encouraging, while a rising teenage smoking prevalence can be a disturbing trend for any future lung cancer pattern. However, the 2003 ISAAC data in the Republic of Ireland shows teenage smoking fell from 20% in 1995 to 13% in 2003 (*Pat Goodman Personal communication*). In addition, the recent Smoking Ban nationwide¹⁰⁶ will further minimise environmental tobacco exposure, which can also influence future lung cancer pattern. In summary, an encouraging trend in lung cancer pattern is expected over the coming years across the Republic of Ireland.

Chapter Seven

LUNG CANCER INCIDENCE BY HISTOLOGICAL SUB-TYPES IN THE REPUBLIC OF IRELAND

7.1 INTRODUCTION

This chapter deals with the lung cancer incidence pattern across major histological sub-types: Adenocarcinoma (AC), Squamous Cell Carcinoma (SQCC), Small Cell Carcinoma (SMCC), and Large Cell Carcinoma (LCC) in the Republic of Ireland from 1994 to 2001, as outlined in the study objective. The chapter describes in detail the methods employed to examine this issue and presents the findings with brief comments following each table/figure. Finally there is a discussion on the main findings of the epidemiological pattern of lung cancer incidence across major histological sub-types over an eight-year study period.

7.2 METHODS

This section describes the methods employed to examine the epidemiological pattern of lung cancer incidence by major histological sub-types in the Republic of Ireland from 1994 to 2001. The data source for lung cancer incidence data is explained, while the source of smoking prevalence and Irish Census population data have already been mentioned in the methods section of chapter six. Calculations of age-standardised incidence rates (ASIR) across specific cell-types, and also of male-to-female age-standardised incidence rate ratios (ASIRR) are explained. When estimating the risk for each cell-type across a specific study covariate, the remaining covariates are controlled for using a multivariable logistic regression model.

7.2.1 Source of cancer incidence data

The Irish National Cancer Registry Board located in Cork (Ireland) has been registering all cancers diagnosed since January 1st, 1994, in persons resident in the Republic of Ireland.²⁵ The Board has also registered deaths due to cancer since that time, and records the deaths, from whatever cause, of patients diagnosed as having cancer since January 1st, 1994. Reporting to the Registry is voluntary, and data collection is mainly active. The only information received passively at present is on notification forms returned by general practitioners. All other information is actively gathered by eighteen nurses trained in cancer registration methods who are employed by the Registry with title of Tumour Registration Officer (TRO). These TRO's are based in hospitals around the country. Each is responsible for gathering cancer data from a group of hospitals, and from other sources within a designated geographical area. Within their catchment areas, they liaise with hospital pathology and haematology laboratories, special clinics, hospital administrators and medical records staff, Hospital In-Patient Enquiry (HIPE) and casemix staff, and any other persons they consider to be a useful source of cancer registration data. They also maintain links with public health nurses and nursing homes in the community.

Most cancer cases (97%) are first recorded in hospital. The predominant source of notification of cases (81% of the total) is from reports provided by pathology departments within hospitals. HIPE has become a more significant source of information, with the proportion of cases reported from this source increasing from 6% in 1994 to 11% in 1998.²⁵ Death certificates are the most important non-hospital source of cancer cases (1.4% only). However, the importance of death certificates as a primary source of case notification has been decreasing from 1.8% (1994) cases to

0.9% cases (1998).²⁵ The Registry, at present, does not register a case based on death certification alone, but only after the diagnosis has been confirmed from another source. The Registry carries out internal quality control checks on the data throughout collection and processing. A simple capture-recapture method shows a completeness of around 96%. A more complex survival method also shows that registration completeness has reached an asymptotic level of just 96% at 2 years after diagnosis.²⁵ However, histological verification is a strong guarantee of the accuracy of the data. The level of histological verification in Ireland is quite high by international standards. The overall level of histological verification has been increasing steadily since 1994, from 88% to 89.5% in 1998,²⁵ although the level of histological verification is quite low for lung cancer (around 75%). The date, cause and place of death are all entered by linkage with death certificates and the ward data by linkage of the address with a national address database.

7.2.2 Lung cancer incidence data by histological sub-types

The Irish lung cancer incidence data from 1994 to 2001 were collected in electronic format (Excel) on a case-by-case basis from the National Cancer Registry Board located in Cork. Based on the morphology codes of the WHO International Histological Classification of Tumours,²⁸¹ invasive carcinomas of lung (ICD Codes: 9 [162] and 10 [C34]) were categorized into four major histological subtypes. They are: squamous cell carcinoma (ICD-O: 8051-52, 8070-76); small cell carcinoma (ICD-O: 8041-45); large cell carcinoma (ICD-O: 8011-12, 8020-21, 8030-33); and adenocarcinoma (ICD-O: 8050, 8140-246, 8260-571).

7.2.3 Study covariates for individual lung cancer patient

Variables such as age, gender, smoking status (former smokers, non-smokers, current smokers), urban cities of residence (Dublin, Cork, Limerick, and Galway), and year of diagnosis with lung cancer were collected for each patient from the Irish National Cancer Registry Board's incidence data. However, details on their smoking patterns (including the operational definitions of smoking status) were not available.

7.2.4 Estimation of age-standardised incidence rates

The year 2001 did not have the updated lung cancer incidence data, and thus was excluded for the estimation of ASIR. Incidence rates for total lung cancer cases by gender, together with their specific histological sub-types, were computed. The rates were age-adjusted for the Irish population data, and were also standardised to the European Population Standard²⁸² for better comparison (**Appendix seven**). ASIRs were also adjusted for smoking status, and were standardised to the annual smoking prevalence of the Irish population for the year 1994 by age groups and gender, as the baseline year. The annual age-specific gender-wise smoking prevalence for the year 1994 was obtained from the publication of Lee and colleagues.¹⁶

So the proportions of ever-smokers (former and current combined) developing lung cancer, with specific cell-types were calculated annually (based on the individual smoking status of the lung cancer incident cases, as notified to the Cancer Registry). Likewise, the proportions of never-smokers developing lung cancer (including the cell-types) were calculated annually to estimate the ASIRs from 1994 to 2000. However, the numbers in never-smoking group were too small to give stable estimates. EAPCs for each cell-types were also calculated.

7.2.5 Estimation of age-standardised incidence rate ratios

The underlying aim of this study is also to examine a possible gender susceptibility to developing lung cancer, therefore male-to-female ASIRR (with 95% confidence intervals) across different time-periods (1994-2000) were estimated. Such estimates were also calculated for squamous-cell lung carcinoma and to lung adenocarcinoma. The male-to-female ratios (with 95% confidence intervals) were calculated using a spreadsheet (quick-calc) developed by Rothman in 2002.²⁸³ Ratios more than one would generally indicate that males have higher lung cancer rates, thereby the less likelihood of supporting the hypothesis that females are more susceptible to developing lung cancer. Likewise, ASIRR between AC and SQCC were also calculated across different periods.

7.2.6 Multivariable logistic regression modelling

The various study covariates (age, gender, year of lung cancer diagnosis, smoking status and main urban locations of Dublin, Cork, Limerick and Galway) were available at the individual-level. The multivariable logistic regression modelling technique (with binary outcome variables of yes/no)²⁸⁴ was used. All the above independent variables to predict the risk estimates for each cell-type (the dependent variable) were entered into separate models that simultaneously controlled for the remaining study covariates, except for the particular cell-type of interest. The reference category for each variable was based on the existing knowledge of a particular exposure of interest having the least lung cancer risk. For example, never-smokers were used as the reference category relative to other sub-groups, such as former and current smokers for risk assessment. All such analyses were done using JMPIN (version 3.0) statistical software.²⁸⁵

7.3 RESULTS

This section describes in detail the results of the gender-breakdown of lung cancer incidence by major histological sub-types in the Republic of Ireland from 1994 to 2001. The first four sub-sections deal with the descriptive epidemiological pattern of lung cancer incidence by major histological sub-types (including age-standardised incidence rates and ratios). The last four sub-sections describe risk estimates for each of the lung cancer cell-types across four independent study variables (geographical location, age distribution, time-period distribution, and smoking status).

7.3.1 Percentage distribution of lung cancer cell-types by year in the Republic of Ireland: 1994-2001

Table 7.3.1	
Percentage distribution of lung cancer cell-types by year in the Republic of Ireland: 1994-2001	
Year	Total
1994	
1995	
1996	
1997	
1998	
1999	
2000	
2001	
Total	

Table 7.1. Male lung cancer incident cases (total LC), and their major cell-types: SQCC, SMCC, AC, LCC in the Republic of Ireland: 1994-2001.

<i>Year</i>	<i>SQCC No (%)</i>	<i>SMCC No (%)</i>	<i>AC No (%)</i>	<i>LCC No (%)</i>	<i>Total LC (100%)</i>
1994	385 (37)	126 (12)	125 (12)	50 (5)	1045
1995	343 (36)	113 (12)	110 (12)	32 (3)	948
1996	319 (33)	113 (12)	136 (14)	28 (3)	968
1997	319 (35)	116 (13)	127 (14)	30 (3)	923
1998	334 (33)	128 (13)	154 (15)	29 (3)	1006
1999	327 (34)	116 (12)	145 (15)	14 (2)	961
2000	271 (28)	135 (14)	138 (14)	17 (2)	972
2001	267 (31)	98 (12)	146 (17)	21 (2)	852
Total	2565(33)	945 (12)	1081(14)	221(3)	7675

Table 7.2. Female lung cancer incident cases (total LC), and their major cell-types SQCC, SMCC, AC, LCC in the Republic of Ireland: 1994-2001.

<i>Year</i>	<i>SQCC No (%)</i>	<i>SMCC No (%)</i>	<i>AC No (%)</i>	<i>LCC No (%)</i>	<i>Total LC (100%)</i>
1994	134 (27)	82 (17)	76 (15)	18 (4)	494
1995	111 (23)	95 (20)	70 (15)	22 (5)	481
1996	125 (25)	68 (14)	82 (16)	20 (4)	500
1997	128 (24)	95 (18)	86 (16)	12 (2)	526
1998	108 (20)	92 (17)	115 (21)	08 (1)	546
1999	104 (18)	105 (18)	109 (19)	14 (2)	568
2000	116 (20)	77 (13)	117 (20)	11 (2)	576
2001	116 (24)	78 (16)	96 (20)	12 (2)	492
Total	942 (23)	692 (17)	751 (18)	117 (3)	4183

Tables 7.1 & 7.2 (male vs. female):

In the Republic of Ireland, SQCC is still the most frequent lung cancer cell-type among both males (33%) and females (23%) for the periods studied (1994-2001). By contrast, AC is relatively higher among female populations across all the periods studied, but the proportions of AC are highest for both sexes in the most recent periods. In addition, the frequency of SMCC is higher among females (17%), while LCC is the least frequent lung cancer histological sub-type across both sexes (3%) in the Republic of Ireland for the periods studied.

7.3.2 Percentage distribution of lung cancer cell-types by smoking status in the Republic of Ireland

Table 7.3. Male lung cancer incident cases by smoking status across the major histological sub-types: AC, SQCC, SMCC, and LCC in the Republic of Ireland: 1994-2001.

	<i>Never-Smokers</i>	<i>Ex-Smokers</i>	<i>Current Smokers</i>	<i>Total</i>
<i>Sub-Types</i>	<i>No (%)</i>	<i>No (%)</i>	<i>No (%)</i>	<i>No (100%)</i>
AC	94 (10)	269 (30)	538(60)	901
SQCC	139 (6)	644 (29)	1450 (65)	2233
SMCC	58 (7)	178 (22)	568 (71)	804
LCC	10 (5)	57 (30)	123 (65)	190

Pearson’s Chi-Square value = 36.4; p<0.0001

Table 7.4. Female lung cancer incident cases by smoking status across the major histological sub-types: AC, SQCC, SMCC, and LCC in the Republic of Ireland: 1994-2001.

	<i>Never-Smokers</i>	<i>Ex-Smokers</i>	<i>Current Smokers</i>	<i>Total</i>
<i>Sub-Types</i>	<i>No (%)</i>	<i>No (%)</i>	<i>No (%)</i>	<i>No (100%)</i>
AC	153 (25)	143 (23)	326 (52)	624
SQCC	90 (11)	221 (27)	503 (62)	814
SMCC	59 (10)	127 (21)	407 (69)	593
LCC	15 (15)	23 (23)	61 (62)	99

Pearson’s Chi-Square value = 74.9; p<0.0001

Tables 7.3 & 7.4 (male vs. female):

In the Republic of Ireland, never-smokers have higher proportions of AC with regard to other lung cancer histological sub-types across both sexes, but are relatively higher in female populations (25% versus 10% in males). However, current smokers have the highest proportions of AC across both males (60%) and females (52%). Also, SQCC and SMCC are common among the current smokers of both sexes. Taken together, the proportions of AC seems to be relatively greater among the ever-smoking populations (both former and current smokers) than among the never-smoking populations in the Republic of Ireland across both sexes.

**7.3.3 Smoking Adjusted Age-Standardised Incidence Rates of Lung
Cancer cell-types in the Republic of Ireland: 1994-2000**

Figure 7.1. Female incidence rates (adjusted for age and smoking) for total lung cancer cases (total), and their major histological sub-types: AC, SQCC, and SMCC in the Republic of Ireland among ever-smokers: 1994-2000.

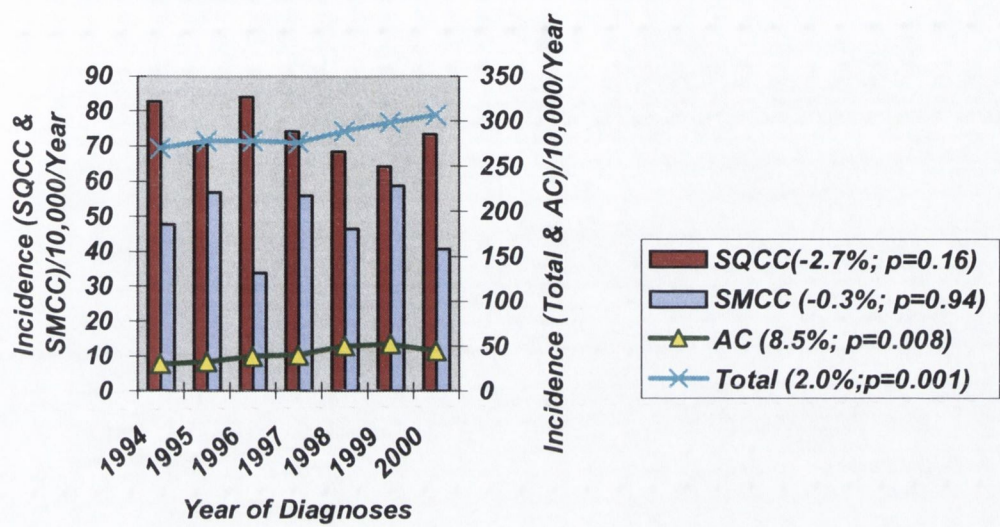
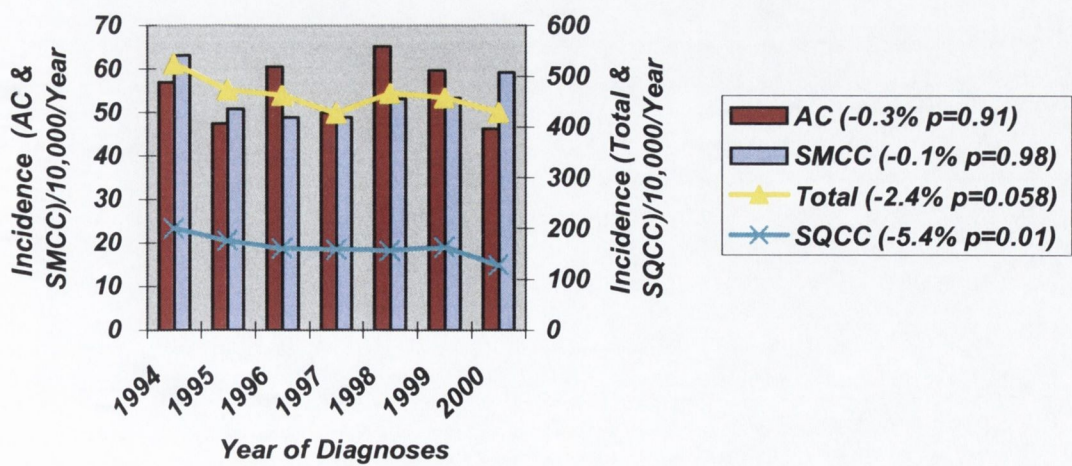


Figure 7.2. Male incidence rates (adjusted for age and smoking) for total lung cancer cases (total), and their major histological sub-types: AC, SQCC, and SMCC in the Republic of Ireland among ever-smokers: 1994-2000.



Figures 7.1 & 7.2 (male and female ever-smokers):

In the Republic of Ireland, the overall age-standardised lung cancer incidence across all the periods studied is higher among male ever-smokers than in female ever-smokers (both former and current). However, the total lung cancer incidence is significantly increasing (2% annually) in females, as opposed to an annual decline of 2.4% among males. In females, the significant increase (2%) in annual total lung cancer incidence corresponds to the significant annual increase (8.5%) in AC incidence, although the respective rates are different. By contrast, the annual decline (-2.4%) in total lung cancer incidence among males runs parallel with the significant annual decline in SQCC incidence (-5.4%), despite variations in annual incidence rates. So the Republic is experiencing a significant annual increase in AC incidence among female ever-smokers (on an average 10 cases/10,000 persons).

Figure 7.3. Female incidence rates (adjusted for age and smoking) for total lung cancer cases (total), and their major histological sub-types: AC, SQCC, and SMCC in the Republic of Ireland among non-smokers: 1994-2000.

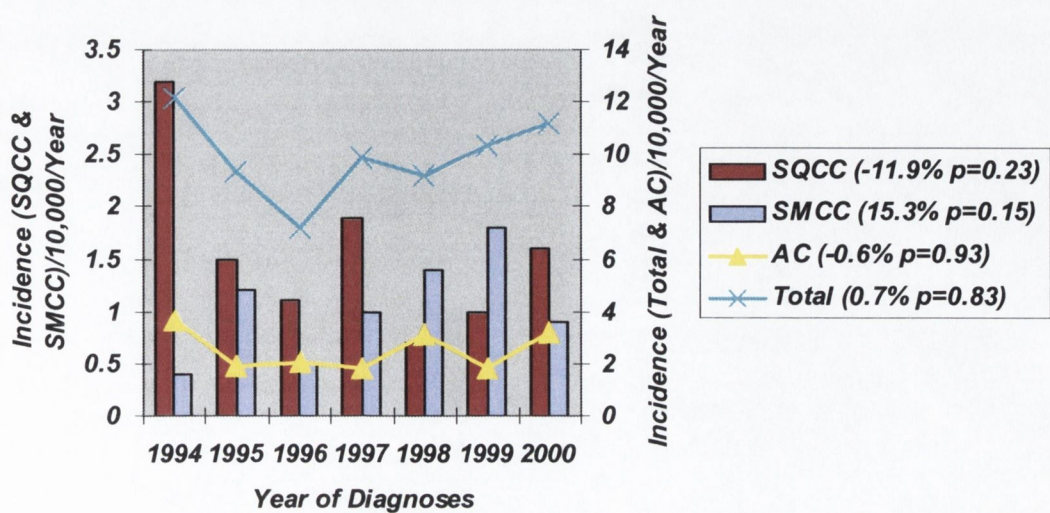
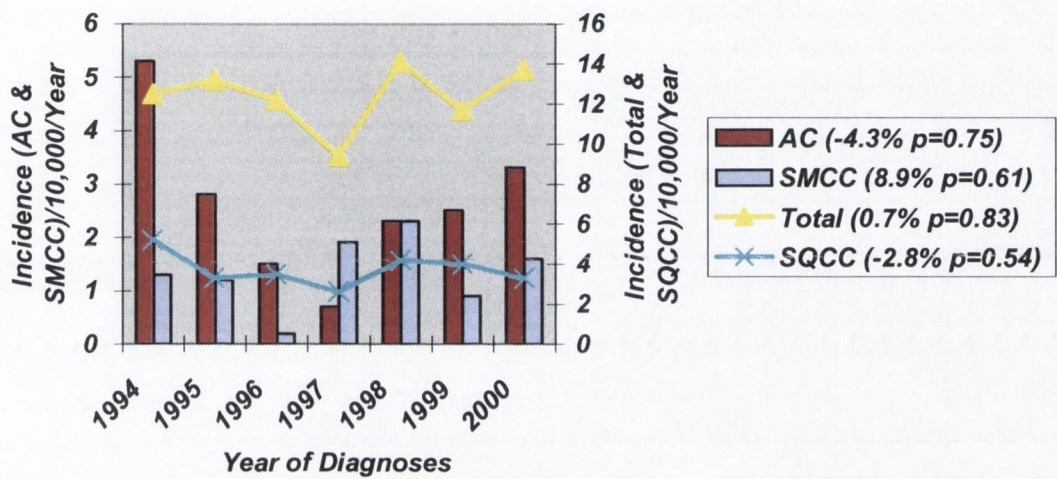


Figure 7.4. Male incidence rates (adjusted for age and smoking) for total lung cancers (total), and their major histological sub-types: AC, SQCC, and SMCC in the Republic of Ireland among non-smokers: 1994-2000.



