The association between air pollution and lung cancer in the North West of Adelaide: a case control study and air quality monitoring

Melissa Jayne Whitrow

Department of Medicine and Department of Public Health
Faculty of Health Science

The University of Adelaide

July 2004
# Table of Contents

1. **Chapter 1 Introduction** ........................................................................................................... 25
   
   1.1. **Lung Cancer** .................................................................................................................. 29
       
       1.1.1. Lung Cancer Demographics ...................................................................................... 29
       
       1.1.2. Lung Cancer in Australia .......................................................................................... 33
       
       1.1.3. Aetiology .................................................................................................................... 37
   
   1.2. **North Western Metropolitan Adelaide** ......................................................................... 38
       
       1.2.1. Lung Cancer in the North West ............................................................................... 40
       
       1.2.2. Industry in the North West ....................................................................................... 40
       
       1.2.3. Ambient Air Quality in the NW ................................................................................. 49
   
2. **Chapter 2 Review of the Literature** .................................................................................... 51
   
   2.1. **Lung Cancer Histology** ............................................................................................... 52
       
       2.1.1. Lung Cancer Classification ....................................................................................... 53
       
   2.2. **Lung Carcinogen Classifications** .................................................................................. 56
       
       2.2.1. Lung Carcinogens ...................................................................................................... 56
   
   2.3. **The Origins of the Association between Air Pollution and Lung Cancer** ................. 59

   2.4. **A review of the Epidemiological Evidence for a Causal Relationship between**
       
       Environmental Exposure to Carcinogens (Air Pollution) and Lung Cancer ............... 59
       
       2.4.1. Literature Review Methodology .................................................................................. 60
       
       2.4.2. Results of the Literature Review ................................................................................. 61
2.4.2.1. Environmental Exposure Classification .................................................. 71
2.4.2.2. Strength of Association ........................................................................... 71
2.4.2.3. Consistency ............................................................................................. 75
2.4.2.4. Specificity and confounder adjustment ................................................... 76
2.4.2.5. Temporality ............................................................................................. 80
2.4.2.6. Dose Response ....................................................................................... 80
2.4.2.7. Biological Plausibility/Coherence ............................................................. 81
2.4.2.8. Analogy ................................................................................................... 82

2.4.3. Discussion of the Literature Review Findings .............................................. 82

2.5. Air Pollution and Lung Cancer in Australia ................................................... 85

2.6. Aims and Hypothesis ..................................................................................... 86

3. Chapter 3 Methodology ................................................................................... 89

3.1. Study Design .................................................................................................. 89

3.1.1. Cases ......................................................................................................... 89

3.1.1.1. Sample ................................................................................................... 89

3.1.1.1.1. Inclusion Criteria ........................................................................... 89

3.1.1.1.2. Exclusion Criteria .......................................................................... 90

3.1.1.2. Sampling Frame .................................................................................... 90

3.1.2. Controls ..................................................................................................... 91

3.1.2.1. Sample .................................................................................................. 91
3.1.2.1.1. Inclusion Criteria ................................................................. 91
3.1.2.1.2. Exclusion Criteria ............................................................... 91
3.1.2.2. Sampling Frame .................................................................. 92
3.1.2.2.1. Selection ........................................................................ 92
3.1.3. Matching ............................................................................... 93
3.1.4. Subject Recruitment .............................................................. 94

3.2. Ethics Approval ...................................................................... 98
3.2.1. Informed Consent ................................................................. 98

3.3. The Design and Development of a Questionnaire to Investigate Lung Carcinogen Exposure in a Case Control Study ......................... 99
3.3.1. Identification of Potential Confounders .................................... 99
3.3.2. Format of Questionnaire ........................................................ 103
3.3.3. Pilot of Questionnaire ............................................................. 105
3.3.4. Method of Data Collection ...................................................... 106
3.3.5. Interviewer Training ............................................................... 107

