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

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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 _____

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Whitrow MJ, Smith B, Pilotto L, Pisaniello D, Selim P, Esterman, A. High lung cancer mortality in the North West of Adelaide is Associated with Cigarette Smoking and Appears Unrelated to Residential Exposure to Industry. Thoracic Society of Australia and New Zealand Annual Scientific meeting, Adelaide, Australia. 2003

Eli Lilly prize for best presentation on lung cancer

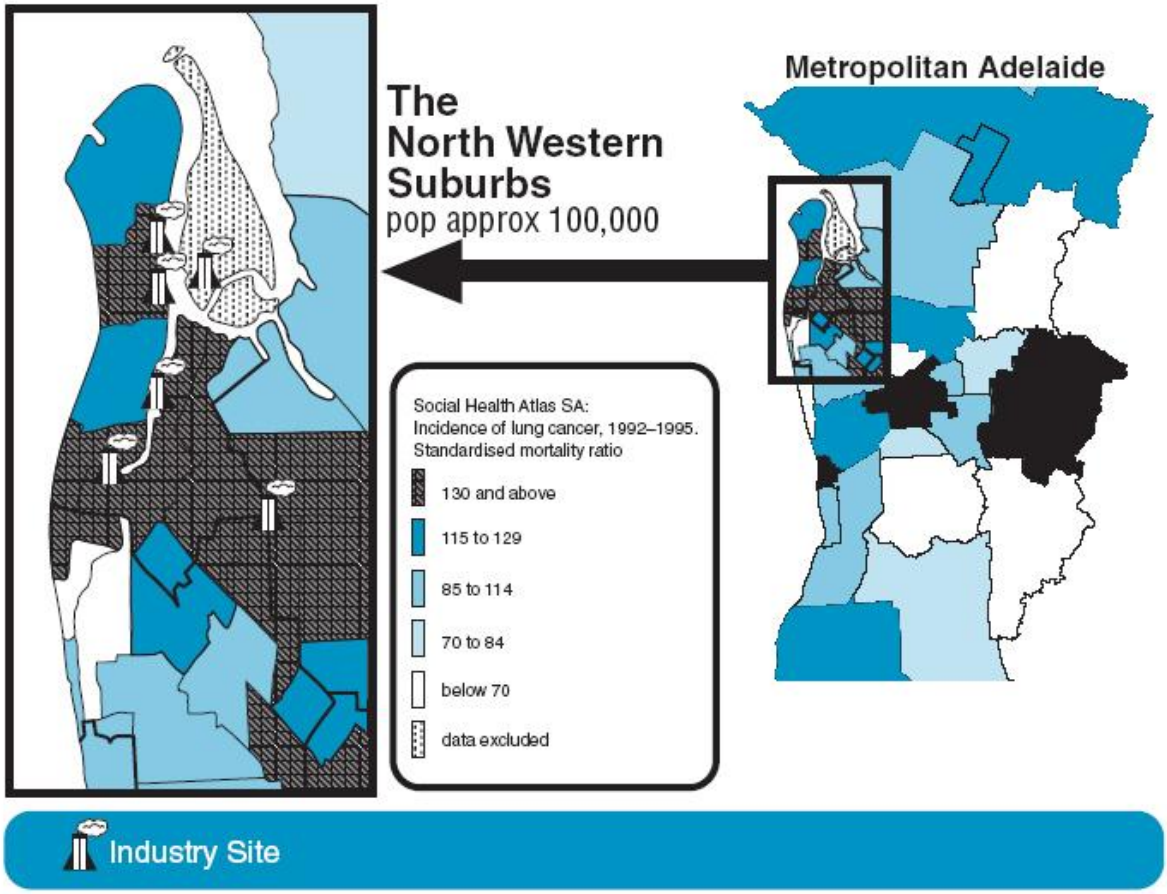
Whitrow MJ, Smith BJ, Pilotto L, Nitschke M, Pisaniello D. Environmental Exposure to Carcinogens Causing Suburban Lung Cancer – Epidemiological Evidence. Australasian Epidemiological Assoc. 10th Annual Meeting, Sydney, Australia. 2003

1. Chapter 1 Introduction

The South Australian (SA) Social Health Atlas indicates the North Western suburbs of Adelaide, in particular the Lefevre Peninsula suburbs, have an alarming excess of lung cancer mortality with standardised mortality ratios ranging up to 236 compared to that expected from Adelaide metropolitan rates[1] (standardised for age and gender).