Figures 7.3 & 7.4 (male and female non-smokers):

In the Republic of Ireland, the observed annual rise of age-standardised total lung cancer incidence among the non-smoking populations is similar across both sexes (0.7%), although not statistically significant. In addition, there is very little gender variation in never-smoking populations for their overall age-standardised annual incidence of all the major lung cancer histological sub-types, including the annual total age-standardised lung cancer incidence. However, SMCC incidence is increasing annually across both sexes for the periods studied (1994-2000).

**7.3.4 Male-to-Female (M: F) Standardised Incidence Rate Ratios of
Lung Cancer cell-types in the Republic of Ireland: 1994-2000**

Table 7.5. M: F Standardised Incidence Rate Ratios²⁸³ (age-adjusted) among ever smokers (former and current combined) for the total lung cancer cases, and for two of the major histological sub-types: 1994-2000.

	All cases	AC	SQCC
<i>Year</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>
1994	1.94 (1.78; 2.12)	1.87 (1.42; 2.43)	2.41 (2.09; 2.78)
1995	1.70 (1.55; 1.86)	1.47 (1.07; 1.93)	2.50 (2.15; 2.90)
1996	1.66 (1.52; 1.82)	1.57 (1.19; 2.01)	1.91 (1.62; 2.23)
1997	1.55 (1.40; 1.70)	1.26 (0.93; 1.66)	2.14 (1.81; 2.49)
1998	1.62 (1.47; 1.77)	1.30 (1.00; 1.65)	2.28 (1.94; 2.67)
1999	1.54 (1.40; 1.68)	1.14 (0.87; 1.47)	2.54 (2.16; 2.96)
2000	1.40 (1.27; 1.54)	1.04 (0.76; 1.38)	1.74 (1.46; 2.08)

²⁸³ Rothman K. Episheet. Available at: <http://members.aol.com/krothman/episheet.xls>.

Table 7.6. M: F Standardised Incidence Rate Ratios (age-adjusted) among never smokers for the total lung cancer cases, and for AC and SQCC: 1994-2000.

	All cases	AC	SQCC
<i>Year</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>
1994	1.02 (0.51; 1.72)	1.43 (0.44; 3.15)	1.63 (0.51; 3.65)
1995	1.42 (0.74; 2.39)	1.47 (0.33; 4.61)	2.20 (0.41; 5.84)
1996	1.69 (0.86; 2.91)	0.71 (0.12; 3.44)	3.18 (0.99; 9.31)
1997	0.95 (0.42; 1.73)	0.39 (0.01; 3.10)	1.37 (0.33; 4.61)
1998	1.53 (0.83; 2.55)	0.74 (0.08; 2.33)	6.00 (1.56; NC*)
1999	1.14 (0.60; 2.04)	1.39 (0.13; 4.01)	4.00 (1.09; NC*)
2000	1.22 (0.68; 2.10)	1.03 (0.19; 2.74)	2.06 (0.39; 5.48)

* NC: Could not be calculated because of extreme values

Tables 7.5 & 7.6:

Both these tables show the comparison between male and female ASIRR ²⁸³ for lung cancer, as well as for AC and SQCC among ever and never smoking populations. The incidence rate ratios are adjusted for both age and smoking. Statistically significant higher rate ratios are observed among ever-smokers, reflecting lower risks in female ever-smokers compared with their male counterparts. Also, there is gradual convergence in ASIRR in the most recent periods, suggesting an increasing trend among the females. The ASIRRs are relatively lower among never smokers, with very wide confidence intervals and unstable estimates, possibly due to small numbers. So the findings indicate that there is less likelihood of females having higher lung cancer risks, together with lower risks for AC when compared with males across the Republic of Ireland from 1994 to 2000.

**7.3.5 Age-Standardised Incidence Rate Ratios of AC: SQCC in the
Republic of Ireland: 1994-2000**

Table 7.7. Age-Standardised Incidence Rate Ratios (RR) of AC: SQCC among ever smokers (former and current combined) and never-smokers by gender distribution in the Republic of Ireland: 1994-2000.

	Smokers		Never-Smokers	
	Male	Female	Male	Female
Year	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95%CI)
1994	0.3 (0.2; 0.4)	0.4 (0.3; 0.5)	1.0 (0.4; 2.0)	1.2 (0.3; 3.2)
1995	0.3 (0.2; 0.3)	0.5 (0.3; 0.6)	0.8 (0.2; 2.3)	1.3 (0.2; 4.8)
1996	0.4 (0.3; 0.5)	0.5 (0.3; 0.6)	0.4 (0.1; 1.8)	1.9 (0.2; 6.6)
1997	0.3 (0.2; 0.4)	0.5 (0.4; 0.7)	0.3 (0.02; 1.8)	0.9 (0.1; 3.8)
1998	0.4 (0.3; 0.5)	0.7 (0.6; 0.9)	0.5 (0.08; 1.5)	4.4 (0.9; NC*)
1999	0.4 (0.3; 0.5)	0.8 (0.6; 1.0)	0.6 (0.90; 1.6)	1.8 (0.2; 7.2)
2000	0.4 (0.3; 0.5)	0.6 (0.5; 0.7)	1.0 (0.2; 2.3)	2.0 (0.4; 5.5)

* NC: Could not be calculated because of extreme values

Table 7.7 (males vs. females):

The age-standardised incidence rate ratios between AC and SQCC are less than unity, especially among smoking populations of both sexes, suggesting that SQCC incidence is still high among the Irish populations. However, the rate ratios are gradually approaching ‘unity’ among female ever-smokers (former and current smokers combined) in the most recent periods, indicating the recent annual rise in AC incidence among the female populations. Such ratios are also very high among female never-smoking populations, although they are not statistically significant.

7.3.6 Risk estimation of lung cancer cell-types by urban locations

Table 7.8 Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by urban locations in the Republic of Ireland: 1994-2001.

<i>Urban locations</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
Dublin	1.35 (1.21, 1.52) *	0.92 (0.84, 1.00)	1.15 (1.02, 1.29) *	1.28 (1.01, 1.63) *
Cork	1.13 (0.95, 1.33)	1.32 (1.17, 1.51) *	1.24 (1.04, 1.46) *	0.80 (0.52, 1.18)
Limerick	0.61 (0.44, 0.83) *	0.87 (0.72, 1.10)	0.74 (0.54, 1.00)	0.40 (0.14, 0.88) *
Galway	1.29 (0.99, 1.66)	0.96 (0.78, 1.18)	0.94 (0.70, 1.24)	1.53 (0.91, 2.43)
Rest of the Republic	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable
 (Outcome of interest: histological sub-types).

**Statistically Significant*

Table 7.9. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by urban locations in the Republic of Ireland among Males: 1994-2001.

<i>Urban locations</i>	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
Dublin	0.72 (0.66, 0.79) *	1.41 (1.22, 1.63) *	0.98 (0.88, 1.10)	1.11 (0.95, 1.30)	1.27 (0.95, 1.70)
Cork	0.96 (0.84, 1.09)	1.05 (0.84, 1.31)	1.46 (1.25, 1.70) *	1.19 (0.95, 1.47)	0.76 (0.44, 1.24)
Limerick	0.93 (0.76, 1.14)	0.55 (0.35, 0.83) *	0.91 (0.70, 1.17)	0.72 (0.47, 1.05)	0.23 (0.04,0.73)*
Galway	0.98 (0.80, 1.19)	1.26 (0.91, 1.73)	1.03 (0.81, 1.31)	0.94 (0.65, 1.33)	1.11 (0.54, 2.05)
Rest of Republic	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable

(Outcome of interest: histological sub-types).

**Statistically Significant*

Table 7.10. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by urban locations in the Republic of Ireland among Females: 1994-2001.

<i>Urban locations</i>	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
Dublin	1.39 (1.27, 1.51) *	1.28 (1.06, 1.53) *	0.76 (0.65, 0.90) *	1.20 (1.00, 1.45) *	1.31(0.87, 1.99)
Cork	1.04 (0.92, 1.18)	1.26 (0.96, 1.64)	1.03 (0.81, 1.31)	1.30 (0.99, 1.69)	0.89 (0.42, 1.72)
Limerick	1.07 (0.88, 1.31)	0.70 (0.42, 1.12)	0.82 (0.54, 1.21)	0.79 (0.47, 1.27)	0.77 (0.19, 2.15)
Galway	1.02 (0.84, 1.25)	1.33 (0.86, 2.02)	0.77 (0.50, 1.14)	0.96 (0.59, 1.51)	2.66 (1.19,5.35)*
Rest of Republic	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable
(Outcome of interest: histological sub-types).

**Statistically Significant*

Tables 7.8-7.10 (males vs. females):

Females living in Dublin City (the capital city of the Republic of Ireland) are one-and-half times (1.39) more likely to develop lung cancer compared to the rest of the Republic, after controlling for the potential confounders. Likewise, the general populations of Dublin City have one-and-half times (1.35) increased risk of developing AC when compared with the rest of the Republic. Males have a modest increased risk of developing AC (1.41) than females (1.39) living in Dublin City.

Males living in Cork City are one-and-half times (1.46) more likely to develop SQCC compared to the rest of the Republic, consistent with the overall risk pattern of SQCC (1.32) in Cork City. By contrast, females in Galway are two-and-half times more likely to develop LCC when compared with the rest of the Republic (2.66), which is higher than the overall risk of developing LCC in Galway across both sexes combined (1.53), after simultaneous adjustment for the potential risk factors. However, the Cork City populations have a modest increased risk of developing SMCC when compared to the rest of the Republic.

Taken together, the observed gender and geographical variations in the overall lung cancer risk development, as well as in the histological sub-types across the Republic of Ireland, suggest an underlying differential impact on lung cancer development of certain ‘urban’ risk factors for lung cancer that would be locally prevalent in excess.

7.3.7 Risk estimation of lung cancer cell-types by age distribution

Table 7.11. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by age distribution in the Republic of Ireland: 1994-2001.

<i>Age (in years)</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
0-54	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
55-59	0.70 (0.57, 0.85) *	1.38 (1.13, 1.68) *	0.93 (0.74, 1.16)	0.92 (0.57, 1.46)
60-64	0.50 (0.42, 0.61) *	1.59 (1.33, 1.90) *	0.95 (0.77, 1.16)	0.83 (0.54, 1.27)
65-69	0.49 (0.42, 0.59) *	1.60 (1.36, 1.89) *	0.85 (0.70, 1.02)	0.78 (0.53, 1.16)
70-74	0.40 (0.33, 0.47) *	1.53 (1.30, 1.80) *	0.64 (0.53, 0.78) *	0.90 (0.62, 1.32)
75+	0.26 (0.22, 0.31) *	1.24 (1.06, 1.45) *	0.48 (0.40, 0.57) *	0.51 (0.35, 0.76) *

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable

(Outcome of interest: histological sub-types).

**Statistically Significant*

Table 7.12. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by age distribution in the Republic of Ireland among Males: 1994-2001.

<i>Age (in years)</i>	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
0-54	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
55-59	1.21 (1.01, 1.46) *	0.69 (0.53, 0.90) *	1.44 (1.15, 1.82) *	1.01 (0.76, 1.35)	0.83 (0.43, 1.55)
60-64	1.14 (0.97, 1.35)	0.50 (0.39, 0.64) *	1.55 (1.26, 1.90) *	0.92 (0.71, 1.19)	0.92 (0.53, 1.61)
65-69	1.18 (1.01, 1.37) *	0.54 (0.44, 0.67) *	1.50 (1.23, 1.81) *	0.83 (0.65, 1.06)	1.03 (0.63, 1.72)
70-74	0.91 (0.79, 1.06)	0.43 (0.34, 0.53) *	1.44 (1.19, 1.74) *	0.65 (0.51, 0.84) *	1.05 (0.65, 1.76)
75+	0.85 (0.74, 0.98) *	0.30 (0.24, 0.37) *	1.08 (0.90, 1.29)	0.53 (0.42, 0.67) *	0.63 (0.39, 1.07)

**Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable
(Outcome of interest: histological sub-types).**

**Statistically Significant*

Table 7.13. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by age distribution in the Republic of Ireland among Females: 1994-2001.

<i>Age (in years)</i>	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
0-54	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
55-59	0.83 (0.69, 0.99) *	0.71 (0.50, 0.99) *	1.13 (0.74, 1.71)	0.82 (0.56, 1.18)	1.13 (0.54, 2.28)
60-64	0.88 (0.74, 1.03)	0.51 (0.37, 0.69) *	1.71 (1.21, 2.42) *	1.01 (0.73, 1.38)	0.71 (0.35, 1.42)
65-69	0.85 (0.73, 0.99) *	0.43 (0.32, 0.57) *	1.91 (1.39, 2.64) *	0.86 (0.64, 1.15)	0.42 (0.20,0.84)*
70-74	1.09 (0.94, 1.27)	0.35 (0.27, 0.46) *	1.77 (1.30, 2.42) *	0.62 (0.46, 0.83) *	0.69 (0.38,1.27)
75+	1.18 (1.02, 1.35) *	0.22 (0.17, 0.28) *	1.69 (1.26, 2.29) *	0.41 (0.31, 0.55) *	0.36 (0.19,0.67)*

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable

(Outcome of interest: histological sub-types).

**Statistically Significant*

Tables 7.11-7.13 (males vs. females):

Middle-aged male populations (55-69 age groups) in the Republic of Ireland have a modest increased risk of developing lung cancer compared to other age groups, following simultaneous adjustment for the potential risk factors. By contrast, the oldest female populations (more than 75 years) in the Republic of Ireland have a modest increased risk of developing lung cancer, after controlling for the potential risk factors available to this study.

There are variations in age distribution with regard to histological sub-types. This is shown in the younger population (less than 54 years) across both sexes, as they are more likely to develop AC. By contrast, the relatively older (more than 60 years) populations are one-and-half times more likely to develop SQCC across both sexes in the Republic of Ireland.

The findings also indicate that the older populations are less likely to develop SMCC, following simultaneous controlling for the potential risk factors studied. Taken together, the observed gender and age-variations in the risk of developing lung cancer, and also across the histological sub-types in particular, suggest the differential impact of the major risk factor for lung cancer smoking in particular on the natural course of lung cancer development across both sexes.

**7.3.8 Risk estimation of lung cancer cell-types by the year of
diagnosis**

Table 7.14. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by time-period in the Republic of Ireland: 1994-2001.

<i>Time-Period</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
1994-1995	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
1996-1997	1.19 (1.02, 1.38) *	0.93 (0.83, 1.03)	0.95 (0.82, 1.11)	0.75 (0.57, 0.99) *
1998-1999	1.38 (1.19, 1.60) *	0.83 (0.75, 0.93) *	1.02 (0.88, 1.18)	0.50 (0.37, 0.68) *
2000-2001	1.37 (1.18, 1.60) *	0.80 (0.71, 0.90) *	0.97 (0.83, 1.13)	0.51 (0.37, 0.70) *

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable
(Outcome of interest: histological sub-types).

**Statistically Significant*

Table 7.15. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by time-period in the Republic of Ireland among Males: 1994-2001.

<i>Time-Period</i>	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
1994-1995	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
1996-1997	0.90 (0.81, 1.00)	1.23 (1.01, 1.49) *	0.90 (0.79, 1.03)	1.03 (0.84, 1.25)	0.75 (0.53, 1.05)
1998-1999	0.86 (0.77, 0.95) *	1.35 (1.12, 1.62) *	0.89 (0.79, 1.02)	1.06 (0.87, 1.28)	0.53 (0.36,0.76)*
2000-2001	0.84 (0.75, 0.93) *	1.40 (1.16, 1.70) *	0.77 (0.67, 0.88) *	1.11 (0.91, 1.36)	0.52 (0.34,0.77)*

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable

(Outcome of interest: histological sub-types).

**Statistically Significant*

Table 7.16. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by time-period in the Republic of Ireland among Females: 1994-2001.

<i>Time-Period</i>	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
1994-1995	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
1996-1997	1.11 (0.99, 1.24)	1.11 (0.87, 1.43)	0.98 (0.80, 1.21)	0.84 (0.66, 1.07)	0.74 (0.45, 1.18)
1998-1999	1.17 (1.05, 1.30) *	1.42 (1.12, 1.79) *	0.70 (0.57, 0.87) *	0.95 (0.76, 1.19)	0.45 (0.26,0.76)*
2000-2001	1.20 (1.07, 1.34) *	1.34 (1.05, 1.70) *	0.88 (0.71, 1.08)	0.78 (0.61, 0.99) *	0.49 (0.28,0.82)*

Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable

(Outcome of interest: histological sub-types).

**Statistically Significant*

Tables 7.14-7.16 (males vs. females):

In the most recent periods (1998-2001), male populations show a decreasing trend in the overall risk of developing lung cancer. This in contrast to the female populations from 1995 onwards who show an increasing risk of developing lung cancer, following simultaneous adjustment for the potential risk factors.

There is no gender variation in the trend of risk pattern for histological sub-types for the periods studied (1994-2001), although there are histologic-specific patterns. This is shown in both sexes in the most recent periods, as they have one-and-half times greater likelihood of developing AC compared to the baseline reference period (1994-1995). By contrast, the recent periods across both sexes show that SQCC and the remaining histological sub-types (SMCC and LCC) have a declining risk pattern when compared to the baseline reference year. Both sexes show a consistent increased risk in AC.

The above findings are consistent with the observed declining smoking prevalence rate in the Republic since the 1970s, showing a more rapid decline in smoking prevalence among male populations.³⁵ This may have a differential gender impact on the recent lung cancer risk pattern. There is an overall declining lung cancer risk pattern in males alone, a declining SQCC and SMCC risk for both sexes, and an increased risk pattern for AC across both sexes. The fact that both sexes show a recent increased risk pattern for AC development suggests the differential impact of tobacco carcinogens on specific histological sub-types, together with the possibility of some emerging environmental risk factors contributing in part to the recent increased AC risk pattern across the Republic of Ireland.

7.3.9 Risk estimation of lung cancer cell-types by smoking status

Table 7.17. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by smoking status in the Republic of Ireland: 1994-2001.

<i>Smoking status</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
<i>Never smokers</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
<i>Current smokers</i>	0.52 (0.44, 0.61) *	1.51 (1.30, 1.77) *	1.52 (1.25, 1.87) *	1.19 (0.79, 1.87)
<i>Former smokers</i>	0.69 (0.57, 0.82) *	1.61 (1.37, 1.91) *	1.17 (0.93, 1.47)	1.31 (0.84, 2.12)
<i>Unspecified</i>	0.64 (0.52, 0.78) *	1.13 (0.94, 1.35)	1.25 (0.99, 1.59)	1.22 (0.75, 2.03)
Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable (Outcome of interest: histological sub-types).				

**Statistically Significant*

Table 7.18. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by smoking status in the Republic of Ireland among Males: 1994-2001.