3.4. Environmental Exposure Assessment and Quantification ............. 107
3.4.1.1. Calculation of Distance from Industry within the Study Geographical Area ......................................................... 113
3.4.1.2. Calculation of Angle of each Residence from each Industry ....... 115
3.4.1.3. Calculation of Exposure Based on Wind Direction ................. 116
3.4.1.4. Calculation of a Final Exposure Score .................................... 118
3.4.1.5. Validity .................................................................................................. 121
3.4.1.6. Reliability ............................................................................................. 121
3.4.2. Exposure Assessment Outside of the Study Area .................................. 121
3.4.2.1. Definition of Exposed .......................................................................... 121
3.4.2.2. Validity .................................................................................................. 124
3.4.2.3. Reliability ............................................................................................. 124
3.4.2.4. Inclusion in Analysis .......................................................................... 124

3.5. Tobacco Exposure Quantification ............................................................. 125
3.5.1. Direct Smoking ...................................................................................... 125
3.5.1.1. Cigars and Tobacco Pipes ................................................................. 128
3.5.2. Environmental Tobacco Smoking ......................................................... 128
3.5.3. Reliability ............................................................................................... 130
3.5.4. Validity ................................................................................................... 130

3.6. Occupational Exposure Assessment and Quantification ...................... 130
3.6.1. The Occupational Hygiene Panel ......................................................... 130
3.6.2. Occupational Data Collected from Subjects for Exposure Assessment ... 132
3.6.3. Levels of Exposure Assessed ................................................................. 132
3.6.4. Levels of Exposure .............................................................................. 133
3.6.5. Occupational Hygiene Panel Output ...................................................... 136
3.6.6. Inclusion in Analysis .......................................................................... 137
3.6.7. Quantification of Exposure Levels in the Analysis .............................. 137
3.11.3. Field Work....................................................................................................152
3.11.4. Meteorological Measurements.................................................................155
3.11.5. Air Quality Monitoring Analysis ...............................................................155

4. Chapter 4 Results .................................................................................................156

4.1. Sample Demographics.....................................................................................156

4.1.1. Study Participants.......................................................................................156

4.1.2. Participants versus Non-participants ..........................................................157

4.1.2.1. Cases .....................................................................................................157

4.1.2.1.1. Differential Participation Rate for Age and Gender .......................160

4.1.2.1.2. Distance from Industry ..................................................................160

4.1.2.2. Controls ...............................................................................................161

4.1.2.2.1. Differential Response Rate for Age and Gender .........................162

4.1.2.3. Distance from Industry .......................................................................164

4.1.3. Occupational Hygiene Panel Agreement ..................................................165

4.1.4. Next of Kin Agreement ............................................................................166

4.2. Univariate Analysis .........................................................................................167

4.2.1. Socio-economic Status ............................................................................167

4.2.2. Residential Exposure within the Study Area ............................................169

4.2.3. Residential Exposure outside of the Study Area .....................................173

4.2.4. Cigarette Smoking ...................................................................................174
4.2.5. Environmental Tobacco Smoke (ETS) ........................................................ 177
4.2.6. Occupational Exposure to Lung Carcinogens.............................................. 178
4.2.7. Hobbies......................................................................................................... 183
4.2.8. Family History of Lung Cancer ................................................................. 184

4.3. Bivariate Analysis .......................................................................................... 185

4.3.1. Subject Demographics.................................................................................. 186
4.3.2. Socio-economic Status ................................................................................ 186
4.3.3. Residential Exposure................................................................................... 188
4.3.4. Cigarette Smoking....................................................................................... 192
4.3.5. Environmental Tobacco Smoke (ETS) ......................................................... 194
4.3.6. Occupational Exposure to Lung Carcinogens.............................................. 195
4.3.7. Hobbies......................................................................................................... 196
4.3.8. Family History of Lung Cancer ................................................................. 198

4.4. Multivariate Analysis ...................................................................................... 199

4.5. Post hoc Analysis .......................................................................................... 208

4.5.1. Post hoc Multivariate Analysis .................................................................... 209

4.6. Air Quality Monitoring .................................................................................. 218

5. Chapter 5 Discussion ....................................................................................... 224

5.1. Limitations of the Case Control Study .......................................................... 226

5.1.1. Bias............................................................................................................... 226
Index to Tables

Table 1-1: Age standardised incidence rate of lung cancer per 100 000 by level of country development\textsuperscript{8} ........................................................................................................................................ 30