The North Western suburbs of Adelaide are a residential zone, bound to the West by the Gulf of St Vincent, to the South and East by dense residential areas, and to the North by residential homes and vacant land (Figure 1-1). The Port River flows from the North (dividing off the Lefevre Peninsula) and is the primary shipping port for metropolitan Adelaide (Figure 1-2). Attracted by access to shipping ports for the transport of goods into and out of the metropolitan area, since Adelaide was settled the land either side of the river has been the site of many industries including power plants, cement and soda product producers and an asbestos factory[2]. This area has historically housed blue-collar workers, with many of the residents employed by the factories clustered along the Port River. The Lefevre Peninsula is characterised by the close proximity of residential homes to large-scale industry, with often no more than a 2-lane road (approximately 20 metres) dividing them. Many of these industries, for example a power station, cement works and mineral building products manufacturer, are licensed by government agencies to carry out "prescribed" polluting activities permitting the release of a range of emissions, including lung carcinogens, into the air.

Figure 1-1: Lung Cancer Incidence[1] and Industry Location in the North West of Metropolitan Adelaide from 1992 to 1995.



Due to the primarily low socio-economic nature of the areas population, the high lung cancer mortality has been anecdotally attributed to a high prevalence of cigarette smoking. However this is yet to be proven in an epidemiological study. Only 1 other peer-reviewed study has been carried out investigating respiratory health in the area[3]. This cross sectional survey found high rates of some respiratory health problems (asthma, bronchitis and emphysema), but more relevantly, found the prevalence of cigarette smoking in the area to be 27%, significantly higher than the national average derived from the National Health Survey at a similar period of time[4], but with an absolute difference of just 3%. Taken at face value the doubling of lung cancer mortality in the area seemed unlikely to be attributable to a 3% increase in smoking prevalence, however the study only used prevalence of cigarette smoking rather than quantifying smoking dose.

Figure 1-2: Aerial View of the Lefevre Peninsula[5]



The following thesis documents an epidemiological study undertaken to investigate whether residing in close proximity to industry likely to emit lung carcinogens is a significant risk factor for lung cancer in the NW suburbs of Adelaide. It begins with a description of the burden of lung cancer worldwide on public health care systems and a detailed description of the NW suburbs of Adelaide and the relevant lung cancer mortality figures. Following that is a systematic review of previous international epidemiology studies investigating the relationship between lung cancer and air pollution. The methodology of the thesis is described in detail, the results of which are documented in a series of tables. Finally there are the discussion and conclusions, which summarise the findings of this research, identifies its limitations, assesses the results in context with previous published studies, and suggests potential avenues for future research. In parallel with the epidemiology study, air quality monitoring was undertaken to determine contemporary concentrations of airborne lung carcinogens in the study area, with the view to identify the potential for future respiratory health risk.

1.1. Lung Cancer

Lung Cancer is the term used to define the uncontrolled growth of malignant cells in the lung. Diagnosis of lung cancer is through a combination of x-ray, sputum cytology, bronchoscopy, MRI (magnetic resonance imaging) or CT (computer assisted topography) chest scan[6]. Early lung malignancies are usually clinically silent, hence lung cancer is rarely diagnosed until patients are symptomatic and the tumour is in an advanced stage. Treatment is by surgery, radiotherapy and/or chemotherapy[7]. Prognosis with or without treatment is poor, Non-small-cell tumours have a 50% survival rate 2 years post diagnosis, and Small-cell tumours have a 1 year prognosis if treated, and 3 month prognosis if not treated[6]. The patient prognosis improves slightly if diagnosis is early, whilst the tumour is still asymptomatic.