Smoking status	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
<i>Never smokers</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
<i>Current smokers</i>	2.27 (1.20, 2.59) *	0.60 (0.47, 0.77)*	1.36 (1.11, 1.66) *	1.14 (0.87, 1.53)	1.42 (0.77, 2.91)
<i>Former smokers</i>	2.57 (2.22, 2.97) *	0.78 (0.60, 1.02)	1.42 (1.15, 1.77) *	0.84 (0.62, 1.15)	1.55 (0.82, 3.25)
<i>Unspecified</i>	2.14 (1.83, 2.49) *	0.71 (0.54, 0.94)*	1.05 (0.83, 1.33)	0.97 (0.71, 1.36)	1.42 (0.71, 3.10)

**Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable
(Outcome of interest: histological sub-types).**

**Statistically Significant*

Table 7.19. Risk estimates (OR=Odds Ratios) with 95% confidence intervals (CI) for the major lung cancer histological incident cases: AC, SQCC, SMCC, and LCC by smoking status in the Republic of Ireland among females: 1994-2001.

Smoking status	<i>All cases</i>	<i>AC (95%CI)</i>	<i>SQCC (95%)</i>	<i>SMCC (95%CI)</i>	<i>LCC (95%CI)</i>
<i>Never smokers</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>	<i>Reference (OR=1)</i>
<i>Current smokers</i>	0.44 (0.39, 0.50) *	0.45 (0.36, 0.56) *	1.81 (1.42, 2.32) *	1.90 (1.44, 2.56) *	1.03 (0.59, 1.91)
<i>Former smokers</i>	0.39 (0.34, 0.45) *	0.61 (0.47, 0.80) *	1.95 (1.50, 2.57) *	1.61 (1.17, 2.25) *	1.17 (0.60, 2.32)
<i>Unspecified</i>	0.47 (0.40, 0.55) *	0.61 (0.46, 0.81) *	1.22 (0.90, 1.64)	1.48 (1.05, 2.10) *	1.13 (0.56, 2.33)
Simultaneously controlling for other covariates (time-period, age and smoking status) in the multivariable logistic regression modelling for each of the dependent variable (Outcome of interest: histological sub-types).					

**Statistically Significant*

Tables 7.17-7.19 (males vs. females):

Detailed individual-level data on smoking status is not available for each lung cancer histologically verified incident case, while 11-17% of the patients have unspecified smoking status. However, on simultaneously controlling for other potential risk factors for lung cancer studied, males with smoking history are two-and-half times more likely to develop overall lung cancer. By contrast, females with no smoking history are more likely to develop overall lung cancer across the Republic. This reinforces the fact that males rather than females with smoking history have an increased risk of developing lung cancer.

There are also histologic-specific risk pattern across both sexes with regard to smoking status. For example, both sexes with smoking history have almost 50% decreased risk for AC when compared with never-smokers. By contrast, current female smokers alone are twice (1.90) as likely to develop SMCC, while smokers in general are one-and-half times more likely to develop SQCC when compared with never-smokers, following simultaneous adjustment for the potential risk factors.

In summary, Irish male and female smokers (former and current) have almost a similar risk pattern for developing certain histologic-sub types (AC and SQCC in particular) when compared with never-smokers although the overall lung cancer risk pattern is greater among male ever-smoking populations. Taken together, female smokers neither has a greater susceptibility to developing lung cancer nor to developing AC and SQCC, following simultaneous adjustment for the potential risk factors for lung cancer studied.

7.3 DISCUSSION

This section discusses in detail the specific findings related to the epidemiological pattern of lung cancer incidence across the cell-types (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma) in the Republic of Ireland from 1994 to 2001. This section has two broad sub-sections: the first sub-section focuses on lung cancer incidence rates and ratios, while the second sub-section addresses lung cancer risk estimates across the major cell-types. Although the underlying emphasis is on the epidemiological evidence surrounding the hypothesis of females having a greater susceptibility to developing lung cancer, quantification of lung cancer histological risk pattern together with the identification of potential emerging risk factors for lung cancer cell-types in the Irish context are also discussed in this section.

Conclusions are also drawn based on the findings of chapter six. Methodological limitations, such as the lack of comprehensive data or information on the potential risk factors for lung cancer across the Republic precluded this study from drawing definite conclusions, although individual-level data of lung cancer incident cases on a few of the factors were available for analyses.

7.4.1 Lung cancer age-standardised incidence rates and ratios

In the Republic of Ireland, SQCC is still the most frequent lung cancer histological sub-type for both sexes, consistent with a few nations.⁴⁹ However, the AC/SQCC ratios are relatively high among females across all the time-periods studied (1994-2001), although the observed AC/SQCC ratios are low compared to other Western European countries.⁴⁹ Such findings suggest that the histological lung cancer

pattern is undergoing an epidemiological transition in the Republic of Ireland. This implies that lung adenocarcinoma is yet to become the most common lung cancer histological sub-type in the Republic, as observed in the US or other Western European countries.⁴⁹ Consequently, a peak in AC would be expected in the Republic over the next few years before showing an actual decline, particularly in females. Because of the very short duration of 8-year study period (1994-2001), any significant changes in diagnostic practices or in histological classification criteria across the Irish hospitals are highly unlikely. Such biases would contribute little to the observed rising AC incidence. So the rising AC incidence in the Republic of Ireland is not an artefact but a real increase in incidence.

Adjusted for age and standardising to the European Population Standard, the incidence rates for AC are also significantly rising annually among female smokers in the Republic. This is consistent with similar findings elsewhere,⁴⁹ and also suggests that AC would be more strongly associated with smoking in women than previously recognised, consistent with a recent prospective cohort study in the US.²¹² The total lung cancer incidence rates among females rose from 270 in 1994 to 306 per 10,000 ever-smokers. This indicates that 2.7-3.1% of female smokers in the Republic would be susceptible to developing lung cancer in some point of their lifetime.

The total lung cancer incidence rates among males declined from 525 in 1994 to 428 per 10,000 ever-smokers. This again gives an estimate of around 5% of male ever-smokers (former and current combined) who would develop lung cancer in their lifetime. Such estimates (3-5%) are remarkably consistent with previous research that showed less than 10% of smokers (either current or former) develop lung cancer.¹⁶¹

Again, the observed gender variation in these estimates (3% in females vs. 5% in males) indicates that the Irish female smokers are less susceptible to developing lung cancer throughout their lifetime when compared with male smokers, consistent with previous findings of this study.

Lung cancer incidence rates among never-smoking populations of the Republic show very little gender variations for the periods studied. This can be seen in female AC incidence rates that are around 3 per 10,000 never-smoking female populations, while males have an average of 5 cases per 10,000 never-smokers. Such AC incidence among female never-smokers in the Republic is relatively higher than that recently reported in the US.²¹² Such findings reinforce the epidemiological transition of lung cancer histological pattern in the Republic.

The male-to-female ASIRRs across both smoking and never-smoking populations are greater than unity for lung cancer together with AC and SQCC, suggesting that the Irish females do not have a greater susceptibility to developing any forms of lung cancer. This is again consistent with the findings in chapter six that the older female birth-cohorts in the Republic do not have a higher relative risk for lung cancer, which is otherwise attributable to a greater background risk profile of the referent youngest birth-cohorts under study.

7.4.2 Lung cancer risks across cell-types

This section discusses lung cancer risks across major histological sub-types after simultaneously adjusting for the potential risk factors studied using multivariable logistic regression models. It also addresses the potential emerging risk factors for

lung cancer cell-types. The consistent observations of gender and geographical variations in lung cancer histological risk pattern across the Republic of Ireland, despite simultaneously controlling for a few of the potential confounders available to this study (age, smoking status and period of diagnosis) do suggest an underlying differential impact of histological-specific 'urban' risk factors on gender susceptibility to developing lung cancer across the Irish populations.

Dublin and Cork are the two largest commercial cities in the Republic of Ireland, and studies have consistently shown a higher association of SQCC and SMCC with active smoking relative to AC.¹ However, no reliable evidence is available for any underlying differences in smoking behaviour across these two major cities, nor any apparent socio-economic variations. The fact that Cork populations have a greater likelihood of SQCC and SMCC risk pattern, while populations in Dublin have an increased AC risk pattern, would mean that local urban environmental risk factors could be contributing in part to the observed variations. This is in addition to the residual confounding effect of active smoking on lung cancer risk development across the specific cell-types.

The alternative explanation for such observed variations would be information bias that was outlined in methods regarding the source and collection of lung cancer incidence data by the TROs of the Irish National Cancer Registry.²⁵ It is less likely that there would be a differential bias in reporting lung cancer histological sub-types. This is because there is a uniform coding and histological verification system across all the hospitals in the Republic. In addition, a robust statistical tool of multivariable logistic regression for controlling for the potential confounders would also have had

taken such variations into account. However, unmeasured and unknown risk factors for lung cancer would have introduced some information bias.

Dublin experienced a greater urbanization in the 1980s, with episodes of smog.³² Rising prevalence of teenage smoking²⁸⁶ and childhood obesity²⁸⁷ are also observed in Ireland. For the reasons discussed in chapter six, the youngest female birth-cohorts of the Republic (born around 1965) would have greater exposure levels to various forms of environmental pollution throughout their lifetime: passive smoking (public and domestic settings), ambient (outdoor) pollution due to vehicular exhausts, indoor pollution caused by burning bituminous coal for domestic heating, and due to residential radon levels. The findings in chapter six also demonstrated that lung cancer risk pattern in the youngest birth-cohorts across the Republic of Ireland would be attributable to factors other than active smoking alone. So the recent increase in lung AC in Dublin City populations can be the cohort effect of those born after 1935, considering the latency period for lung AC in particular. Unfortunately, historical information on cell-types is not available prior to 1994.²⁵

Consistent with other epidemiological studies,¹ younger and non-smokers in the Republic also have an increased AC risk pattern. This confirms that the relatively young birth-cohorts diagnosed with AC in the Republic have been exposed to potential risk factors other than active smoking alone, consistent with chapter six findings. Unfortunately, the Republic does not have data on lung cancer histological sub-types for longer durations. However, the birth-cohort analyses in chapter six indicated that lung cancer risk among the relatively young birth-cohorts (born after 1935) had a lower risk pattern compared with older birth-cohorts. The lung cancer

risks (before and after adjusting for cumulative cigarette consumption across one's lifetime) were also similar for both sexes from 1935 onwards. All these findings suggest that the observed increased AC risk pattern in the most recent periods across the Republic and particularly in Dublin, would reflect the emergence of 'urban-specific' risk factors other than active smoking alone acting differentially to modify the lung cancer histological risk pattern throughout a person's lifetime.

Taken together, the observed gender and geographical variations in lung cancer incidence (including histological sub-types) suggest different aetiological profile modified by some emerging urban-specific environmental risk factors. As outlined in chapter six, females in Ireland would not be at greater risk of developing lung cancer, but could have a unique lung cancer pattern across different epidemiological settings, such as Dublin versus Cork populations within the Republic of Ireland. However, the increasing AC incidence among female ever-smokers suggests that females are more susceptible to the cancer-causing effects of tobacco with a biological mechanism not quite similar to male smokers,²³¹ although epidemiological studies to date have shown mixed results.^{194,230}

The limited experimental studies to date indicate a different biological mechanism among female lung cancer patients. For example, females show higher levels of DNA adduct formation and increased *CYP1A1* expression,¹⁷⁴ together with a decreased DNA repair capacity¹⁷⁰ and an increased incidence of *K-ras* gene mutations,¹⁷⁵ supporting that a different biological mechanism exists among female lung cancer patients. A novel oestrogen receptor β has also been detected in lung tumours,¹⁷⁶ suggesting that oestrogen signalling has a biological role in

tumorigenesis, and it has also been reported that females have longer survival rates following treatment.¹⁷³ Nonetheless, this study has identified potential high-risk populations for further explorations in the observed gender variations in lung cancer incidence across the cell-types. Such targeted investigations would give a better insight into any underlying biological mechanisms, provided traditional epidemiological approaches are also integrated with modern molecular techniques.

A few of the potential 'urban' environmental risk factors worth considering are air pollution (outdoor and indoor), ETS, lifestyle pattern (increased mechanisation, changing dietary habits, increased physical inactivity), and residential radon. All these potential risk factors in part would contribute to the observed gender and geographical variations within the Republic of Ireland.

Dublin did experience rapid urbanization in the 1970s and 1980s in the form of huge construction work. Consequently, raw asbestos imports (mostly crocidolite and later chrysotile) were indiscriminately used until the EU Directive in the late 1980s.²⁸⁸ Also, a total ban of 'all' forms of asbestos silicate fibres has yet to be introduced across the Republic of Ireland. Incidentally, asbestos is strongly associated with lung AC development, unlike other histological sub-types.²²¹ It has also been shown that mesothelioma incidence, and pleural cancer deaths have been significantly rising annually across the Republic of Ireland, particularly from 1990 onwards.²⁸⁹ Although a strong interaction between smoking and asbestos on the causal pathway to lung cancer risk is well known,²²¹ such observations with lung AC are yet to be established. Asbestos fibre is not only an occupational exposure, but also

considered an environmental risk factor. Consequently, women washing their spouses' clothes have been reported to suffer from asbestos exposure.²⁹⁰

Another possible explanation compounded with any rapid urbanization is a changing lifestyle that is also becoming a growing problem in the majority of the Western European and North American countries.²⁹¹ Lung adenocarcinoma has a weak association with higher waist circumference (a better indicator for central adiposity),²³⁹ although epidemiological evidence suggests an inverse association with overall lung cancer.²³⁸ Very few studies have taken into account of any changing weight patterns throughout a person's lifetime.

Smokers usually lose weight, and later develop lung cancer, but 'reverse causality' bias is always a possibility.²⁴⁴ The fact that former smokers have a greater likelihood of developing lung cancer than current smokers (in this study and elsewhere) also hint at 'reverse causality' bias. This is because of the possibility of quitting smoking earlier when one is simultaneously afflicted with other severe illnesses such as COPD,²⁴⁵ or the individual changes smoking habits due to reasons other than lung cancer alone.²⁹² Exposure misclassification bias remains an important issue in such epidemiological studies, but long-term follow-ups of large historical cohorts could help to quantify exposure levels more accurately, especially through the novel epidemiological approach of life course epidemiology.⁷⁰

Recently, hormonal factors have also been shown to be associated with lung cancer risk. In addition, endogenous hormone metabolism is modified in presence of adiposity that would later stimulate cell proliferation, inhibit apoptosis and enhance

angiogenesis.^{240, 243} Steroid oestrogens have been recently classified as a potential human carcinogen.²³⁶ HRT and oral contraceptives with high oestrogen content were also more prevalent in the early 1960s and the 1970s across the industrialised nations, and have been implicated in AC risk.¹⁹² Ireland is also experiencing increased obesity prevalence, with increased physical inactivity levels.²⁹³ An apparent association between the rising obesity prevalence and an increased AC incidence across major cancer sites,²³⁷ including lung cancer,²⁹⁴ is definitely an interesting hypothesis. Incidentally, a recent study has shown an increased risk of adult lung cancer (and other smoking-related cancers in particular) with childhood obesity.²⁹⁵

Indoor pollution in the form of burning coal is associated with SQCC.¹⁴ The Cork populations have an increased SQCC risk pattern in my study. In 1995 the Coal Ban in Cork City, five years later in Dublin City, after which it was gradually expanded into other major cities.³³

There is also limited evidence of historical indoor radon exposure levels in the Irish dwellings, although the dwellings in Cork City had experienced a very high concentration of radon in the 1980s,²⁹⁶ and the 1990s.²⁹⁷ Galway City, lying on a geologic bedrock, has the second highest maximum radon levels in the dwellings surveyed in the 1990s only after Kerry.²⁹⁷

Evidence suggests that residential radon exposure is associated with both SQCC and SMCC,²⁹⁸ while in smoking populations a strong interactive effect of SMCC together with radon, smoking and urbanization has been reported.⁶⁶ This particular evidence can explain the increased SMCC risk pattern observed in Dublin

and Cork populations. Evidence also suggests that AC incidence significantly rises in non-smoking urban females when exposed to indoor radon levels.²⁹⁹ This again goes some way to the increased AC risk pattern across Dublin populations.

The absolute lung cancer risk due to increased residential radon level will be relatively small in the Republic of Ireland pending further explorations. However, 15,000 to 22,000 (8%) radon-attributed lung cancer cases are projected in the US⁷⁵ from a total of 160,000 lung cancer cases reported annually across the US.⁴⁵ Information on ETS is limited in the Republic, but its potential contribution to lung cancer risk in the Republic has been discussed in greater detail in earlier chapters.

7.4.3 Summary and Conclusion

In summary, the observed gender and geographical variations in lung cancer histological sub-types in the Republic of Ireland suggest the emergence of potentially new environmental risk factors, especially among young female adults producing an ‘urban’ effect, although such effects will be relatively small. One such ‘urban’ effect has been investigated in this study (urban air pollution mixture in Dublin City) in chapter nine. Although active smoking would always remain a residual confounder for any lung cancer epidemiological studies, it is also imperative to investigate any underlying gender susceptibility of specific lung cancer histological sub-types to certain emerging local environmental risk factors in a potentially high-risk population, for example, Dublin vs. Cork populations.

Furthermore, biases, such as detection bias, diagnostic bias, and histopathological classification bias would have little influence in this study, because

of the very short duration (1994-2001). Bias would also be reduced due to the fact that the Irish National Cancer Registry Board's registered tumour cases are more than 90% histologically verified, following a rigorous uniform method of data collection and reporting across the whole nation.²⁵ Any underlying demographic changes would also have little contribution to such observations in this study, because of relatively lower survival rates of lung cancer, and also for population standardisation.

In conclusion, females in the Republic do not have a greater susceptibility to developing lung cancer (including the cell-types) when compared with males, although molecular-laboratory based studies are further warranted not only in the Republic of Ireland, but also across the globe. Unfortunately, large historical cohorts are practically non-existent in the Republic of Ireland for novel epidemiological approaches, such as life course epidemiology.⁷⁰ It has also been argued¹⁹² that if certain segments of the population are at higher risk of lung cancer (Cork or Dublin populations, for example), cancer prevention programs need to be especially targeted toward these groups.

Chapter Eight

LUNG CANCER DEATHS IN DUBLIN CITY

8.1 INTRODUCTION

This chapter exclusively deals with the epidemiological pattern of lung cancer deaths within the Dublin City (Dublin County Borough until 1996 Census) from 1981 to 2000, as outlined in the study objective. According to the Census 2002, Dublin City does not include Dun Laoghaire-Rathdown, Fingal and South Dublin areas. The chapter describes the research methodology employed to examine this particular study objective, which is broadly similar to the methods employed in chapter six. Each table or figure in section three highlights the underlying message, followed by detailed discussion in section four. The observed epidemiological lung cancer death pattern in Dublin City is discussed both from the local and a national perspective.

8.2 METHODS

This second section describes briefly the methodology used to examine the epidemiological pattern of lung cancer deaths within the Dublin City, the capital city of the Republic of Ireland, from 1981 to 2000. Joinpoint regression modelling and age-cohort modelling were employed for examining this particular study objective. Methods are similar to those described in chapter six. The source of the lung cancer mortality data for Dublin City is same for both the study objectives described in chapter six and in this chapter, namely, the CSO mortality data. Also a brief background into the methods employed for lung cancer death pattern in Dublin City is provided in the following two sub-sections.

8.2.1 Estimation of EAPC and age-standardised lung cancer rates

As mentioned in the methods section of chapter six, lung cancer mortality data for Dublin City were also extracted from the CSO mortality data for the periods (1981-2000), using the SAS program. The Joinpoint regression modelling employed in chapter six for EAPC in lung cancer death rates for the whole of the Republic of Ireland was also used for the EAPCs in lung cancer death rates for Dublin City populations. In addition, lung cancer death rates were adjusted for age and standardised to the European Population Standard²⁸² for calculating age-standardised lung cancer death rates for Dublin City across gender from 1981 to 2000. For age-specific EAPCs in lung cancer death rates, both sexes were combined for stable estimates. However, EAPCs in age-standardised lung cancer death rates were calculated separately for both sexes. Also, the age-specific lung cancer rates for Dublin City were calculated across the year of birth.