Table 1-2: Key Industry Identified as having the Potential to Emit Lung Carcinogens, and Operational in the Study Area (North West Suburbs of Adelaide) in the period 1970 to 2000 ........................................................................................................................................ 46

Table 2-1: Features of each Lung Cancer Cell Type ........................................................................................................ 54
Table 2-2: Carcinogen Classifications Employed by IARC\textsuperscript{37} .............................................................................. 56
Table 2-3: Known (1) or Probable (2a) Respiratory Carcinogens and their Potential Sources\textsuperscript{38,39} ........................................................................................................................................ 57
Table 2-4: Adjustments for the Confounding Effects of Smoking and Occupation .......................................................... 63
Table 3-1: Lung Cancer Risk Factors ......................................................................................................................... 100
Table 3-2: Assessment of Questionnaires .................................................................................................................. 104
Table 3-3: Studies using dispersion modelling to determine the relationship between proximity to industry and adverse health effects ......................................................................................................................... 109
Table 3-4: X and Y Coordinates for the 6 Key Industries in the North West ........................................................................... 114
Table 3-5: Calculation of the Percentage of Time the Wind Blows ± 15° around each Angle from North in 10° Increments ......................................................................................................................... 119
Table 3-6: List of Industry Types Identified by the Occupational Hygiene Panel as Likely to Emit Lung Carcinogens ........................................................................................................................................ 122
Table 3-7: Tobacco Smoking - Data collected and its Inclusion in the Analysis ............................................................... 126
Table 3-8: Environmental Tobacco Smoke - Data Collected and its Inclusion in the Analysis ........................................................................................................................................ 129
Table 3-9: Contemporary Health Based Daily (8hr) Occupational Exposure Guidelines ............................................................ 134
Table 3-10: Percentage of Exposure Guidelines Assigned to Each Level of Exposure
(Average Daily Exposure) .......................................................................................... 135

Table 3-11: Scores Assigned to Each Level of Occupational Exposure ..................... 138

Table 3-12: Potential Lung Carcinogen Exposures for Reported Hobbies as Determined by
the Occupational Hygiene Panel .......................................................................... 141

Table 3-13: Interpretation of the Kappa Statistic....................................................... 144

Table 3-14: Lung Carcinogens (IARC rating 1* and 2A**) and potential sources in North
West of Adelaide ...................................................................................................... 147

Table 4-1: Age and Gender of Study Participants ....................................................... 156

Table 4-2: Case Participation Rates .......................................................................... 158

Table 4-3: Distance from Industry* (kms) of Current Residence of Participating and Non-
Participating Cases ............................................................................................... 161

Table 4-4: Control Participation Rates ...................................................................... 162

Table 4-5: Distance from Industry* (kms) of current Residence of Participating and Non-
Participating controls ............................................................................................ 164

Table 4-6: Inter-rater Reliability of Hygiene Panel Exposure Scores Measured by Kappa 165

Table 4-7: Test-Retest Analysis of Hygiene Panel Exposure Scores Measured by weighted
Kappa (n=30 pairs) ............................................................................................ 166

Table 4-8: Indices of Socio-economic Status for Cases and Controls ......................... 168

Table 4-9: A Comparison between Cases and Controls of Residential Scores* for each
Identified Industry ..................................................................................................... 170

Table 4-10: A Comparison between Cases and Controls of Residential Exposure* outside
of the Study Area ....................................................................................................... 173

Table 4-11: Comparison of the Cigarette Smoking Habits of Cases and Controls† .......... 174

Table 4-12: Environmental Tobacco Smoke (ETS) Exposure by Cases and Controls..... 177
Table 4-13: Occupational Exposure to each Lung Carcinogen for Cases and Controls -
Jockel equation method*(units are exposure years) ........................................... 179

Table 4-14: Duration of Probable or Possible Occupational Exposure to each Lung
Carcinogen for Cases and Controls (units are years of exposure) ..................... 181

Table 4-15: Hobby Participation for Cases and Controls (yes or no) ..................... 183

Table 4-16: Number of Family Members* with Lung Cancer Diagnosis for Cases and
Controls ............................................................................................................. 184