1.1.1. Lung Cancer Demographics

Worldwide mortality figures indicate approximately 1.1 million deaths were attributed to lung or bronchial cancer in 2000[8]. The incidence of lung cancer is greater in more developed than less developed countries (Table 1-1). Compared to other regions of the world (Figure 1-3 and Figure 1-4), Australia and New Zealand combined have the 3rd highest female and 7th highest male incidence rates of lung cancer (age standardised[8]). As developed regions, both European and North American countries have consistently elevated incidence amongst females and males, with North America having the overwhelmingly highest rates in females (Figure 1-4). In the majority of countries there is little difference between the incidence and mortality lung cancer figures, illustrating the poor prognosis for lung cancer patients.

Table 1-1: Age standardised incidence rate of lung cancer per 100 000 by level of country development[8]

	More developed countries	Less developed countries
Males	55.62	24.79
Females	15.62	8.44

Lung cancer places a large burden on health care systems around the world. In America alone lung cancer costs the health system US$8 billion annually[9]. Canadian estimates are that the treatment of 1 Non-small-cell lung cancer patient from diagnosis until death is CDN$19,781, and the corresponding cost for Small-cell is CDN$25,988. The major component of this expense is hospitalisation[9].

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])

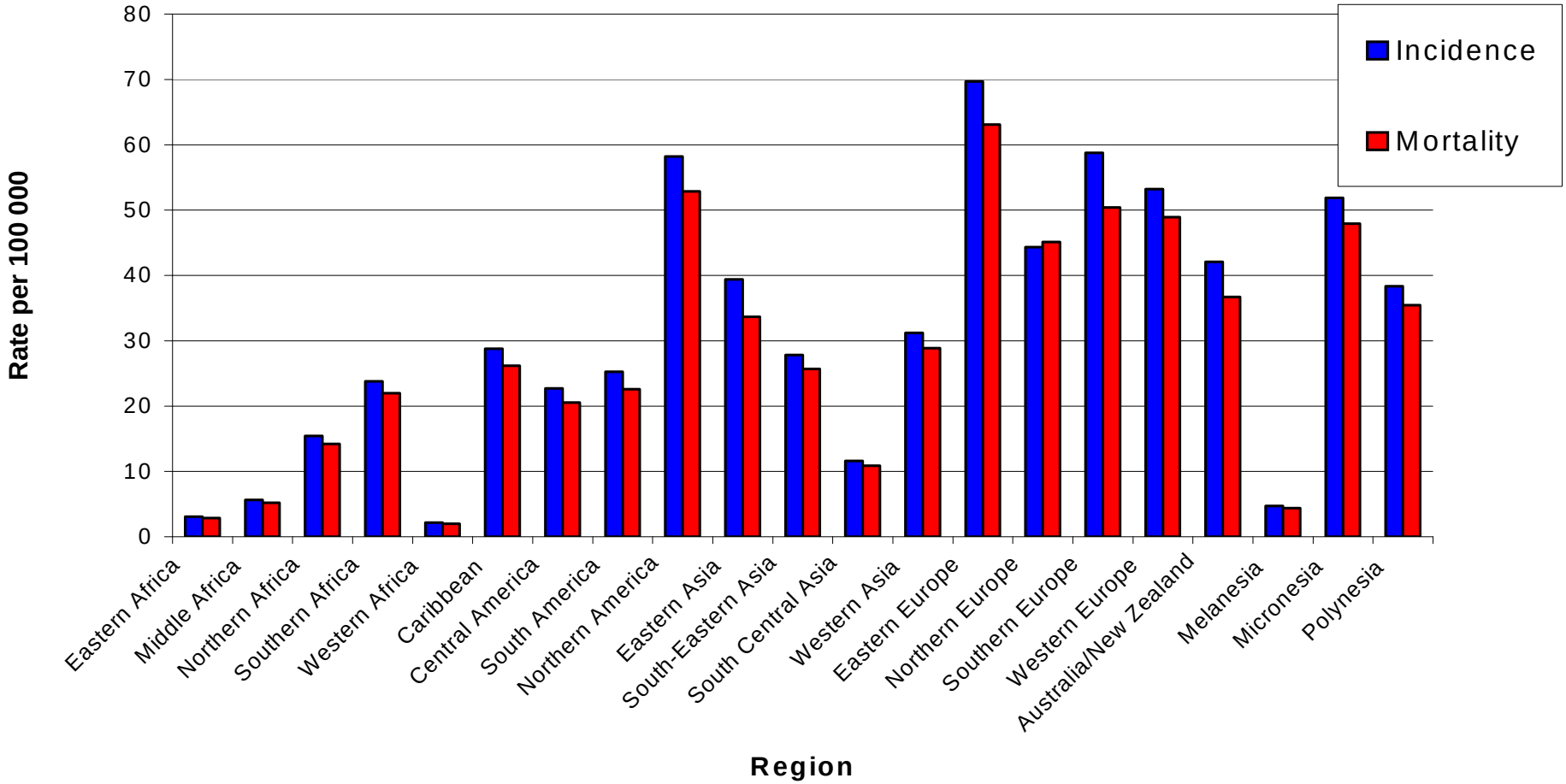
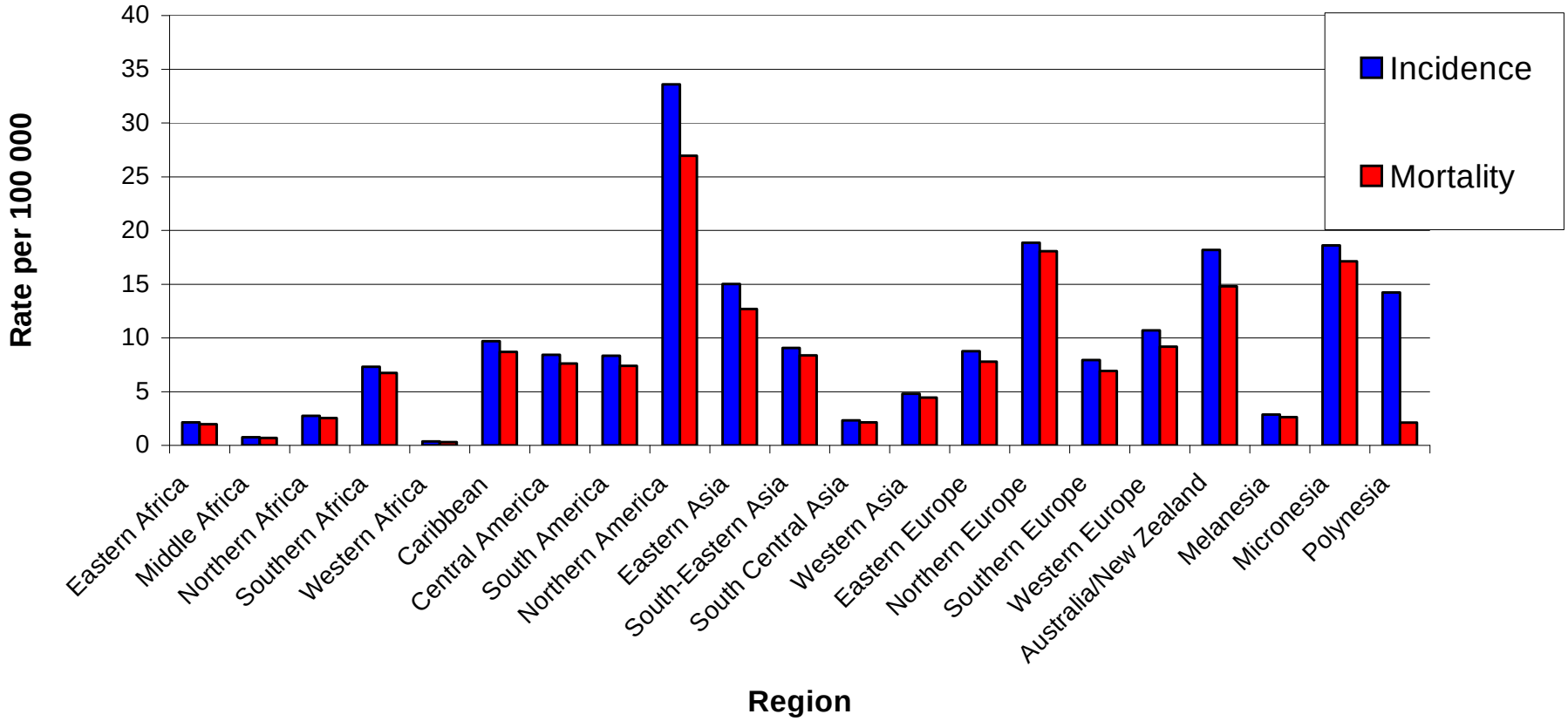