8.2.2 Age-Cohort Analyses and Poisson Modelling

A simple age-cohort model (similar to the birth-cohort analysis in chapter six) has been employed to estimate lung cancer risks across different birth-cohorts in Dublin City populations. Similar to model II used in chapter six, the following model has been used for birth-cohort analysis across the Dublin City populations.

$E_{ij} = A_i B_j N_{ij}$ (Model IV)

E_{ij} = expected number of lung cancer deaths in age group ‘i’ and birth cohort ‘j’

A_i = the effect of age group ‘i’

B_j = the effect of birth cohort ‘j’

N_{ij} = population at risk (year and age-specific population from the Census data)

8.3 RESULTS

This section describes in detail the results of the gender-breakdown of lung cancer death patterns in Dublin City from 1981 to 2000. The following four subsections on results concentrate on age-standardised lung cancer death rates, age-specific lung cancer rates by the year of birth, the EAPCs in death rates, and the findings of birth-cohort analysis, respectively.

**8.3.1 Age-standardised lung cancer death rates in Dublin City: 1981-
2000**

Table 8.1. Lung cancer deaths and age-standardised (European Population Standard) lung cancer death rates in Dublin City by gender: 1981-2000.

<i>Males</i>			<i>Females</i>	
<i>Year</i>	<i>No</i>	<i>Rate/100,000</i>	<i>No</i>	<i>Rate/100,000</i>
1981	255	38.3	111	15.6
1982	232	34.9	109	18.2
1983	243	32.5	111	20.2
1984	250	41.3	119	20.9
1985	248	38.1	105	20.6
1986	231	36.4	133	29.9
1987	234	35.6	110	17.4
1988	241	37.0	110	17.4
1989	230	35.1	150	27.7
1990	208	33.8	129	18.6
1991	231	35.8	122	18.2
1992	188	28.3	128	21.4
1993	217	32.2	122	20.1
1994	219	35.8	140	25.7
1995	237	39.9	130	25.3
1996	184	24.1	130	21.7
1997	180	29.6	125	22.4
1998	210	35.6	121	22.5
1999	199	37.1	136	31.3
2000	195	34.0	139	25.2
1981-1990	2372		1187	3559
1991-2000	2060		1293	3353
TOTAL	4432		2480	6912

Table 8.1 (males vs. females):

Table 8.1 shows that age-standardised (European Population Standard) lung cancer death rates in Dublin City are two-fold higher in males than in females, especially in the earlier decade (1981-1990). In the most recent decade (1991-2000), the gender gap in age-standardised lung cancer rates is declining. Both sexes are showing an annual increase in their rates, but the increase is more rapid in females. The annual change in death rates became clearer in Joinpoint analyses (table 8.2).

In comparison with the age-standardised lung cancer death rates across the whole of the Republic (in chapter six: figures 6.1 and 6.2), the observed rates among male populations in Dublin City are almost 50% lower than the national average, although this could be in part due to different population standardisation. By contrast, female death rates in Dublin City are almost similar to the national average. A birth-cohort analysis across Dublin populations would further confirm whether the birth-cohorts in Dublin City have a gender variation in lung cancer risk pattern similar to the national pattern. Such an analysis would also give an insight into the future lung cancer pattern in Dublin City (figure 8.3).

8.3.2 Age-specific lung cancer rates by the year of birth in Dublin

City

Figure 8.1 Male age-specific standardised death rates across different birth cohorts in Dublin City (log scale).

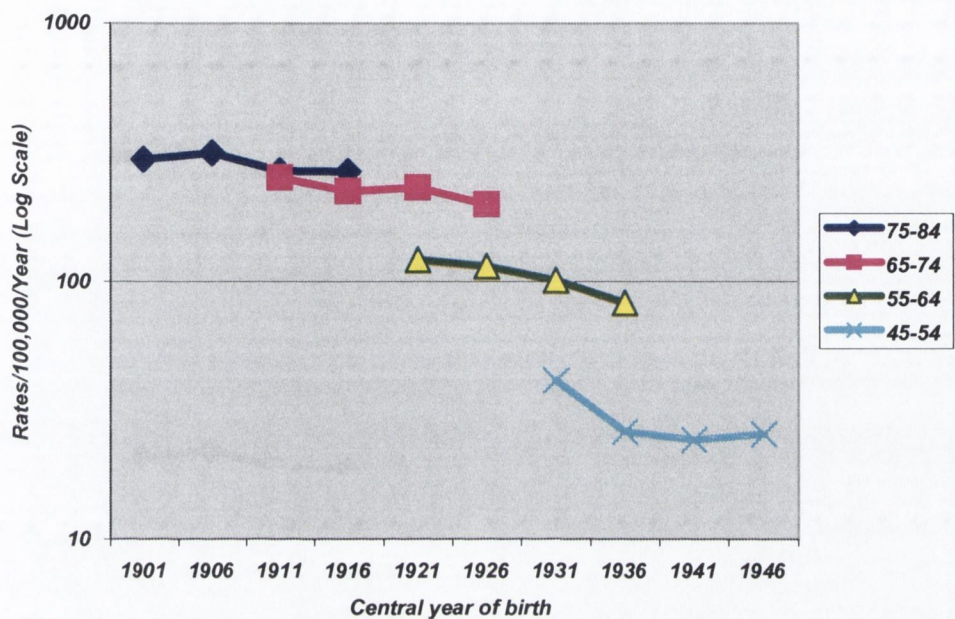


Figure 8.1 male age-specific rates:

The observed peak in male lung cancer death rates in 1984 (table 8.1) corresponds to the 75-84 year-old male age-cohorts born around 1906 as shown in figure 8.1, considering a long latency period for lung cancer. These cohorts experienced the highest lung cancer death rates. Likewise, the peak observed in male death rates again in 1995 (table 8.1) corresponds to the lung cancer death rates among the age-cohorts 65-74 year-olds born around 1921 (figure 8.1). Taken together, the observed peaks in male lung cancer death rates (table 8.1 and figure 8.1) suggest an age-cohort phenomenon. However, significant changes in the direction of lung cancer death rates (increasing or decreasing) can be better understood through a Joinpoint analysis to confirm the observed peaks (around 1984 and 1995). Such significant shifts would also suggest a change in any of the potential environmental risk factors for lung cancer death pattern in Dublin City populations.

Figure 8.2. Female age-specific standardised lung cancer death rates across different birth-cohorts in Dublin City (log scale).

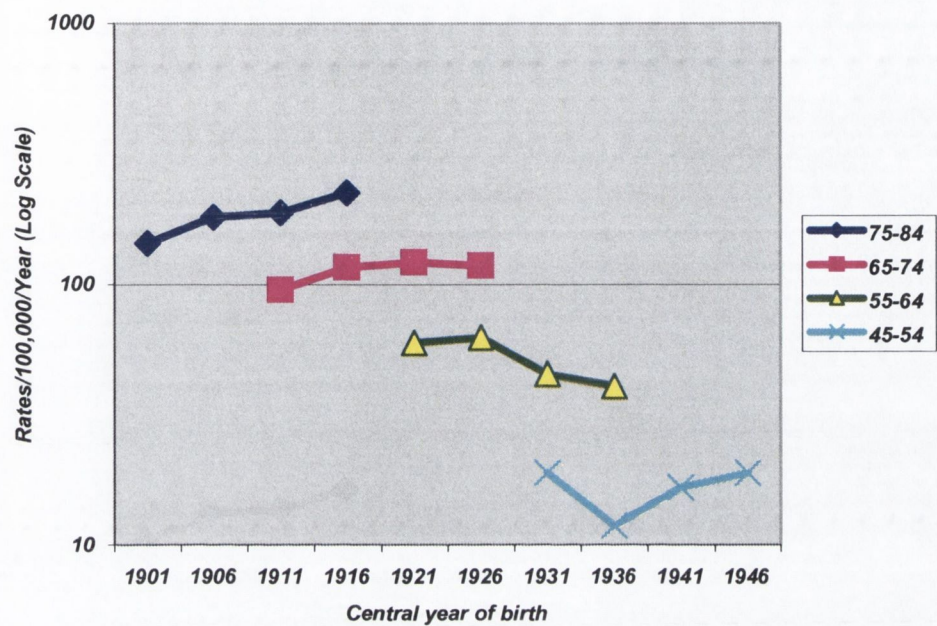


Figure 8.2 female age-specific rates:

The peak observed in female lung cancer death rates in 1986 (table 8.1) corresponds well with the higher rates among the 65-74 year-old female age-cohorts born around 1916 (figure 8.2), considering a long latency period for lung cancer. Likewise, the persistent increase in female lung cancer death rates from 1990 onwards (table 8.1) are the combined effects of a continual rise in lung cancer death rates among the older (75-84) and the younger (45-54) age-cohorts, which are yet to stabilise. Taken together, the continual rise in female lung cancer death rates from 1990 onwards (table 8.1 and figure 8.2) does suggest an age-cohort phenomenon. However, a significant change in the direction of such rates corresponding to the observed peaks (through Joinpoint analysis) would indicate a changing profile of any of the potential environmental risk factors for lung cancer. In summary, both male and female lung cancer deaths in Dublin City have a combined effect of an age-cohort and an age-period phenomenon.

8.3.3 EAPC in Lung Cancer Death rates in Dublin City

Table 8.2. EAPC (Estimated-Annual-Percent-Changes) with 95% CI (Confidence Intervals) of Lung Cancer Death Rates and Joinpoint Analysis: age-specific (both sexes combined) and age-standardised (gender-breakdown) rates in Dublin City: 1981-2000.

Age-Specific	EAPC (95% CI)	Trend 1	(First slope)	Trend 2	(Second slope)
	1981-2000	Years	EAPC (95% CI)	Years	EAPC (95% CI)
35-44	-0.2 (-3.1; 2.9)	1981-1984	-22.6 (-51.3; 22.9)	1984-2000	3.0 (-1.5; 7.7)
45-54	-2.6 (-4.4; -0.8)	1981-1989	-7.7 (-13.5; -1.4)	1989-2000	1.3 (-3.4; 6.2)
55-64	-2.4 (-3.5; -1.3)	1981-1986	1.4 (-6.1; 9.4)	1986-2000	-3.3 (-5.1; -1.5)
65-74	-0.2 (-0.9; 0.4)	1981-1997	-0.5 (-1.4; 0.3)	1997-2000	3.1 (-8.0; 15.5)
75-84	0.7 (-0.3; 1.7)	1981-1985	4.4 (-8.3; 18.9)	1985-2000	0.2 (-1.3; 1.8)
85+	2.4 (0.3; 4.5)	1981-1997	1.0 (-2.2; 4.3)	1997-2000	14.1 (-18.8; 60.2)
Age-Standardised Rates		Males		Females	
<i>(Two Joinpoints=Three slopes)</i>		<i>Years</i>	<i>EAPC (95%CI)</i>	<i>Years</i>	<i>EAPC (95%CI)</i>
<i>Overall Trend</i>		1981-2000	-0.7 (-1.7; 0.3)	1981-2000	1.7 (0.4; 3.1)
<i>Trend 1(First slope)</i>		1981-1985	1.4 (-8.2; 12.1)	1981-1986	7.6(-0.7;16.5)
<i>Trend 2(Second slope)</i>		1985-1996	-1.9 (-4.3; 0.5)	1986-1990	-4.9(-20.4;13.6)
<i>Trend 3(Third slope)</i>		1996-2000	4.3 (-5.6; 15.3)	1990-2000	3.3 (0.5; 6.2)

Table 8.2 EAPC in age-specific and age-standardised rates:

For Dublin City, the EAPCs in age-specific lung cancer death rates are combined for both sexes to give robust estimates. So, it is quite evident that the overall annual rates (from 1981 to 2000) among the relatively old age-cohorts (less than 74 year-olds) are declining, while the oldest age-cohorts (85+ year-olds) show a significant annual rise in death rates. Also there are variations in Joinpoint analyses (one Joinpoint gives two slopes), thereby showing significant changes in the direction of annual death rates across two specific points of time. Overall, the annual change in rates is faster and greater in the most recent periods across all age groups, suggesting a recent increase in lung cancer death rates, despite age and population standardisation.

Regarding the EAPCs in age-standardised (European Population Standard) death rates, moderate gender variations are observed, but a pattern consistent with the earlier observations in table 8.1 has also been identified. Males show an annual overall decline in lung cancer death rates from 1981 to 2000, unlike a significant annual rise among females during the same periods. Also significant changes in the direction of annual death rates are observed in Joinpoint analyses (two Joinpoints give three slopes), thus identifying three specific time-trends. So the highest rates observed in table 8.1 (around 1985 in both sexes, and also in 1995 in males and from 1990 onwards in females) are now confirmed through Joinpoint analyses.

In summary, the significant change in direction in lung cancer death rates around 1985-1986 across both sexes is a reflection of environmental influence, while the annual rise from 1990 onwards among females suggests an age-cohort phenomenon due to delayed smoking debut among the older female cohorts.

8.3.4 Birth-Cohort Analysis (Lung cancer risk estimates) in Dublin

City populations

Figure 8.3. Relative Risks (RR) of Lung Cancer deaths (age-adjusted) in the Republic of Ireland (ROI) versus Dublin City across different birth-cohorts by gender.

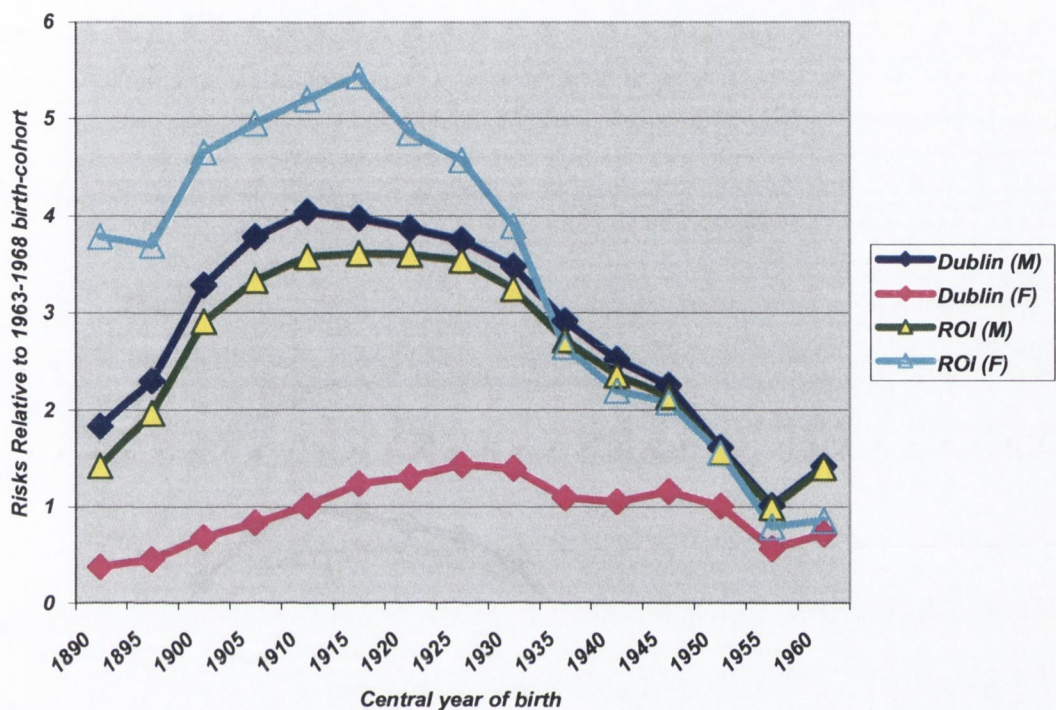


Figure 8.3 lung cancer risks:

Figure 8.3 shows lung cancer risk estimates across different birth cohorts. The observed lung cancer risk pattern among the same birth-cohorts for both sexes across the two study populations (Dublin versus the whole nation) is similar. However, there is gender variation in the risk estimates. The older birth-cohorts have a lung cancer risk pattern greater than the youngest birth-cohorts for both populations. The lung cancer risk is declining in those born after 1935, a pattern consistent with both the populations. Importantly, females show a delayed peak (10-15 years later) after the male populations did, which is more pronounced with Dublin City populations. This reinforces the fact that the older females did start smoking a few years later.

8.4 DISCUSSION

This section discusses in-depth the findings of the epidemiological pattern of lung cancer deaths within the Dublin City over a 20-year study period (1981-2000). It has two main sub-sections: the first sub-section focuses on the age-standardised lung cancer death rates employing Joinpoint regression modelling, while the second sub-section addresses lung cancer risk pattern through birth-cohort modelling. The strengths and limitations of such methods employed have already been discussed in greater detail in chapter six. However, this section outlines the distinct features observed in lung cancer death pattern in Dublin populations with regard to the national lung cancer pattern, as discussed in chapter six.

8.4.1 Lung cancer rates

Consistent with the national pattern, the age-specific lung cancer death rates for the oldest age groups (85+ year-olds) in Dublin City are rising annually for the recent periods. However, the age-specific lung cancer death rates for the younger age groups (35-54 year-olds) at the national level is declining annually for the recent periods, while an annual rise in lung cancer death rates for the 35-54 year-olds is occurring for Dublin City populations in the most recent periods. Likewise, both sexes in Dublin City show an annual rise in the overall age-standardised lung cancer death rates in the most recent periods (from 1990 onwards in females), but the annual rates are declining at the national level across both sexes from 1990 onwards (slower decline among females). Such observations suggest that the overall national lung cancer death rates would continue rising over the coming years due in part to the upward lung cancer trend across Dublin City populations, especially among the younger female populations.

Furthermore, the rising annual lung cancer death rates across both sexes observed in Dublin City populations for the most recent periods are unlike the declining national pattern. This suggests an underlying variation in temporal pattern across Dublin City populations. In addition, the overall Joinpoint analyses across both the populations are surprisingly not consistent, further suggesting an underlying temporal variation in lung cancer death rates across both the populations.

In summary, the observed temporal shifts in annual lung cancer death rates across both sexes around 1985 indicate a changing profile in any of the potential environmental risk factors for lung cancer in Dublin City. The annual increase in lung cancer death rates, especially from 1990 onwards among females, however, suggests an age-cohort phenomenon due to delayed smoking debut among the older females, which is quite evident in the birth-cohort analysis, as discussed next.

8.4.2 Lung cancer risks

The birth-cohort analyses for estimating lung cancer risk pattern across different birth-cohorts for both sexes in Dublin City populations are compared with the observed lung cancer risk pattern at the national level. Based on the discussion in chapter six, such observations suggest that the older female generations in Dublin have started smoking 10-15 years later than their male counterparts did. This observation, however, is less pronounced at the national level. Consistent with the national lung cancer risk pattern, the older birth-cohorts for both sexes in Dublin have a greater lung cancer risk relative to the referent youngest birth-cohorts. Also, the lung cancer risk pattern is declining in those born after 1935 for both sexes across the whole nation, including the Dublin populations.

The birth-cohort analysis on Dublin populations was not adjusted for cumulative lifetime smoking consumption, because such historical information on Dublin populations was not available. Nonetheless, as outlined in chapter six on birth-cohort findings (before and after adjusting for lifetime cumulative cigarette consumption), the younger generations for both sexes across the Dublin City also have lower lung cancer risk patterns, irrespective of cigarette adjustment.

In summary, the older birth cohorts of both sexes in Dublin have a lung cancer risk profile not quite similar to the risk profile of the youngest birth-cohorts (those born around 1965), consistent with the national pattern. Those born after 1965 in Dublin City have a lung cancer risk profile greatly influenced by any of the potential environmental risk factors for lung cancer recently emerging compounded with changing active smoking habits (rising teenage smoking, for example).

In conclusion, the lung cancer risk pattern in Dublin City populations is broadly similar to the national lung cancer risk pattern across corresponding birth-cohorts, while the temporal pattern for lung cancer rates recently emerging across these two study populations is different, especially among females from 1990 onwards. This temporal variation in lung cancer death rates is due to the delayed smoking debut among the older females of Dublin City populations (figure 8.3). This implies the recent temporal pattern observed across Dublin populations is a reflection of the changing smoking pattern across successive generations. Nonetheless, any changing risk profile of the potential environmental risk factors for lung cancer (through public-health interventions, for example) would also contribute in part to the observed temporal variations in Dublin City.