Table 4-17: Bivariate Analysis - Odds Ratio for Subject Demographics with Adjustment
for Matching ..................................................................................................... 186

Table 4-18: Bivariate Analysis - Odds Ratios for Socioeconomic Status Variable with
Adjustment for Matching .................................................................................. 187

Table 4-19: Bivariate Analysis - Odds Ratio for Residential Exposure Scores# with
Adjustment for Matching .................................................................................. 189

Table 4-20: Bivariate Analysis - Odds Ratio for Duration of Residential Exposure*
outside of the North West of Adelaide, with Adjustment for Matching ........... 192

Table 4-21: Bivariate analysis - Odds Ratio for Smoking (as defined by durations in years,
average cigarettes per day or pack years) with Adjustment for Matching....... 193

Table 4-22: Bivariate Analysis - Odds Ratio for Duration of Exposure (yrs) to
Environmental Tobacco Smoke (ETS) at home or work with adjustment for
matching ............................................................................................................. 194

Table 4-23: Bivariate Analysis - Odds Ratio for greater than or equal to 1 year of Probable
or Possible Occupational Exposure with Adjustment for Matching ............... 195

Table 4-24: Bivariate Analysis - Odds Ratio for Participation (greater than or equal to 1
year) in Mechanical, Pottery or House Renovation Hobbies with Adjustment
for Matching .................................................................................................... 197
Table 4-25: Bivariate Analysis - Odds Ratio for the Number of Family Members* who have been Diagnosed with Lung Cancer with Adjustment for Matching........... 198

Table 4-26: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and Residential Exposure* to Adelaide Brighton Cement.......................... 200

Table 4-27: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and Residential Exposure* to CSR .................................................... 201

Table 4-28: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and Residential Exposure* to Finsbury.............................................. 202

Table 4-29: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and Residential Exposure* to Penrice Soda Products......................... 203

Table 4-30: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and Residential Exposure* to James Hardies..................................... 204

Table 4-31: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and Residential Exposure* to Torrens Island Power Station............. 205

Table 4-32: Final Multivariate Model of Case Control Study Data - Significant Factors (p≤0.05) and the Composite† Residential Exposure* Score......................... 206

Table 4-33: Post hoc Multivariate Analysis - Significant Factors (p≤0.05) and Adjusted Residential Exposure* to Adelaide Brighton Cement ............................................. 210

Table 4-34: Post hoc Multivariate Analysis - Significant factors (p≤0.05) and Adjusted Residential Exposure* to CSR................................................................. 211

Table 4-35: Post hoc Multivariate Analysis - Significant Factors (p≤0.05) and Adjusted Residential Exposure* to Finsbury ............................................................. 212

Table 4-36: Post hoc Multivariate Analysis - Significant Factors (p≤0.05) and Adjusted Residential Exposure* to James Hardies ................................................. 213
Table 4-37: Post hoc Multivariate Analysis - Significant Factors ($p \leq 0.05$) and Adjusted Residential Exposure* to Penrice Soda Products .......................................................... 214

Table 4-38: Post hoc Multivariate Analysis - Significant Factors ($p \leq 0.05$) and Adjusted Residential Exposure* to Torrens Island Power Station ........................................ 215

Table 4-39: Post hoc Multivariate Analysis - Significant Factors ($p \leq 0.05$) and the Adjusted Composite† Residential Exposure* Score .................................................. 216

Table 4-40: Ambient Concentrations of Respiratory Carcinogens in the North West of Adelaide ........................................................................................................ 219

Table 5-1: Common Sources of Misclassification in Community-based Case Control Studies of Occupational Exposures .......................................................... 233

Table 5-2: Results for Smoking and Lung Cancer Relationship from European Case Control Study - OR($95\% CI$) .......................... 248

Table 5-3: Comparison of the Epidemiological Design Strengths of the 5 Studies Identified in Chapter 2, and the Present Case Control Study .......................... 252
Index to Figures

Figure 1-1: Lung Cancer Incidence\(^1\) and Industry Location in the North West of Metropolitan Adelaide from 1992 to 1995. ................................................................. 26

Figure 1-2: Aerial View of the Lefevre Peninsula\(^5\) .................................................................................................................. 27