Figure 1-4: World Female Lung Cancer Incidence and Mortality Rates by Region (Age standardised estimates for 2000 based on 3-5 years earlier and adjusted for increase in population[8])



1.1.2. Lung Cancer in Australia

Twenty-nine percent of all male primary cancer diagnoses in Australia are of lung cancer (Figure 1-5). It is the most common cancer diagnosis in Australian males, and in females is second only to breast cancer (19% vs 24% of all female cancer diagnoses, Figure 1-6[8]). As Figure 1-7 illustrates, the rate of male deaths from lung cancer has been decreasing since the mid 1980's, whilst over the same period female mortality rates have increased[8].

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])

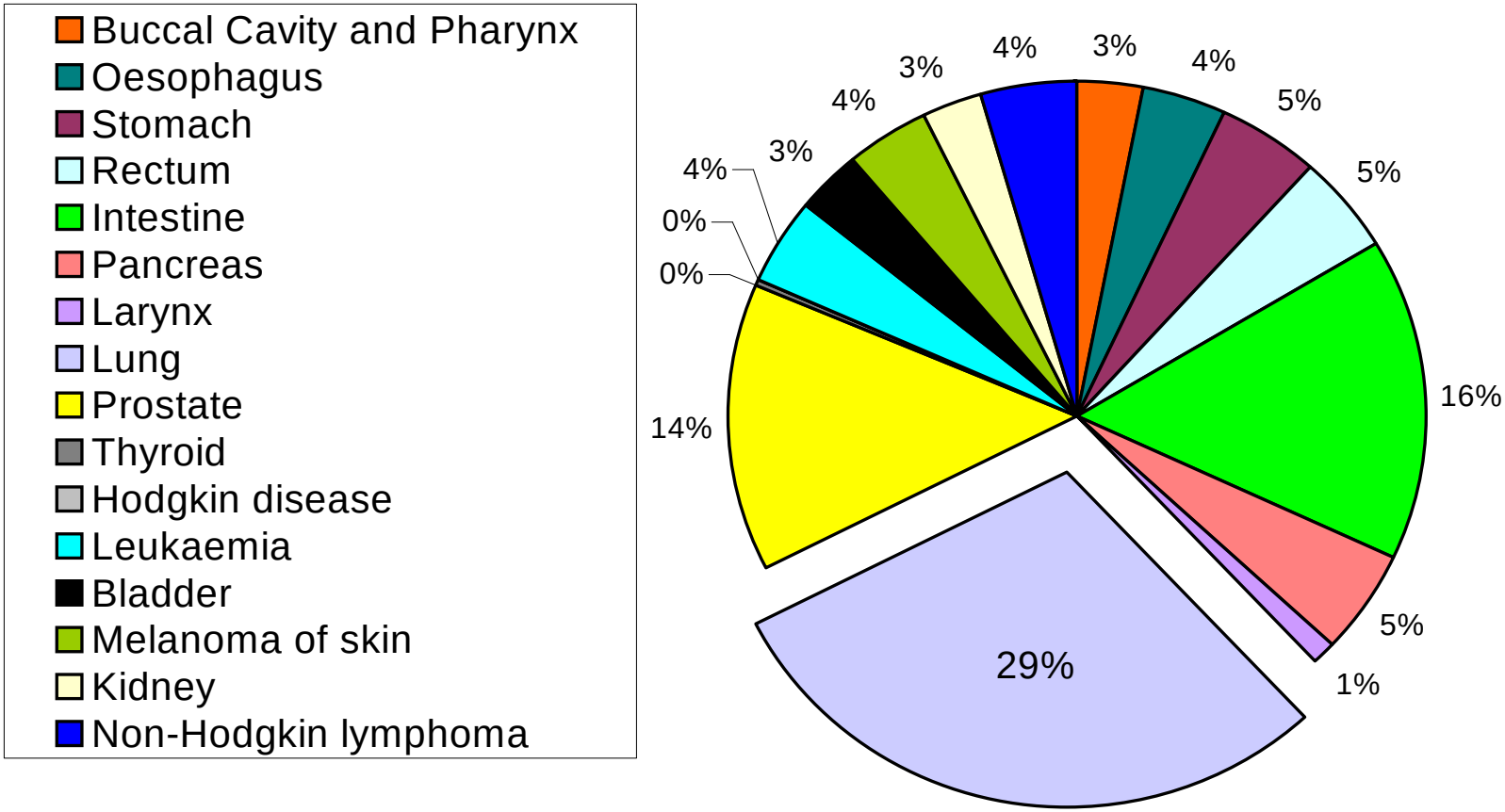


Figure 1-6: Australian Female Cancer Mortality Rate by Type of Cancer (Age standardised, per 100 000, estimates for 2000 based on 3-5 yrs earlier and adjusted for increase in population[8])