Dublin experienced rapid urbanization in the 1970s, with smog episodes in the 1970s and the 1980s. The smog episode in the 1980s in Dublin City did report increased case fatality,³² and a recent study also showed that all-cause mortality (all-respiratory cases in particular) decreased significantly following the ban and sale of bituminous coal burning used for domestic heating in 1990 across Dublin City.³³ The observed temporal pattern around 1985-1986 could be attributed to poor air quality in the early 1980s.³⁰⁰ Association studies on air pollution and lung cancer, however, have shown a relatively small 'urban' effect, with less than 10 lung cancer cases attributable to air pollution alone per 100,000 populations.³⁰

The recent rise in annual lung cancer rates in Dublin populations is consistent with the rising incidence of certain lung cancer cell-types (lung AC in particular) together with an increased risk pattern, which was demonstrated in chapter seven. Conversely, the increased lung AC risk pattern for Dublin populations is in part attributed to a few of the potential environmental risk factors, as discussed in chapter seven. The next chapter (nine) investigates into one such potential risk factor (urban air pollution mixture) for lung cancer pattern in Dublin City from 1981 to 2000.

8.4.3 Conclusion

In conclusion, a declining lung cancer risk pattern among those born after 1935 has been observed in Dublin City, as opposed to an annual rise in lung cancer death rates from 1990 onwards (females in particular). In addition to the age-cohort phenomenon due to changing smoking habits, a changing risk profile of certain local environmental factors for lung cancer, and also across specific lung cancer cell-types (lung AC in particular) could in part contribute to such observations.

Chapter Nine

LUNG CANCER DEATHS AND AIR POLLUTION LEVELS IN DUBLIN CITY

9.1 INTRODUCTION

This chapter investigates one of the potential risk factors for lung cancer (urban air pollution mixture) in Dublin City, using annual black smoke (BS) levels as the indicator variable for urban air pollution mixture. The primary objective of this chapter is to examine a temporal association between annual lung cancer deaths and the mean annual BS levels in Dublin City over a 20-year study period (1981-2000). In addition, the absolute number of lung cancer deaths attributable to BS levels has been estimated, particularly before the ban and sale of bituminous coal was introduced across Dublin City in 1990. BS is a measure of particulates, which are around 4.5 micrometers or smaller, and is based on the “blackness” of the particles. They are ideal for coal burning and for diesel emissions.³⁰⁰

9.2 METHODS

This section deals with the methods employed for examining a temporal association. A simple age-period model has been employed, the potential implication of a significant ‘period’ effect on lung cancer risk vis-à-vis a simple age-cohort modelling technique (in chapter six) is also outlined. The sources of air pollution and smoking prevalence data are highlighted. The source of lung cancer mortality data for Dublin City (1981-2000) is similar to that analysed in chapter eight.

9.2.1 Implication of a ‘Period’ Effect on Lung Cancer Risk

A significant ‘period’ effect with regard to lung cancer temporal pattern suggests a changing risk profile in any of the potential environmental risk factors for lung cancer that affects simultaneously across all age groups in a specific calendar period.^{274, 275} So a public-health intervention in the form of a Coal Ban can introduce a period effect for lung cancer risk, while a cohort effect suggests a changing smoking pattern across successive generations. Similar to the incorporation of cumulative lifetime cigarette consumption in an age-cohort model as discussed in chapter six, annual mean BS levels can also be included in a simple age-period model. Such inclusion of risk factors provides a better biological explanation for any temporal variations, and also quantifies risks across specific calendar periods.

Epidemiologically, a significant decline in any of the potential environmental risk factors for lung cancer following a public-health intervention, together with a real increase in another risk factor, should have a competing risk pattern.²³ Such a phenomenon modifies an observed lung cancer risk pattern. For example, a real increase in the major risk factor (smoking for lung cancer) together with an annual decline in BS (a relatively ‘weak’ risk factor for lung cancer) across a certain calendar period following the Coal Ban could modify lung cancer risk pattern, especially when there is an interactive effect (greater than additive) between the two risk factors. So any significant ‘period’ effects observed around 1990 (if used as a reference period in the age-period model) in Dublin City with regard to lung cancer deaths and BS levels could not be attributed entirely to the Coal Ban introduced in 1990. Based on such *a-priori* hypothesis, the following analyses were conducted.

9.2.2 Age-Period Analyses and Poisson Modelling

Similar to Models II and III in chapter six, the following age-period models (probabilistic multiplicative risk models) were employed for examining the temporal association between lung cancer deaths and annual mean BS levels:

$$E_{ij} = A_i B_j N_{ij} \text{ (Model V)}$$

E_{ij} = expected number of lung cancer deaths in age group ‘i’ and period ‘j’

A_i = the effect of age group ‘i’

B_j = the effect of period ‘j’

N_{ij} = population at risk (year and age-specific population from the Census data)

$$E_{ijk} = A_i B_j C_k N_{ij} \text{ (Model VI)}$$

C_k = the effect of annual mean BS levels at a particular period on observation ‘k’

Similar to age-cohort models in chapter six, the age-period models are also adjusted for age, and the **goodness-of-fit** for each model was assessed by deviance.²⁷⁸ A core model was created based on Poisson regression analysis using **Proc GenMod** Program of SAS software. Age groups were divided into six major bands (less than 45; 45-54; 55-64; 65-74; 75-84; 85+ years). This classification identified the cohorts for each calendar period based on their year of deaths.

Initially, two broad periods (1981-1990 and 1991-2000) were examined, followed by shorter time intervals (five-year and two-year). Into each core model, the mean annual BS levels for the corresponding periods are incorporated initially, followed by step-wise inclusion of annual smoking prevalence alone, and then both BS and smoking prevalence, while the cross-product **interactive** term (BS*smoking) was included into each of these four models. The data for the best models (including

interaction term) are presented. A one-year **lag** between the mean annual BS levels and lung cancer deaths fitted well, although several lag-periods (three years; five years and eight years) were modelled but did not work. In this study, female and male lung cancer deaths were combined to give robust estimates. All lung cancer risk estimates across the models are relative to the reference period of 1990 (the year when Coal Ban was introduced in Dublin City). This indirectly takes into account of any 'period' effects other than the Coal Ban alone. Output of the four models with the *Proc GenMod* program of SAS is presented in **appendices from eight to eleven**.

9.2.3 Air pollution data

Since 1973, the Dublin Corporation's air pollution monitoring stations (12 in total) obtained a comprehensive picture of air pollution in the city, although patchy evidence of air quality for Dublin dates back to the early 1930s.^{300,301} Over the years many of these 12 stations were either relocated or discontinued, and additional stations were added to the network. The air pollution data (on a daily basis) for Dublin County Borough from 1973 onwards were independently assessed for its accuracy and completeness.³⁰¹ The present study utilized the mean annual black smoke concentrations with measurements from the residential monitoring stations in the city of Dublin (Dublin County Borough) from 1973 to 2000. Air pollution data were restricted to six 'fixed' monitoring stations across Dublin City (RDS, Mountjoy Square, Contarf, Finglas, Herbert Street, Bluebell).

The pollution data are aggregate values, thus introducing exposure ascertainment bias in the estimates. However, such biases have been reduced, because of a homogenous study population across a well-defined geographical location

(Dublin City) whose air pollution monitoring stations are broadly representative of the overall exposure levels of the populations. The air pollution data source used in the study is similar to that analysed in a recent study.³³

9.2.4 Estimation of Attributable Risk (AR)

Assuming a causal relation between lung cancer deaths and BS levels, the attributable risk (AR) or the risk difference of lung cancer across different calendar periods (1981-1990) were estimated based on the following formula²⁸⁴

$$(RR - 1)_A - (RR - 1)_B$$

$$(RR - 1)_A = \text{Lung Cancer Risk in Model 'A' (Core Model) relative to the reference period 1990 (RR=1)}$$

$$(RR - 1)_B = \text{Relative Risk of Lung Cancer in Model 'B' (following the incorporation of Black Smoke levels in the Core Model 'A')}$$

9.2.5 Smoking prevalence data

As outlined in chapter six, Lee and colleagues¹⁶ have compiled international smoking statistics, and the present study has used their data. For age-cohort models, it was assumed that lung cancer risk pattern reflects the changing smoking pattern throughout a person's lifetime across successive generations. Hence, cumulative lifetime cigarette consumption for each birth-cohorts was used in chapter six. For age-period models examining lung cancer risks across calendar periods, annual smoking prevalence rates are more appropriate. So in the beginning the age-specific annual smoking prevalence rates for the Irish populations (adjusted for gender) were included into the core age-period model then the annual mean BS levels.

9.3 RESULTS

This section presents the findings of the temporal association between lung cancer deaths and the mean annual BS (Black Smoke) levels from 1981 to 2001 across different calendar periods (10-year interval; 5-year interval; 2-year interval). At the outset, the distribution of mean annual BS levels ($\mu\text{g}/\text{m}^3$) is provided together with the total (males and females combined) number of lung cancer deaths across Dublin City from 1981 to 2000. This section ends with the estimated lung cancer deaths attributable to BS levels (AR), including the estimated annual lung cancer death rates per 100,000 populations attributable to BS levels in Dublin City (PAR). Each of the tables and/or figures has specific comments, while a detailed discussion on such findings follows in section four of this chapter.

**9.3.1 Mean annual black smoke (BS) levels in Dublin City: 1980-
2000**

Figure 9.1. Mean annual black smoke (BS) levels and the total number of lung cancer deaths in Dublin City: 1980-2000.

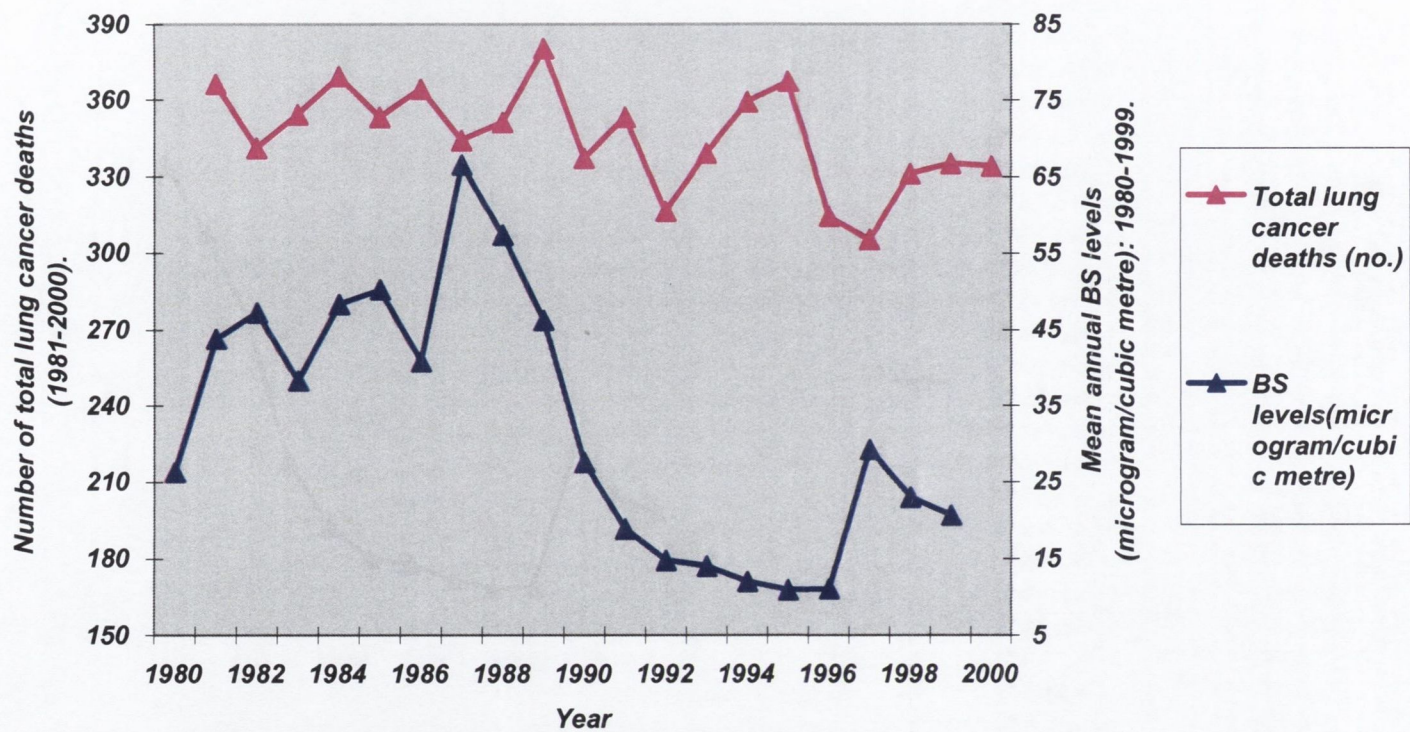


Figure 9.1:

The total number of lung cancer deaths in Dublin City peaked in 1989, one-year after the annual mean black smoke (BS) levels had peaked. The two relatively small peaks for the total number of lung cancer deaths prior to 1989 closely correspond to two similar peaks observed in the annual mean BS levels, again with a lag-time of one-year. The subsequent peaks for the total lung cancer deaths after 1995 did not follow a similar pattern, but the peak observed in 1998 again corresponds well with the 1997 peak observed in the annual mean BS levels.

Importantly, the peak observed in 1982 for BS levels is consistent with the smog episode reported in Dublin City, with increased case-fatality rates for patients admitted into a tertiary hospital catering for a particular catchment area.³² The same study³² mentioned that there were no epidemics, such as influenza, which also contributes to increased case fatality. In summary, one-year lag period between lung cancer deaths and BS levels is biologically plausible, although the mechanistic pathway is not adequately understood to date.

It is also important to note that the annual mean BS levels started declining rapidly even before the official introduction of the Coal Ban in 1990 across Dublin City. Such an observation is also consistent with the recent nationwide Smoking Ban in the Republic that came into force only in March 2004, but already a drop in cigarette sales has been reported since January 2004 (*L Clancy Personal communication*). Such observations do suggest that a changing risk profile of a certain environmental factor across a specific calendar period does not necessarily correspond to the actual timing of its public-health intervention.

9.3.2 Lung cancer deaths and BS levels across 10-year period intervals

Table 9.1. Relative Risk (RR) estimates (including the interactive effect) with 95% Confidence Intervals (CI) of Total Lung Cancer deaths in Dublin City between 1981-1990 and 1991-2000, before and after their adjustment for black smoke levels (BS) and smoking prevalence separately and combined, using 1990 as the reference period (RR=1).

<i>Period of Death</i>	<i>Core Model (A) (Adjusted for age and gender)</i>	<i>A + Black Smoke (B)</i>	<i>A + Smoking Prevalence (C)</i>	<i>B+ Smoking Prevalence (D)</i>
	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>
1981-1990	1.06 (0.93, 1.22)	1.01 (0.86, 1.18)	0.96 (0.82, 1.13)	0.98 (0.83, 1.15)
1991-2000	0.97 (0.85, 1.11)	0.98 (0.86, 1.12)	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)
<i>Black Smoke Estimate</i>	<i>Not Applicable</i>	<i>-99% (p=0.04)</i>	<i>Not Applicable</i>	<i>-99.6% (p=0.29)</i>
<i>Smoking Prevalence Estimate</i>	<i>Not Applicable</i>	<i>Not Applicable</i>	<i>+1.5% (p=0.04)</i>	<i>+0.9% (p=0.28)</i>
<i>Interaction term: (Black Smoke* Smoking Prevalence)</i>	<i>Not Applicable</i>	<i>p=0.02</i>	<i>p=0.26</i>	<i>p=0.15</i>
<i>Period Effect</i>	<i>p=0.01</i>	<i>p=0.01</i>	<i>p=0.01</i>	<i>p=0.01</i>
<i>Deviance:</i>	<i>1.40</i>	<i>1.36</i>	<i>1.35</i>	<i>1.35</i>

Table 9.1:

Table 9.1 shows lung cancer risk estimates across a 10-year period interval relative to the reference period (1990). All the estimates include the interactive effect between BS and smoking prevalence, except for the core model A. The core model is adjusted for age and gender, and indicates that lung cancer risk in the post-ban period (1991-2000) is 3% lower relative to 1990 (**RR=1**), while the risk is 6% higher in the pre-ban period (1981-1990). This core model improved its fit (deviance changed from 1.40 to 1.36) when the annual mean BS levels were included into the core model.

Following adjustment for BS levels alone, the attributable risk (**AR**) formula $[(RR-1)_A - (RR-1)_B]$ shows that 5% excess lung cancer deaths (n=177) are attributable to BS levels in the pre-ban period. Not surprisingly, only 1% excess lung cancer deaths are attributable to BS levels in the post-ban period (1991-2000).

The AR formula was also applied to models C and D (relatively better statistical models that simultaneously adjusted for smoking prevalence). A 2% excess lung cancer death attributable to high BS levels in the pre-ban period (n=72 deaths from a total of 3559 lung cancer deaths observed between 1981 and 1990), while no excess lung cancer deaths attributable to very low BS levels in the post-ban period, is observed. These estimates are conservative compared to the estimates when BS levels alone are adjusted for.

In the post-ban period, a 99% significant risk reduction in BS levels have occurred, while a 1.5% increased risk in smoking. In summary, a significant ‘period’ effect around 1990 in Dublin City (p=0.01) has been demonstrated.

9.3.3 Lung cancer deaths and BS levels across 5-year period

Table 9.2. Relative Risk (RR) estimates with 95% CI for Lung Cancer deaths in Dublin City from 1981 to 2000 in five-year intervals, before and after adjustment for BS levels and smoking prevalence separately and combined, using 1990 as the reference period (RR=1).

<i>Period of Death</i>	<i>Core Model (A) (Adjusted for age and gender)</i>	<i>A + Black Smoke (B)</i>	<i>A + Smoking Prevalence (C)</i>	<i>B+ Smoking Prevalence (D)</i>
	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>
1981-1985	1.12 (0.97, 1.30)	1.09 (0.94, 1.26)	1.06 (0.91, 1.23)	1.06 (0.91, 1.23)
1986-1990	1.11 (0.96, 1.29)	1.04 (0.89, 1.22)	1.00 (0.85, 1.17)	1.00 (0.85, 1.18)
1991-1995	1.05 (0.91, 1.22)	1.13 (0.94, 1.36)	1.19 (1.00, 1.42)	1.18 (0.98, 1.43)
1996-2000	1.01 (0.87, 1.17)	1.09 (0.91, 1.30)	1.18 (0.98, 1.41)	1.17 (0.95, 1.42)
<i>Black Smoke Estimate</i>	<i>Not Applicable</i>	<i>-99.6% (p=0.13)</i>	<i>Not Applicable</i>	<i>-99.9% (p=0.84)</i>
<i>Smoking Prevalence Estimate</i>	<i>Not Applicable</i>	<i>Not Applicable</i>	<i>+1.6% (p=0.03)</i>	<i>+1.5% (p=0.15)</i>
<i>Interaction term: (Black Smoke* Smoking Prevalence)</i>	<i>Not Applicable</i>	<i>p=0.01</i>	<i>p=0.03</i>	<i>p=0.15</i>
<i>Period Effect</i>	<i>p=0.051</i>	<i>p=0.04</i>	<i>p=0.04</i>	<i>p=0.04</i>
<i>Deviance:</i>	<i>1.41</i>	<i>1.35</i>	<i>1.33</i>	<i>1.34</i>

Table 9.2:

A similar pattern to that observed in table 9.1 is also evident in table 9.2 while estimating lung cancer risks across a shorter time interval (5-year), but the estimates are more realistic and consistent with a biological explanation. For example, lung cancer risks are consistently declining across successive 5-year periods (model A), but the risks are greater than ‘unity’ across the two post-ban periods (1991-1995 and 1996-2000), unlike the observation in table 9.1 for 10-year intervals. The models in table 9.2 are also relatively better statistically when compared to those in table 9.1.