Figure 1-3: World Male Lung Cancer Incidence and Mortality Rates by Region (Age standardised estimates for 2000 based on 3-5yrs earlier and adjusted for increase in population\(^8\))................................................................. 31

Figure 1-4: World Female Lung Cancer Incidence and Mortality Rates by Region (Age standardised estimates for 2000 based on 3-5 years earlier and adjusted for increase in population\(^8\))........................................................................... 32

Figure 1-5: Australian Male Cancer Mortality Rate by Type of Cancer (Age standardised, per 100 000, estimates for 2000 based on 3-5yrs earlier and adjusted for increase in population\(^8\))....................................................................................... 34

Figure 1-6: Australian Female Cancer Mortality Rate by Type of Cancer (Age standardised, per 100 000, estimates for 2000 based on 3-5 yrs earlier and adjusted for increase in population\(^8\))....................................................................................... 35

Figure 1-7: Australian Age Standardised Rates of Lung Cancer Mortality (Adjusted for increase in population\(^8\))................................................................. 36

Figure 1-8: Aerial View of the Port River\(^21\) ................................................................................................................................. 41

Figure 1-9: The Torrens Island Power Station\(^23\) .................................................................................................................... 43

Figure 1-10: Aerial View of Adelaide Brighton Cement\(^25\) ............................................................................................................. 44

Figure 2-1: Two Levels of Tumour Differentiation ............................................................................................................................ 55

Figure 2-2: Fixed Effects Forest Plot of Case Control Studies ........................................................................................................... 73

Figure 2-3: Strength of Association - Results from Cohort Studies .................................................................................................. 74

Figure 3-1: Stata Do File used for Generation of Random Numbers .................................................................................................. 93
Index to Appendices

Appendix 1: Copy of standard information letter to recruit potential cases ......................... 270

Appendix 2: Information letter to the Next of Kin of a deceased case when the diagnosing
Doctor had already approached them by phone ............................................................... 273

Appendix 3: Original information letter to the Next of Kin (NOK) of a deceased case,
when the diagnosing doctor had been unable to speak to the NOK by phone
prior to the letter .............................................................................................................. 276

Appendix 4: "Calling a Patient" Information Sheet Provided to Recruiting Doctors ........... 279

Appendix 5: "Calling the Next of Kin of a Patient" Information Sheet Provided to
Diagnosing Doctors ....................................................................................................... 280

Appendix 6: Original information letter to controls ........................................................ 281

Appendix 7: Script for Follow Up Calls to Non-responding Potential Control Subjects ... 284

Appendix 8: Example of a Flyer Sent to Recruiting Doctors to Encourage Further Case
Recruitment and Completion of the Study ........................................................................ 285

Appendix 9: Examples of Articles in the Print Media about the Case Control Study ....... 286

Appendix 10: Copies of Ethics Approval Letters from Adelaide Metropolitan Hospitals.. 287

Appendix 11: The Queen Elizabeth Hospital Research and Ethics Committee Consent
Form Utilised in this Study ............................................................................................. 294

Appendix 12: Part 'a' of the Data Collection Process utilised to Enhance Recall Prior to the
Structured Interview ..................................................................................................... 295

Appendix 13: The Structured Questionnaire used to elicit Lifetime Information on Risk
Factors Relevant to Lung Cancer Diagnosis ............................................................... 298

Appendix 14: Booklet Used to Record Data Collected at Interview ................................. 319

Appendix 15: Example of Occupational Information Provided to Occupational Hygiene
Panel for Exposure Assessment .................................................................................... 327
Appendix 16: Occupational Hygiene Panel Output Sheet ................................................................. 328

Appendix 17: Survey of Members of the Australian Institute of Occupational Hygienists
to Determine the Percentage of Exposure Guidelines Assigned to Each
Category of Occupational Exposure .......................................................................................... 329

Appendix 18: Questionnaire used for the Next Of Kin Substudy .............................................. 331

Appendix 19: Information Letter Distributed to Participating Subjects to Summarise the
Study Results .................................................................................................................................. 333
Abstract

Some suburbs within North West (NW) metropolitan Adelaide have lung cancer mortality up to twice that expected from state averages. Previous international research investigating high lung cancer rates in similar shared industrial and residential areas have had inconsistent results. This case control study was conducted to determine whether residential exposure to industry is a risk factor for lung cancer in NW Adelaide. Contemporary ambient air monitoring was undertaken as an indicator of future respiratory health risk.