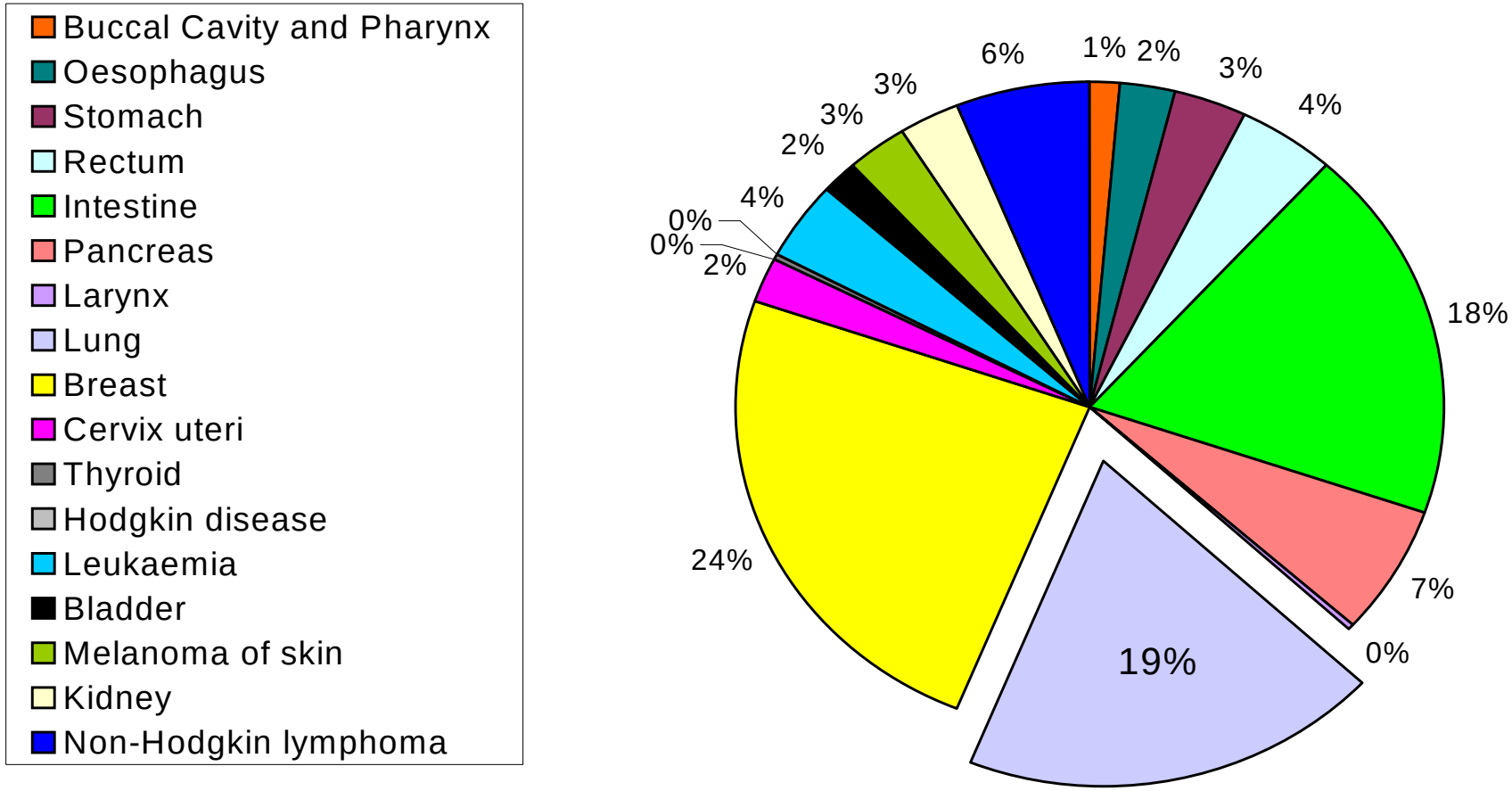