The increased risk pattern for lung cancer across the post-ban period (1991-2000) is clearer in table 9.2 because of shorter intervals. The lung cancer risk pattern from 1990 onwards has been magnified. This implies a strong interactive effect (greater than additive) between decreased BS risk (99%) and a corresponding increased risk for smoking (1.5%) in the post-ban period.

A significant ‘period’ effect ($p=0.04$) around 1990 is also observed in table 9.2. The application of the AR formula $[(RR-1)_A - (RR-1)_B]$ shows 3-7% excess lung cancer deaths attributable to high BS levels across the two distinct pre-ban periods (1981-1985 and 1986-1990, respectively). Likewise, the AR formula on models C and D shows 1% excess lung cancer deaths attributable to very low BS levels across each of the two distinct post-ban periods (1991-1995 and 1996-2000).

In summary, the estimate (1%) of excess lung cancer deaths in the post-ban period in table 9.2 is remarkably consistent with the earlier estimate of 1% following adjustment for BS levels alone (models A and B of table 9.1).

9.3.4 Lung cancer deaths and BS levels across 2-year period

Table 9.3. Relative Risk (RR) estimates with 95% CI for Lung Cancer deaths in Dublin City from 1981 to 2000 across 2-year intervals, before and after adjustment for BS levels and smoking prevalence separately and combined, using 1990 as the reference period (RR=1).

<i>Period of Death</i>	<i>Core Model (A) (Adjusted for age and gender)</i>	<i>A + Black Smoke (B)</i>	<i>A + Smoking Prevalence (C)</i>	<i>B+ Smoking Prevalence (D)</i>
	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>	<i>RR (95% CI)</i>
1981-1982	1.10 (0.93, 1.29)	1.10 (0.93, 1.29)	1.06 (0.90, 1.24)	1.06 (0.90, 1.25)
1983-1984	1.14 (0.97, 1.34)	1.10 (0.94, 1.29)	1.05 (0.89, 1.23)	1.05 (0.89, 1.23)
1985-1986	1.18 (1.00, 1.38)	1.10 (0.93, 1.29)	1.03 (0.88, 1.22)	1.03 (0.87, 1.22)
1987-1988	1.05 (0.89, 1.23)	0.96 (0.80, 1.13)	0.88 (0.73, 1.05)	0.86 (0.72, 1.05)
1989-1990	1.16 (0.97, 1.40)	1.08 (0.89, 1.30)	1.02 (0.85, 1.24)	1.01 (0.83, 1.23)
1991-1992	0.98 (0.83, 1.15)	1.08 (0.89, 1.32)	1.17 (0.97, 1.41)	1.20 (0.97, 1.49)
1993-1994	1.08 (0.92, 1.27)	1.21 (0.97, 1.51)	1.26 (1.04, 1.54)	1.30 (1.04, 1.63)
1995-1996	1.02 (0.87, 1.20)	1.17 (0.92, 1.47)	1.29 (1.04, 1.59)	1.34 (1.03, 1.74)
1997-1998	1.00 (0.85, 1.18)	1.12 (0.92, 1.38)	1.27 (1.03, 1.55)	1.32 (1.03, 1.68)
1999-2000	1.07 (0.91, 1.26)	1.18 (0.97, 1.44)	1.27 (1.06, 1.53)	1.31 (1.06, 1.62)
<i>Deviance:</i>	<i>1.41</i>	<i>1.33</i>	<i>1.27</i>	<i>1.28</i>
<i>Interaction term:</i>	<i>Not Applicable</i>	<i>p=0.007</i>	<i>p=0.007</i>	<i>p=0.16</i>
<i>Period Effect:</i>	<i>p=0.11</i>	<i>p=0.08</i>	<i>p=0.06</i>	<i>p=0.07</i>

Table 9.3:

Table 9.3 presents the results from an analysis across very short time intervals (2-year) to accurately delineate the changing pattern for BS levels on lung cancer deaths across short calendar periods in Dublin City from 1981 to 2000. In general, the principles applied to generate the results as presented in tables 9.1 and 9.2 are also applied to produce the results contained in table 9.3. The emerging lung cancer pattern is robust across specific calendar periods in table 9.3. For example, statistically significant estimates are observed in models C and D from 1992 onwards. So the magnification of lung cancer risk pattern observed across the post-ban periods in table 9.2 is not a chance occurrence that is consistent with the corresponding significant rising risk (1.5%) of annual smoking prevalence rates from 1990 onwards.

Although the ‘period’ effects are borderline statistically significant, the interactive effects are also highly significant statistically ($p=0.007$) when either of the variables (BS/smoking) is included into the core model. This suggests that the magnified lung cancer risk from 1990 onwards is also a reflection of their strong interactive effects.

The greatest excess lung cancer risk (9%) occurred in 1987-1988 (the period with very high concentration of annual BS levels), following adjustment for BS levels alone, and then applying the AR formula $[(RR-1)_A - (RR-1)_B]$ to models A and B. However, better statistical models C and D (also simultaneously controlling for smoking) show excess lung cancer deaths attributable to BS levels only when the annual BS concentrations are very high (in 1987-1988). This indirectly suggests an underlying ‘threshold’ effect of air pollutants on lung cancer deaths.

9.3.5 Attributable Risk (AR) and PAR (Population Attributable Risk) of Lung Cancer Deaths in Dublin City

Table 9.4. Attributable Risk (AR) and PAR estimates of Lung Cancer Deaths attributed to Black Smoke levels (the number of preventable lung cancer deaths) in the Pre-Coal Ban Period across Dublin City: 1981-1990.

Year of Death	Observed Deaths	AR (RR _A -RR _B)	Average Population (Dublin City)	PAR _D
	No	No (%)	No/Year	Rates/100,000/year
1981-1990	3559	178 (5.0)	465000	4
1981-1985	1783	53 (3.0)	460000	2
1986-1990	1776	124 (7.0)	470000	5
1983-1984	723	29 (4.0)	455000	3
1985-1986	717	57 (8.0)	460000	6
1987-1988	695	63 (9.0)	465000	7
1989-1990	717	57 (8.0)	470000	6

RR_A: (RR – I)_A
 RR_B: (RR – I)_B
 PAR_D: Population Attributable Risk for Dublin City populations (annual estimates)

Table 9.4:

Assuming a causal relation between BS levels and lung cancer deaths, the results presented in table 9.4 estimates the attributable risk (AR) calculated from the findings presented in tables 9.1, 9.2 and 9.3 (models A and B), utilizing the AR formula (**RR_A-RR_B**). The estimates are also standardised to the Dublin Census Population for estimating PAR (Population Attributable Risk). Around 177 to 206 excess lung cancer deaths have occurred in Dublin City from 1981 to 1990 (prior to the Coal Ban in 1990). Such estimates varied across different time-periods depending on the concentrations of the annual mean BS levels. As expected, the highest AR (9%) was observed when the annual mean BS levels were the greatest (1987-1988).

Importantly, the estimated annual lung cancer death rates attributable to BS (PAR) ranged from 2 to 7 deaths per 100,000 persons in Dublin City between 1981 and 1990. Following simultaneous adjustment for smoking prevalence and BS levels, and then applying the AR formula $[(RR-1)_A - (RR-1)_B]$ to models C and D in tables 9.1 and 9.2, 1% excess lung cancer deaths are attributable to very low BS levels. This 1% estimate translates into 34 excess lung cancer deaths (from a total of 3353 observed deaths in 1991-2000) in the post-ban period.

9.4 DISCUSSION

This section deals with the epidemiological findings presented in section three of this chapter on the temporal association between lung cancer deaths and urban air pollution levels in Dublin City from 1981 to 2000. As mentioned earlier, annual mean one-year lag period of black smoke levels have been used as the indicator variable for urban air pollution mixture. So pollutants such as ozone, sulphur dioxide (SO₂), nitrogen oxide, etc. have not been considered in this study. Comprehensive national data on such pollutants (except for SO₂) are not available historically, and it is still not clear whether any of the above pollutants cause lung cancer alone or in concert.

An auto-correlation between the pollutants is also a methodological issue. Black smoke levels have been used in a recent study³³ investigating into the effect of the Coal Ban of 1990, as a public-health intervention, on all-cause mortality in Dublin City. This section mainly discusses the inherent methodological issues surrounding air pollution epidemiological studies with regard to lung cancer pathogenesis, and also draws conclusions of the present study findings based on the evidence of several air pollution epidemiological studies across different settings.

A simple age-period model was employed, and such a technique accounts for any known public-health interventions, such as the Coal Ban introduced across Dublin City in 1990. So an observed significant 'period' effect, despite adjusting for the period when a known public-health intervention was implemented (for example, using 1990 as the reference period), indicates the effect of such a public-health intervention together with the effect of factors other than the public-health intervention alone. Any model effects are easier to explain biologically whenever a potential risk factor associated with such a ban is also included into such models (BS, for example).²³ Hence, a multiplicative risk model based on Poisson distribution and simultaneously including a risk factor, whose information is also available, is a robust modelling technique for demonstrating any temporal associations.²³

A one-year lag period was used, because the models developed fitted well for 1-year lag when tested across different lag-periods (three, five and eight-year interval, which was the maximum lag-period possible owing to the lack of comprehensive data on BS in Ireland prior to 1973). Prospective studies have allowed a 3-year lag period, although the exact biological mechanism for lung cancer pathogenesis with black smoke, or with urban air pollution mixture in general, is still not clear.³⁰²

Products of combustion of fossil fuels, such as PM₁₀ containing benzo[*a*]pyrene, are reported to damage the respiratory epithelium.³⁰³ Potential mechanisms for lung cancer promotion could include slowing of mucociliary clearance, impairment of alveolar macrophage function, and other specific or non-specific effects on the immune response, such as increased epithelial permeability facilitating absorption of carcinogenic components of particulate matter.³⁰⁴ If air

pollution exerts a carcinogenic effect at a 'late' stage of the multi-stage process, more recent exposures will be the important determinants of risk.¹¹⁵

Lung cancer deaths could also be brought forward when associated with increased urban air pollutants, because disorders other than lung cancer could be associated with lung cancer patients, who are also otherwise elderly and immunologically compromised. This phenomenon is recently termed 'harvesting' in air pollution epidemiological studies.^{305,306} Both the above phenomena adequately explain the biological plausibility of the present study findings. The sudden decline in lung cancer mortality rates in Britain in the mid-1950s was also partially due to the implementation of the 1956 Clean Air Act.²⁴ The effect of quitting smoking on reduction in lung cancer risk has also been reported within two years of quitting.^{104, 307} Thus, the observed 1% excess lung cancer risk reduction in the post-ban period (using 1990 as the reference period) is attributable in part to the Coal Ban introduced in 1990 across Dublin City.

The magnification of lung cancer risk pattern from 1990 onwards also suggests the influence of risk factors other than active smoking and BS contributing in part to such an observation. So the increased lung cancer risk pattern across Dublin City from 1990 onwards is real, and could be associated with 'urban' factors such as rapid urbanization. Such a phenomenon can give rise to increased environmental pollution because BS has been used only as an indicator variable for urban air pollution mixture masking the natural effects (if any) of other potential air pollutants, including increased asbestos and ETS exposure.

The increased lung cancer risk pattern from 1990 onwards is also consistent with the observed annual rise in lung cancer death rates across the most recent periods in Dublin City, as demonstrated in chapter eight. Consistent with chapter seven findings, an increased lung adenocarcinoma risk pattern is also observed in Dublin City across both sexes compared to the rest of the Republic in the most recent periods, following simultaneous adjustment for a few of the potential confounders.

As discussed in chapter six and seven, the younger birth cohorts (born after 1935 in particular) across the whole of the Republic, and also in Dublin City demonstrated a lung cancer risk pattern that is less influenced by factors other than active smoking alone. Lung adenocarcinoma is relatively more common among the younger individuals, and also among non-smokers. So all these observations suggest a **common link**: the recent increased lung adenocarcinoma risk pattern that is more commonly associated with factors other than active smoking alone is a cohort effect of those born after 1935. Unfortunately, historical information on cell-types prior to 1994 is not available in Ireland.

Gender differences in urban air pollutants have also been reported. The secondary pollutant ozone (a gaseous ‘summer’ pollutant following chemical reaction) is more commonly associated with lung cancer among males even in very low levels.³⁰⁷ The present study did not include multi-pollutant analyses for the reasons mentioned earlier. Although pollution data on SO₂ were available for the periods studied, a consistent association with lung cancer for females in particular is lacking.^{302, 308} The main source of black smoke emissions in Dublin in the 1980s,

however, was bituminous coal burning for domestic heating. This alone accounted for 76% of total smoke emissions in Dublin in the 1980s.³⁰⁰

Furthermore, exposure ascertainment bias in any ecological analyses is an inherent methodological issue. However, between-city heterogeneity and gender variation in exposure assessment is greatly reduced in this study for restricting to total populations at risk (males and females combined) in Dublin City alone. The recent urban air pollution due to vehicular exhausts in major cities (including Dublin) is also a growing problem, and studies with multi-pollutant analyses would be more helpful for epidemiological studies in the near future. One of the primary pollutants (nitrogen oxide) is already being included in air-pollution studies as the main source of emission from vehicles in some European cities.^{302, 224}

The lung cancer risk in the post-ban period also magnified, following further adjustment for BS levels. This reflects an underlying interaction (greater than additive) between very low levels of BS (99% risk reduction) and a corresponding increased risk due to smoking prevalence (1.5%), with a competing risk pattern. Such significant interactions are also observed.²²⁴ The observed 20-30% magnified risk in the post-ban period also corresponds well with the joint effect of urban air pollution and smoking elsewhere.³⁰⁹

An underlying interaction between unknown/unmeasured potential risk factors is a possibility, because BS has been used as an indicator variable in this study. Consequently the observed interaction would also be due to rising levels in any of the urban air pollution mixtures not accounted for in this study. Such interactions are

mainly associated with non-adenocarcinoma lung tumours alone.²⁴⁴ In summary, the increased lung cancer pattern from 1990 onwards across Dublin City is also in part due to the strong interactive effects between BS and smoking.

In present day industrialized countries, most people spend 90% of their time indoors, where exposures to particulate and volatile organic air pollution can often exceed ambient concentrations.¹¹⁵ Theoretically, a minimum outdoor air pollution exposure level of 10% could contribute one to six excess lung cancer cases for every 100 cases detected at the national/regional level.¹¹⁵ Such estimates are remarkably consistent with this study finding. Assuming a causal relation between lung cancer and black smoke, 5% (n=177) excess lung cancer deaths are attributable to high BS levels from 1981 to 1990 (pre-ban period) in Dublin City. By contrast, only 1% (n=34) excess lung cancer deaths are attributable to very low BS levels in the post-ban period (1991-2000). In conclusion, the estimates of lung cancer deaths in Dublin City attributable to black smoke levels seem to be conservative.

9.4.1 Summary and Conclusion

In summary, the estimated annual lung cancer death rates attributable to urban air pollution exposure in Dublin (2-7/100,000) strongly correspond with the observed PAR attributed to urban air pollution mixture elsewhere (less than 10 cases/100,000/year).³⁰ The excess 5% (n=177) lung cancer deaths across Dublin City in the pre-ban period is well within the limits of 12% excess lung cancer cases attributed to any 'urban' effects.²⁹ Evidence suggesting that 1-2% of all future lung cancers are attributable to very low levels of urban air pollution mixture,²⁸ again corresponds to the study estimate of 1% (n=34) excess deaths in the post-ban period.

In conclusion, an underlying temporal association between urban air pollution levels (black smoke, in particular) and lung cancer deaths across Dublin City from 1981 to 2000 has been demonstrated in this study. The overall 'period' effect around 1990 is contributed in part due to the Coal Ban across Dublin City in 1990. Nonetheless, the lung cancer risk pattern from 1990 onwards magnified following simultaneous adjustment for BS and smoking prevalence. This also reflects the residual confounding effects of unmeasured and unknown risk factors for lung cancer, in addition to an underlying interactive effect (greater than additive) between very low black smoke levels and rising smoking prevalence rates in the post-ban period.

Chapter Ten

SUMMARY, CONCLUSIONS, RECOMMENDATIONS

The present study investigated the epidemiological pattern of lung cancer deaths (1970-1999), and lung cancer incidence pattern across cell-types (1994-2001) in the Republic of Ireland. The study also examined the temporal association between lung cancer deaths and urban air pollution levels (using black smoke levels as the indicator variable) in Dublin City from 1981 to 2000 (ten years before and after the introduction of the Coal Ban in 1990 across Dublin City).

As the study objectives are distinct, and no single data source is 100% complete or comprehensively available at the national level, the study utilised various data sources pertinent to each of the study objectives. Despite such inherent methodological limitations, the study has made the best use of data available to date, and employed advanced statistical tools to investigate each of the study objectives. This may have minimised potential biases.

Lee and colleagues¹⁶ have collected historical data on cigarette consumption patterns for the Irish populations from various sources (**Appendix III**). This source of data has been used within the present study. Overall, this study is an ecological analysis. Due to the limitations in the data available, in particular the lack of comprehensive smoking data, and the non-existence of a national cancer registry prior to 1994, some results should be interpreted with caution. All the lung cancer estimates (risks, rates, ratios) are adjusted for age and standardised to the Irish and the European Population Standards. This will have minimised bias due to underlying population changes across the Republic of Ireland.

In summary, the main findings of the study are as follows:

- In general, females do not have a greater susceptibility to developing lung cancer risk when compared with males. However, gender susceptibility to specific tobacco carcinogens cannot be ruled out.
- Age-standardised lung cancer death rates for females are significantly rising on an annual basis (2.4%) from 1970 onwards, although a deceleration in their annual rise (0.1%) have been observed from 1989 onwards. By contrast, age-standardised lung cancer death rates for males are declining on an annual basis, significantly from 1990 onwards (-2.4%).
- Both sexes in Dublin City are showing an annual rise in their age-standardised lung cancer death rates in the most recent periods, significantly in females from 1990 onwards (3.3%). The highest annual rise is observed among the oldest adults (85+ year-olds), particularly for females, suggesting an age-cohort phenomenon due to delayed smoking habits among females.
- Those born before World War II have a three-fold increased lung cancer risk relative to those born in 1963-1967 across both sexes (50-90% risk reduction following adjustment for cumulative lifetime cigarette consumption). This confirms an underlying age-cohort phenomenon due to changing smoking patterns across successive generations for lung cancer risk development
- Among all the cell-types investigated, lung adenocarcinoma (AC) is significantly rising (adjusted for smoking) annually (8%) in females from 1994 to 2000. An increased AC: SQCC age-standardised incidence rate ratios (adjusted for smoking) from 1994 onwards are also observed. Both imply a real recent increase in lung AC.

- Following simultaneous adjustment for other cell-types and a few of the potential confounders available to the study (age, smoking status, geographical locations, period of diagnosis), Dublin populations have a modest increased risk pattern for lung AC compared to the rest of the Republic.
- The study also estimated that around 5% of the smoking populations in the Republic of Ireland develop lung cancer in some point of their lifetime.
- This study demonstrated a significant 'period' effect in Dublin City around 1990 with regard to lung cancer deaths, after controlling for age, gender, black smoke (BS) levels and annual smoking prevalence rates from 1981 to 2000. This suggests an impact of the Coal Ban in 1990 across Dublin City.
- Overall, a 6% increased lung cancer risk is observed between 1981 and 1990 (pre-coal ban period), while 3% decreased lung cancer risk is observed between 1991 and 2000 (post-coal ban period).
- Assuming a cause-effect relation, lung cancer deaths attributable to high BS levels following adjustment for smoking prevalence ranges from 2% to 5% (n=74-177) in the pre-ban period, while $\leq 1\%$ (n=0-34) excess lung cancer deaths are attributable to very low BS levels in the post-ban period.
- The estimated PAR (population attributable risk) ranges from 2 to 7 annual lung cancer death rates per 100,000 persons in Dublin City in the pre-ban period. Overall, the lung cancer estimates in relation to BS are conservative.