142 lung cancer patients and 415 age, gender matched population controls were interviewed utilising an event history calendar. Lifetime exposure indices were calculated for cigarette smoking, passive smoking, occupation, air pollution (residential proximity to industry) and hobbies. Data was analysed utilising chi-squared and conditional logistic regression. Ambient carcinogens and fine particulates with potential industrial sources in the region were monitored in five locations.

In the final multivariate model leaving school early, pack-years of cigarettes and not living in close proximity to the power station or light industrial area were statistically significant risk factors for lung cancer. A composite score of residential exposure to all industries was not significant. However cautious interpretation is required as it was noted participating controls resided significantly closer to industry than non-participants. Average concentrations of ambient carcinogens were within guidelines; however diesel exhaust particulate and Polycyclic Aromatic Hydrocarbons were elevated at sites in
proximity to heavy vehicle traffic. Diurnal variations in PM$_{2.5}$ included weather and traffic-related short term peaks, and other peaks potentially related to industrial activity.

Cigarette smoking is likely to be the primary cause of elevated lung cancer mortality in suburbs of NW Adelaide. The negative effect of residential exposure to two industries may be due to participation bias. Whilst having more thorough exposure assessment than previous research, this study may have been limited by low participation rates in cases and controls. Air monitoring data suggests there is not a significant public health risk at present; however these results are unlikely to be indicative of historical exposures. Future public health initiatives to curb high lung cancer mortality in the NW should focus on smoking prevention and reduction strategies.
This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Signed ________________________________

Date ___________
Acknowledgements

This research was funded by a project grant from the National Health and Medical Council.

Thank you to my three supervisors, Brian Smith, Louis Pilotto and Dino Pisaniello for their advice, expertise and support.

I would like to gratefully acknowledge the original research team that initiated the project concept and secured funding – Brian Smith, Monika Nitschke, Dino Pisaniello, Richard Ruffin and Janet Hiller.

Thank you to the staff of the Clinical Epidemiology and Health Outcomes Unit for their friendship and support. Particularly to Pam Selim, Adrian Heard and Jesia Berry for their assistance with interviewing subjects, and Daniel Field and Crystal Read for assistance with data entry.

Thank you to Adrian Esterman for assistance with the statistical analysis of the case control study data.

Thank you to the study subjects who so freely gave their time to be interviewed for this study.

To my family, in particular Mum, Phil, Denise, Neville and Stacey, thank you for the love, support and friendship you have provided to me throughout this entire process.

To my partner Damien – I couldn’t have done this without your unwavering support and love. Thanks for believing in me.
**Thesis Collaborations**

I would like to thank the following people and organisations for their assistance with the project:

**BHP** (analysis of diesel air monitoring samples)

**CEMSSA** – Prof John Terlett (analysis of asbestos air monitoring samples)

**Charles Sturt Council** (supply of GIS coordinates)

**Collaborative Centre in Occupational Health and Safety – University of Adelaide** – in particular Andrew Orfanos for assistance with air quality monitoring and sample analysis

**Epidemiology, Flinders Medical Centre** – Adrian Esterman (statistical advice), Paul Hakendorf (Geographical Information System advice)

**Environmental Health Branch, Dept of Human Services** – David Simon (advice on wind direction calculations)

**Environmental Protection Authority** (advice on air quality monitoring protocols and interpretation of monitoring results)

**MPL** (loan of air quality monitoring equipment and hygiene panel participation)

**Pt Adelaide Enfield Council** (supply of GIS coordinates)

**South Australian Cancer Registry, Dept of Human Services** – David Roder and Colin Luke (provision of lung cancer patient information to the recruitment hospitals)

**Dept of Pathology, The University of Adelaide** – Angela Barbour (supply of lung cancer histology pictures)
Publications Arising from this Thesis

Refereed Journals:


Conference Presentations:

*Oral*


Conference Presentations: (continued)

*Poster*


**Eli Lilly prize for best presentation on lung cancer**