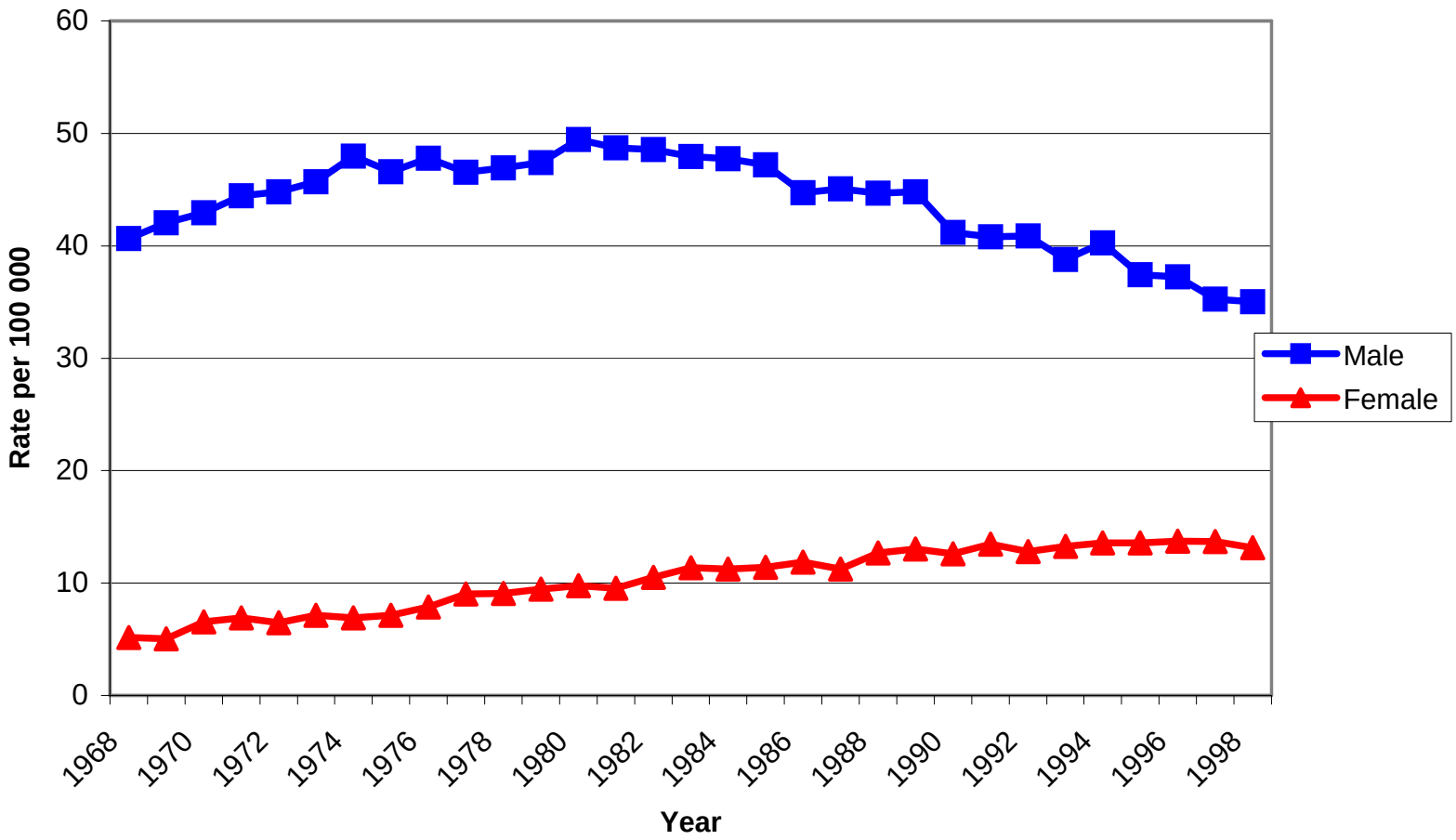