This study has three important implications. Firstly, an encouraging lung cancer pattern is expected in the Republic, assuming no changing risk profile of the youngest cohorts (born in 1963-1967) in particular. The present study demonstrated a declining lung cancer risk pattern in those born after 1935. These are the cohorts who represent the underlying lung cancer pattern for the most recent periods (1990 onwards) in the

Republic. The latest ISACC 2003 data also shows teenage smoking fell from 20% in 1995 to 13% in 2003 (*Pat Goodman Personal communication*). Importantly, the recent Smoking Ban nationwide will further minimise environmental tobacco exposure, which can also influence future lung cancer pattern.

Secondly, the annual rise in lung AC (from 1995 onwards) is also a cohort effect of those born after 1935, although no historical information on cell-types is available prior to 1994. Lung AC is more commonly associated with factors other than active smoking alone. Lung AC risk pattern is modestly increased in Dublin City populations compared to the rest of the Republic. These observations imply a greater urbanization pattern for Dublin City in the early 1970s and the 1980s relative to other urban locations in the Republic compounded with a changing life style pattern.

Thirdly, a temporal association between annual lung cancer deaths and the mean annual BS levels have been demonstrated in this study, ten years before and after the Coal Ban was introduced in 1990 across Dublin City. Following the Coal Ban, lung cancer risk due to BS has significantly declined in Dublin City. Together with the overall increased risk due to smoking prevalence, the lung cancer risk pattern has also recently magnified in Dublin City. This indicates the strong interactive effect (greater than additive) between BS levels and smoking prevalence rates, in addition to underlying interactions between unknown/unmeasured risk factors.

In conclusion, lung cancer death rates in females are predicted to continue rising over the coming years in the Republic of Ireland. It is also imperative to identify and to quantify potential environmental factors for the increased lung AC risk pattern across Dublin City populations. Nonetheless, the residual confounding effect of active smoking on lung cancer risk is always an inherent methodological issue.

This study also identifies some broader issues surrounding epidemiological research in general within the Republic of Ireland that should be addressed in the future, possibly through the following recommendations:

- A high quality epidemiological study, with robust conclusion, is feasible only when a large historical cohort is followed-up for a substantial period of time. For this, a large cohort has to be established in the Republic that can be a national resource for a host of epidemiological studies similar to North America and in the UK. Such epidemiological evidence should also lay the foundation of bold public-health policy initiatives in line with the Coal Ban.
- Novel epidemiological approaches (life course epidemiology in particular) could then be applied to such large historical cohorts, and integrated with modern molecular techniques for a better understanding of the biological mechanism for all the chronic diseases of public health importance.
- In general, multicentre, collaborative, inter-disciplinary studies, with a strong component of epidemiological input, should certainly supplement very many individual epidemiological studies even within the Republic.
- It is imperative to establish a comprehensive national smoking database for academic pursuits, and also for providing with sound epidemiological evidence to fight against the multi-national tobacco industries. Such evidences would reinforce comprehensive anti-smoking cessation activities nationwide.
- Last but not the least, a political commitment to appreciate the importance, and also the need for in-depth epidemiological research within the Republic of Ireland. In addition to investing in advanced medical technology and to funding clinical therapeutic trials, a critical mass of epidemiologists is necessary to lead through a better health gain for the Irish populations.

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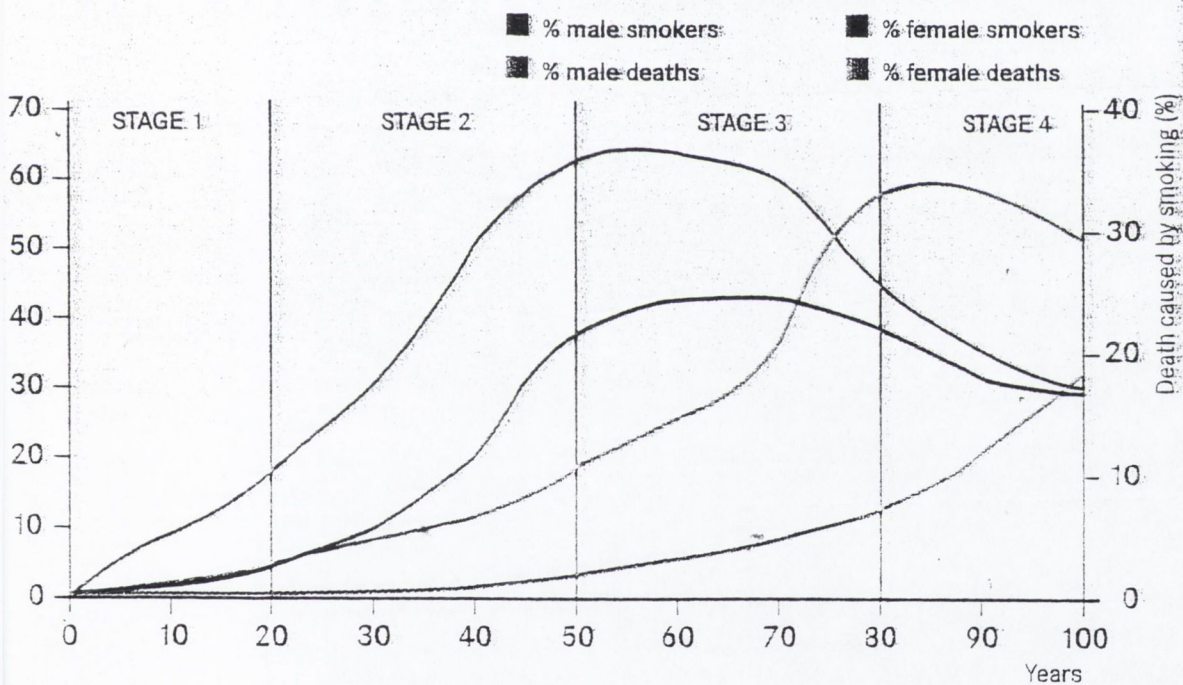
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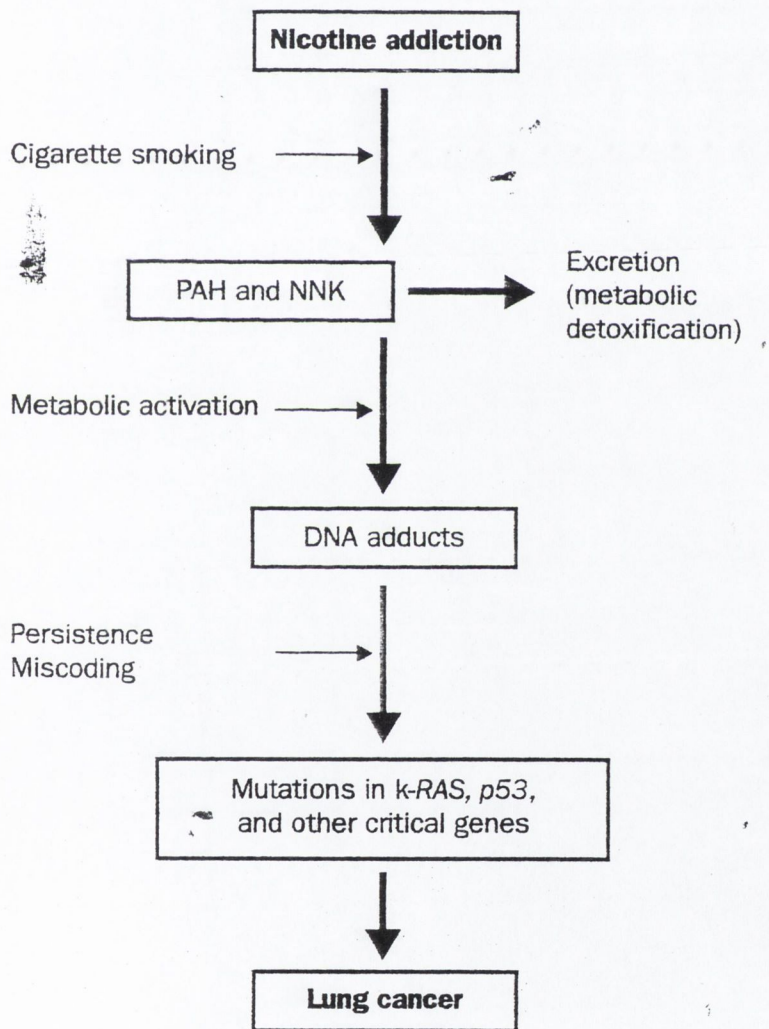
APPENDIX ONE

(Tobacco Epidemic Model)



APPENDIX TWO

(Tobacco Carcinogenic Pathway)



APPENDIX THREE

(Sources of Irish Smoking Data)

Notes on sources of survey data

Each source of survey data—either an individual survey or a series of surveys repeated over a number of years—is cited by a source number. This number is shown in the tables and corresponds to the source numbers given below, where details of the source publication and of the survey methodology are given. Full citations of the sources are given on p. 354 under *References*.

Source
number

- 1 **Todd (1986) quoting Health Education Bureau**
- a. Percentage smokers given from national probability sample. Sample size approximately 5 000 each year. Year commencing July
 - b. Cigarettes per smoker given from national stratified random sample in summer 1980. Sample size 3 000

- 2 **O'Rourke *et al* (1968, 1971, 1983a)**
- a. Studies of smoking in randomly selected post-primary schools in City and County of Dublin. Anonymous questionnaires completed by all pupils at the schools, with teachers usually absent. Sample size in 1967 (boys) 2 710, (girls) 1 792, in 1970 (boys) 3 015, (girls) 2 468, and in 1980-1981 (boys) 3 068, (girls) 2 085
 - b. Regular smokers: smoked at least once a week. All smokers (1980 only): smoked regularly, or on holiday, at parties etc
 - c. Consumption per smoker has been converted from weekly

- 3 **Todd (1986), quoting O'Rourke *et al* (1983b) and O'Rourke *et al* (in press)**
- a. Rural areas.

Year	Sample size	
	Males	Females
1971	2 897	2 853
1982	2 092	2 716

- b. Regular smokers: smoked at least 1 cigarette per week every week
- 4 **Grube and Morgan (1986)**
- a. Study conducted in 24 randomly selected post-primary schools (excluding boarding and special schools) in greater Dublin. Years randomly selected within schools. Anonymous questionnaire completed on two occasions a month apart, in class with teachers absent. Sample size (males) 1 837, (females) 1 732. Two schools refused to participate
 - b. Regular smokers: smoke cigarettes daily in last month. All smokers: smoked at least a few cigarettes in last month
- 5 **Corridan (1963)**
- a. Survey in Cork City in April-May 1962, administered by doctor with teachers absent. Sample size (boys) 1 588, (girls) 1 532
 - b. Regular smokers: smoked 1 or more cigarettes a week
 - c. Consumption category estimation adult method, which may not be appropriate, based on 1-4, 5-9, 10-19, 20-29, and 30+ cigarettes/smoker/week
- 6 **Todd (1986)**
- a. Estimated by Todd

- 7 Herity *et al* (1976), Ward *et al* (1978), Council of Europe (1978), quoting Irish Tobacco Manufacturers' Advisory Committee, and Cleary and Shelley (1983) quoting Research Services (1962)
 - a. National quota samples
 - b. Assumed extension to age distribution for percentage smokers, age 15: males 30%; females (1961) 10%, (1967, 1971) 15%, (1975) 20%. Number of cigarettes/person/day: males: 3.0; females (1961, 1967) 1.0, (1971, 1975) 2.0
- 8 Cleary and Shelley (1983) and Department of Health/Health Promotion Unit
 - a. Joint National Media Research surveys. 1972 represents July 1972-June 1973 etc. Conducted by (1972-1983) Irish Marketing Surveys Ltd, (1984-1989) Market Research Bureau of Ireland, (1990-1993) Lansdowne market Research. Random samples of around 5 000 each year
 - b. Regular smokers: smoked at least 1 cigarette on average per day
 - c. Assumed extension to age distribution for percentage smokers, age 15: males 30%; females (1972-1974) 15%, (1975-1984) 20%
- 9 Merzdorf *et al* (1982), quoting Health Education Bureau Research and Information Division (1979)
- 10 Adriaanse *et al* (1986), quoting Cleary and Shelley (1983)
 - a. National sample. Age not stated
- 11 Flynn (1961)
 - a. Survey conducted Sep 1959-Feb 1960 in schools in Co. Westmeath. Included all secondary and vocational schools; also older pupils at all primary schools in larger towns and villages, and some in isolated rural areas. Anonymous questionnaire usually completed in assembly hall, with teachers absent. Sample size (males) 1 389, (females) 1 317. All pupils present on the day participated, but 20 (0.7%) questionnaires rejected
 - b. Results presented in the *All ages* column of Table 14.4 include a few pupils age 9-11 (117 males and 85 females)
 - c. Regular smokers: smokes 1+ cigarettes per week. All smokers: smokers regularly or occasionally, including those who smoke only on festive occasions. There were no pipe smokers
 - d. Consumption category estimation based on 1-4, 5-9, 10-19, 20-29, 30-49, 50-89, 90+ cigarettes/smoker/week. The questionnaire allowed the pupils to give their consumption as daily, weekly or monthly, so the standard method of estimation should be regarded with caution
 - e. 75% of the pupils' fathers and 43% of their mothers smoke
- 12 O'Rourke *et al* (1970)
 - a. Study by the Irish Cancer Society of pupils at all vocational schools in Co. Kerry. Sample size (males) 899, (females) 617, comprising over two thirds of vocational school students in the county
- 13 International Agency for Research on Cancer (IARC) (1986) quoting Health Education Bureau (1980)
 - a. National survey, no further details available. Age not stated
- 14 Grube *et al* (1984)
 - a. Study of pupils at 27 Catholic primary schools in Dublin. Approximate ages corresponding to 6th class, median age 12.4. Anonymous questionnaires completed in class with student teacher present and regular teacher absent. Sample size (males) 331, (females) 418
 - b. Regular smokers: smoked daily in last month. All smokers: smoked at least 1 cigarette in last month
 - c. Consumption category estimation based on 1-2, 3-5, 6-10, 11-15, 16-20, 21+ cigarettes/smoker/day

- 15 **Shelley *et al* (1996)**
- Random sample in county Offaly, reference area for a community prevention and health promotion programme conducted in Kilkenny
 - Smokers of all products: smoked cigarettes daily, 1 g tobacco daily, 1 cigar weekly, or a mixture of tobacco products. Prevalence shown with product * is for cigarette only smokers. It is unclear whether consumption per smoker relates to this group or to all cigarette smokers
- 16 **van Reek *et al* (1992), van Reek and Adriaanse (1995)**
- A series of surveys of Young Europeans. About 800 children aged 11-15 years interviewed in each EC country except Luxembourg (where only 250 interviewed). Lowest age group 11-12. Interviews conducted at home, with parents absent
 - Regular smokers: smoked daily. All smokers: smoked at least once a week
- 17 **WHO (1997)**
- No original source. National survey among 4 000 students
 - Regular smoker: smoked at least one or two cigarettes daily
 - This survey is also reported by Joossens *et al* (1994), except prevalence among girls is given as 13%
- 18 **Hibell *et al* (1997)**
- Nationally representative survey forming part of ESPAD (European School Survey Project on Alcohol and Other Drugs). Target was pupils born in 1979, thus age 15-16 at time of survey in March/April 1995. Approximately 80% of this group still in school. Anonymous questionnaire completed and sealed in envelope by pupil, in class. Teachers present, but discouraged from walking round the classroom. Sample size (males) 907, (females) 942. Response rate approximately 96%
 - Regular smokers: smoked 1 or more cigarettes per day in last 30 days. All smokers: smoked in last 30 days
 - Consumption category estimation based on 1-5, 6-10, 11-20, 21+ cigarettes/smoker/day
- 19 **Joossens *et al* (1999) quoting Commission of European Community**
- 1987 represents 1988/1988 etc. Age group not stated
- 20 **Clancy and Manning (1999)**
- Study of 3 418 children randomly selected from 30 schools throughout Republic of Ireland. Self-completion questionnaire on smoking and chest symptoms
 - Regular smokers: no further definition, but it is stated that two thirds of these smokers smoked daily

APPENDIX FOUR

(Output of Joinpoint Regression Model)

Joinpoint Regression Program: Version 2.7

Model Specifications:

Response Variable	=	Response
Independent Variable	=	Male Death Years (1970-1999) in the ROI
Type of Change Point Model	=	Join Point
Loglinear Model	=	Yes
Heteroscedastic Errors Model	=	No
Autocorrelation Parameter (AR(1))	=	0.0000
Minimum Number of Join Points	=	0
Maximum Number of Join Points	=	3
Minimum Number Obs Before First Joinpoint	=	2
Minimum Number Obs Between Two Joinpoints	=	2
Number of Grid Points Between Data Points	=	0
Overall Significance Level of Permutation Tests	=	0.0500
Number of Permutations to Perform for Each Test	=	4499
Seed 1 for Randomly Permuting Data	=	7160
Seed 2 for Randomly Permuting Data	=	82961

Joinpoint Regression Program: Version 2.7

Model 0: 0 Join Point(s)

Number of Observations	=	30
Number of Parameters	=	2
Degrees of Freedom	=	28
Sum of Squared Errors	=	1.46165E-01
Mean Squared Error	=	5.22017E-03

Estimated Regression Coefficients (Beta):

Parameter	Parameter Estimate	Standard Error	Z	Prob > t
Intercept	4.03074658	0.02705593	148.9783	0.00000
Slope	0.00047563	0.00152403	0.3121	0.75729

Estimated Annual Percent Change (EAPC):

Segment	EAPC	(95% Confidence Interval)
1	0.04757433	(-0.26426970, 0.36039341)

Joinpoint Regression Program: Version 2.7

Model 1: 1 Join Point(s)

Number of Observations = 30
Number of Parameters = 4
Degrees of Freedom = 26

Sum of Squared Errors = 5.27090E-02
Mean Squared Error = 2.02727E-03

Estimated Join Point(s):

Join Pt	Estimate	(95% Confidence Interval)	
1	21.00000000	(14.00000000,	26.00000000)

Estimated Regression Coefficients (Beta):

Parameter	Parameter Estimate	Standard Error	Z	Prob > t
Intercept1	3.96125580	0.02093094	189.2536	0.00000
Intercept2	4.63299997	0.15198559	30.4832	0.00000
Slope1	0.00805450	0.00174728	4.6097	0.00010
Slope2	-0.02393332	0.00581699	-4.1144	0.00037
Slope2-Slope1	-0.03198782	0.00607374	-5.2666	0.00002

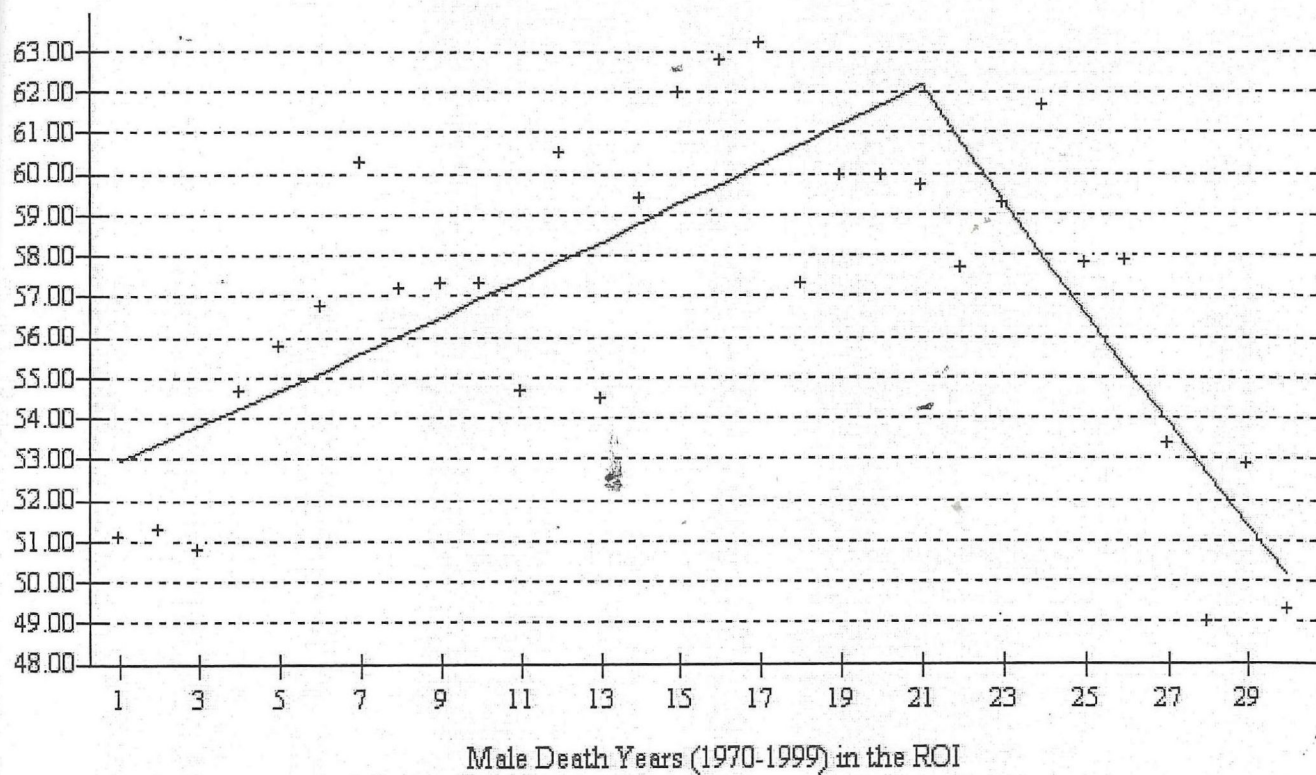
Estimated Annual Percent Change (EAPC):

Segment	EAPC	(95% Confidence Interval)	
1	0.80870262	(0.44658502,	1.17212567)
2	-2.36491858	(-3.52763817,	-1.18818549)

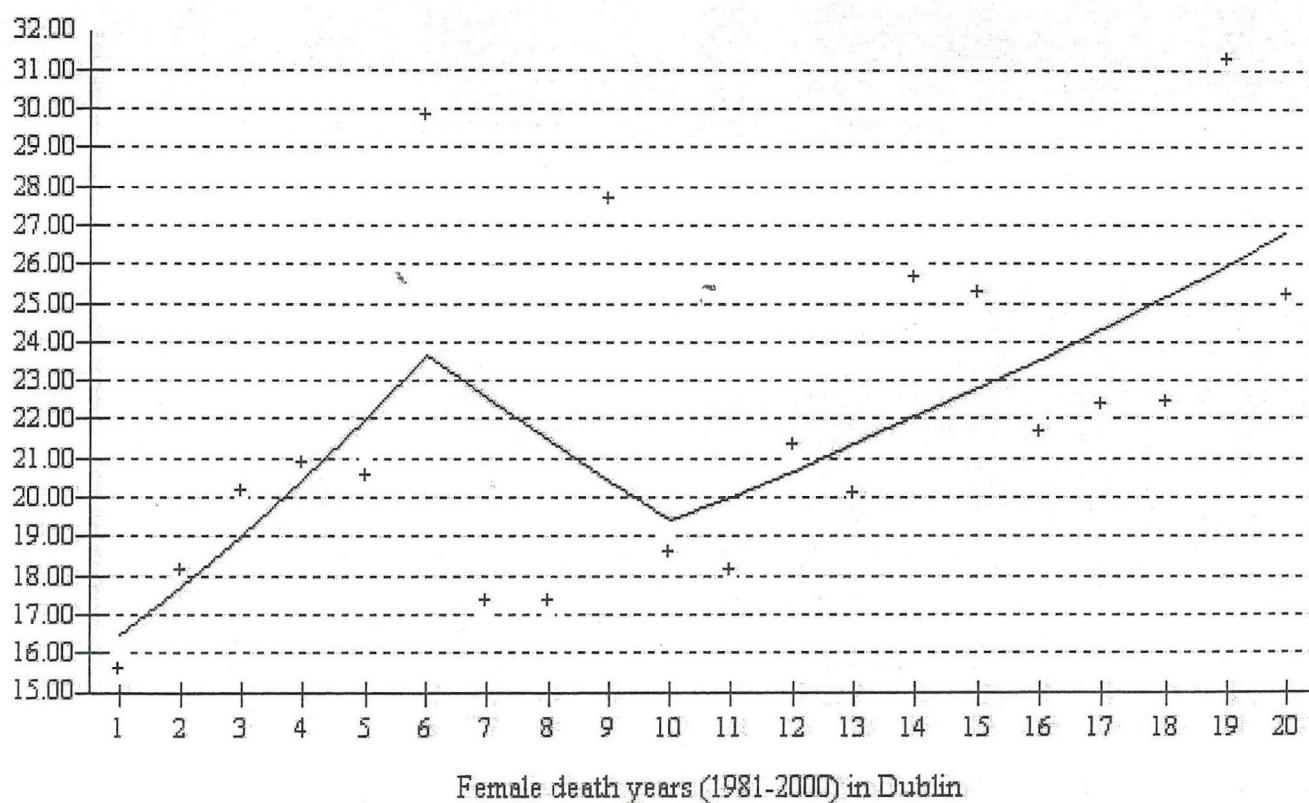
APPENDIX FIVE

(Graphs of Joinpoint Regression Segments)

Joinpoints = 1



Joinpoints = 2



APPENDIX SIX

(SAS programme and output of cohort analysis)

MODEL II (age-cohort) in Chapter Six

```
proc genmod data=Sashelp.roitotfinal;
class newage newbthyr;
model totdths=newage newbthyr newdyr /TYPE1 offset=l_par dist=Poisson SCALE=PEARSON ;
run;
```

The GENMOD Procedure

Model Information

Data Set	SASHELP.ROITOTFINAL	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	totdths	totdths
Offset Variable	l_par	l_par
Observations Used	270	

Class Level Information

Class	Levels	Values
newage	9	1 2 3 4 5 6 7 8 9
newbthyr	16	188892 189397 189802 190307 190812 191317 191822 192327 192832 193337 193842 194347 194852 195357 195862 196367

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	245	392.2990	1.6012
Scaled Deviance	245	245.3326	1.0014
Pearson Chi-Square	245	391.7672	1.5990
Scaled Pearson X2	245	245.0000	1.0000
Log Likelihood		105109.5876	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter		DF	Estimate	Standard Error	Wald	95% Confidence Limits	Chi-Square	Pr > ChiSq
Intercept		1	-25.5186	8.3512	-41.8866	-9.1505	9.34	0.0022
newage	1	1	3.8186	0.2191	3.3892	4.2480	303.82	<.0001
newage	2	1	3.8282	0.1989	3.4383	4.2181	370.33	<.0001
newage	3	1	3.6499	0.1794	3.2982	4.0015	413.84	<.0001
newage	4	1	3.4402	0.1606	3.1255	3.7549	459.03	<.0001
newage	5	1	3.1187	0.1423	2.8397	3.3977	480.04	<.0001
newage	6	1	2.6527	0.1249	2.4079	2.8974	451.30	<.0001
newage	7	1	2.1697	0.1091	1.9558	2.3836	395.21	<.0001
newage	8	1	1.4856	0.0967	1.2961	1.6750	236.16	<.0001
newage	9	0	0.0000	0.0000	0.0000	0.0000	.	.
newbthyr	188892	1	0.6035	0.3456	-0.0738	1.2808	3.05	0.0807

The GENMOD Procedure

Analysis Of Parameter Estimates

Standard	Wald	95% Confidence	Chi-
----------	------	----------------	------

Parameter	DF	Estimate	Error	Limits		Square	Pr > ChiSq
newbthyr	189397	1	0.7894	0.3201	0.1621 1.4167	6.08	0.0136
newbthyr	189802	1	1.1247	0.2992	0.5383 1.7112	14.13	0.0002
newbthyr	190307	1	1.2498	0.2802	0.7007 1.7989	19.90	<.0001
newbthyr	190812	1	1.3153	0.2616	0.8026 1.8279	25.29	<.0001
newbthyr	191317	1	1.3245	0.2439	0.8465 1.8024	29.50	<.0001
newbthyr	191822	1	1.2831	0.2265	0.8392 1.7271	32.09	<.0001
newbthyr	192327	1	1.2497	0.2101	0.8378 1.6615	35.37	<.0001
newbthyr	192832	1	1.1491	0.1948	0.7673 1.5309	34.80	<.0001
newbthyr	193337	1	0.9180	0.1802	0.5649 1.2712	25.96	<.0001
newbthyr	193842	1	0.7654	0.1660	0.4401 1.0908	21.26	<.0001
newbthyr	194347	1	0.6837	0.1583	0.3735 0.9939	18.66	<.0001
newbthyr	194852	1	0.3853	0.1544	0.0827 0.6879	6.23	0.0126
newbthyr	195357	1	-0.1471	0.2015	-0.5420 0.2479	0.53	0.4655
newbthyr	195862	1	0.1223	0.1676	-0.2063 0.4508	0.53	0.4658
newbthyr	196367	0	0.0000	0.0000	0.0000 0.0000	.	.
newdyr		1	0.0001	0.0000	-0.0000 0.0002	3.11	0.0778
Scale		0	1.2645	0.0000	1.2645 1.2645		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

LR Statistics For Type 1 Analysis

Source	Deviance	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Intercept	67127.0155						
newage	1404.7408	8	245	5137.60	<.0001	41100.8	<.0001
newbthyr	397.2719	15	245	42.00	<.0001	630.04	<.0001
newdyr	392.2990	1	245	3.11	0.0791	3.11	0.0778

APPENDIX SEVEN

(European Standard Population)

WHO Standard European Population

AGE (IN YEARS)	EUROPEAN STANDARD POPULATION
0-4	8,000
5-9	7,000
10-14	7,000
15-19	7,000
20-24	7,000
25-29	7,000
30-34	7,000
35-39	7,000
40-44	7,000
45-49	7,000
50-54	7,000
55-59	6,000
60-64	5,000
65-69	4,000
70-74	3,000
75+	4,000
TOTAL	100,000

APPENDIX EIGHT

(SAS programme and output of period analysis: core model)

Model A (Core Model) in Chapter Nine

```
proc genmod data=sashelp.dubsmk;  
class agegrp revdyr2;  
model totdths= agegrp revdyr2 /TYPE1 offset=l_par dist=Poisson SCALE=PEARSON ;  
run;
```

The GENMOD Procedure

Model Information

Data Set	SASHELP.DUBSMK	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	totdths	totdths
Offset Variable	l_par	l_par
Observations Used	120	

Class Level Information

Class	Levels	Values
agegrp	6	1 2 3 4 5 6
revdyr2	3	198190 199120 200000

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	112	156.6238	1.3984
Scaled Deviance	112	110.2981	0.9848
Pearson Chi-Square	112	159.0404	1.4200
Scaled Pearson X2	112	112.0000	1.0000
Log Likelihood		15698.8750	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	-5.6729	0.0916	-5.8524	-5.4935	3838.16	<.0001
agegrp 1	1	-5.5265	0.1398	-5.8005	-5.2524	1562.20	<.0001
agegrp 2	1	-2.0257	0.0870	-2.1962	-1.8551	542.02	<.0001
agegrp 3	1	-0.7810	0.0736	-0.9252	-0.6368	112.72	<.0001
agegrp 4	1	-0.0235	0.0708	-0.1622	0.1152	0.11	0.7397
agegrp 5	1	0.2797	0.0724	0.1379	0.4216	14.95	0.0001
agegrp 6	0	0.0000	0.0000	0.0000	0.0000	.	.
revdyr2 198190	1	0.0602	0.0687	-0.0744	0.1948	0.77	0.3805
revdyr2 199120	1	-0.0265	0.0685	-0.1608	0.1078	0.15	0.6990
revdyr2 200000	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale	0	1.1916	0.0000	1.1916	1.1916		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

The GENMOD Procedure

LR Statistics For Type 1 Analysis

Source	Deviance	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Intercept	17723.4375						
agegrp	168.4898	5	112	2472.52	<.0001	12362.6	<.0001
revdyr2	156.6238	2	112	4.18	0.0178	8.36	0.0153

APPENDIX NINE

(SAS programme and output of period analysis: BS included)

Model B (adding BS levels) in Chapter Nine

```
proc genmod data=sashelp.dubsmk;  
class agegrp revdyr2;  
model totdths=agegrp revdyr2 bs1lag bs1lag*smkprvtot/TYPE1 offset=l_par dist=Poisson SCALE=PEARSON ;  
run;
```

The GENMOD Procedure

Model Information

Data Set	SASHELP.DUBSMK	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	totdths	totdths
Offset Variable	l_par	l_par
Observations Used	120	

Class Level Information

Class	Levels	Values
agegrp	6	1 2 3 4 5 6
revdyr2	3	198190 199120 200000

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	110	149.0799	1.3553
Scaled Deviance	110	108.3310	0.9848
Pearson Chi-Square	110	151.3766	1.3762
Scaled Pearson X2	110	110.0000	1.0000
Log Likelihood		16201.8764	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits	Chi-Square	Pr > ChiSq
Intercept	1	-5.5952	0.0998	-5.7907 -5.3997	3146.30	<.0001
agegrp	1	-5.7564	0.1694	-6.0884 -5.4243	1154.48	<.0001
agegrp	2	-2.2183	0.1189	-2.4513 -1.9853	348.21	<.0001
agegrp	3	-0.9246	0.0947	-1.1103 -0.7390	95.29	<.0001
agegrp	4	-0.1037	0.0774	-0.2554 0.0479	1.80	0.1801
agegrp	5	0.2498	0.0723	0.1080 0.3915	11.93	0.0006
agegrp	6	0.0000	0.0000	0.0000 0.0000	.	.
revdyr2	198190	1	0.0068	0.0800 -0.1501 0.1636	0.01	0.9328
revdyr2	199120	1	-0.0202	0.0675 -0.1524 0.1121	0.09	0.7652
revdyr2	200000	0	0.0000	0.0000 0.0000 0.0000	.	.
bs1lag	1	-0.0057	0.0028	-0.0111 -0.0002	4.18	0.0409
bs1lag*smkprvtot	1	0.0003	0.0001	0.0000 0.0005	5.47	0.0194
Scale	0	1.1731	0.0000	1.1731 1.1731		

The GENMOD Procedure

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

LR Statistics For Type 1 Analysis

Source	Deviance	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Intercept	17723.4375						
agegrp	168.4898	5	110	2551.31	<.0001	12756.6	<.0001
revdyr2	156.6238	2	110	4.31	0.0158	8.62	0.0134
bs1lag	156.6214	1	110	0.00	0.9672	0.00	0.9671
bs1lag*smkprvtot	149.0799	1	110	5.48	0.0210	5.48	0.019

APPENDIX TEN

(SAS programme and output of period analysis: smoking included)

Model C (adding smoking prevalence) in Chapter Nine

```
proc genmod data=sashelp.dubsmk;  
class agegrp revdyr2;  
model totdths= agegrp revdyr2 smkprvtot smkprvtot*bsllag/TYPE1 offset=l_par dist=Poisson SCALE=PEARSON ;  
run;
```

The GENMOD Procedure

Model Information

Data Set	SASHELP.DUBSMK	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	totdths	totdths
Offset Variable	l_par	l_par
Observations Used	120	

Class Level Information

Class	Levels	Values
agegrp	6	1 2 3 4 5 6
revdyr2	3	198190 199120 200000

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	110	148.9982	1.3545
Scaled Deviance	110	108.5886	0.9872
Pearson Chi-Square	110	150.9348	1.3721
Scaled Pearson X2	110	110.0000	1.0000
Log Likelihood		16249.3283	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits	Chi-Square	Pr > ChiSq
Intercept	1	-5.8501	0.1215	-6.0881 -5.6120	2319.97	<.0001
agegrp	1	-5.9220	0.2200	-6.3531 -5.4908	724.70	<.0001
agegrp	2	-2.3575	0.1676	-2.6860 -2.0290	197.87	<.0001
agegrp	3	-1.0285	0.1295	-1.2823 -0.7747	63.08	<.0001
agegrp	4	-0.1634	0.0923	-0.3444 0.0175	3.13	0.0767
agegrp	5	0.2255	0.0749	0.0787 0.3723	9.06	0.0026
agegrp	6	0.0000	0.0000	0.0000 0.0000	.	.
revdyr2	198190	1	-0.0388	0.0836 -0.2025 0.1250	0.22	0.6426
revdyr2	199120	1	-0.0097	0.0677 -0.1425 0.1231	0.02	0.8859
revdyr2	200000	0	0.0000	0.0000 0.0000 0.0000	.	.
smkprvtot	1	0.0146	0.0071	0.0008 0.0285	4.28	0.0386
smkprvtot*bs1lag	1	0.0001	0.0001	-0.0001 0.0002	1.25	0.2636
Scale	0	1.1714	0.0000	1.1714 1.1714		

The GENMOD Procedure

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

LR Statistics For Type 1 Analysis

Source	Deviance	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Intercept	17723.4375						
agegrp	168.4898	5	110	2558.78	<.0001	12793.9	<.0001
revdyr2	156.6238	2	110	4.32	0.0156	8.65	0.0132
smkprvtot	150.7083	1	110	4.31	0.0402	4.31	0.0379
smkprvtot*bs1lag	148.9982	1	110	1.25	0.2667	1.25	0.264

APPENDIX ELEVEN

(SAS programme and output of period analysis: BS & smoking)

Model D (adding both BS and smoking prevalence) in Chapter Nine

```
proc genmod data=sashelp.dubsmk;  
class agegrp revdyr2;  
model totdths= agegrp revdyr2 smkprvtot bsllag smkprvtot*bsllag/TYPE1 offset=l_par dist=Poisson SCALE=PEARSON ;  
run;
```

The GENMOD Procedure

Model Information

Data Set	SASHELP.DUBSMK	
Distribution	Poisson	
Link Function	Log	
Dependent Variable	totdths	totdths
Offset Variable	l_par	l_par
Observations Used	120	

Class Level Information

Class	Levels	Values
agegrp	6	1 2 3 4 5 6
revdyr2	3	198190 199120 200000

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	109	147.4900	1.3531
Scaled Deviance	109	107.5608	0.9868
Pearson Chi-Square	109	149.4635	1.3712
Scaled Pearson X2	109	109.0000	1.0000
Log Likelihood		16260.6692	

Algorithm converged.

Analysis Of Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits	Chi-Square	Pr > ChiSq
Intercept	1	-5.7349	0.1636	-6.0556 -5.4143	1228.72	<.0001
agegrp	1	-5.9083	0.2202	-6.3398 -5.4768	720.21	<.0001
agegrp	2	-2.3460	0.1678	-2.6748 -2.0172	195.56	<.0001
agegrp	3	-1.0199	0.1295	-1.2738 -0.7660	61.99	<.0001
agegrp	4	-0.1580	0.0923	-0.3388 0.0229	2.93	0.0869
agegrp	5	0.2283	0.0749	0.0816 0.3751	9.30	0.0023
agegrp	6	0.0000	0.0000	0.0000 0.0000	.	.
revdyr2	198190	-0.0238	0.0848	-0.1900 0.1423	0.08	0.7785
revdyr2	199120	-0.0121	0.0678	-0.1449 0.1207	0.03	0.8582
revdyr2	200000	0.0000	0.0000	0.0000 0.0000	.	.
smkprvtot	1	0.0093	0.0087	-0.0077 0.0263	1.16	0.2817
bs1lag	1	-0.0036	0.0034	-0.0102 0.0031	1.10	0.2946
smkprvtot*bs1lag	1	0.0002	0.0001	-0.0001 0.0005	2.02	0.1548
Scale	0	1.1710	0.0000	1.1710 1.1710		

NOTE: The scale parameter was estimated by the square root of Pearson's Chi-Square/DOF.

LR Statistics For Type 1 Analysis

Source	Deviance	Num DF	Den DF	F Value	Pr > F	Chi-Square	Pr > ChiSq
Intercept	17723.4375						
agegrp	168.4898	5	109	2560.48	<.0001	12802.4	<.0001
revdyr2	156.6238	2	109	4.33	0.0156	8.65	0.0132
smkprvtot	150.7083	1	109	4.31	0.0402	4.31	0.0378
bs1lag	150.2656	1	109	0.32	0.5711	0.32	0.5699
smkprvtot*bs1lag	147.4900	1	109	2.02	0.1577	2.02	0.154