Figure 1-7: Australian Age Standardised Rates of Lung Cancer Mortality (Adjusted for increase in population[8])



In Australia, it has been estimated that the treatment cost per lung cancer patient (excluding terminal care) averages A$14 413[9]. With 5553 lung cancers diagnosed in Australia in 2000[8], the annual cost to the health system is tremendous. Again, the major component of this expense is hospitalisation (42%)[9]. Not only does lung cancer hospitalisation accrue direct cost in terms of treating the patient, but also by using beds, putting added strain on the health care system as a whole.

The incidence rate of lung cancer in metropolitan Adelaide between 1986 and 1993 was 474 per year (Figure 1-1)[1], with the highest incidence ratios (age and gender standardised) in North Western, Central and outer Southern areas of metropolitan Adelaide. The overall incidence of lung cancer is 10% lower in rural areas when compared to urban, however there are a number of towns with elevated incidence ratios, in particular Whyalla, Port Augusta and Wallaroo (rate ratios of 141, 132 and 131 respectively[1]). It has been noted that lung cancer incidence correlates with areas of single parent and low income families, disability pensioners, unemployment beneficiaries and male use of health service providers[1], all potential indicators of poor socioeconomic status.

1.1.3. Aetiology

Molecular research has demonstrated lung cancer to be a result of substances (lung carcinogens) entering the lungs, and mutating and altering the function of the DNA in lung cells. Two primary sources of lung carcinogens are cigarette smoke and industrial processes. There is strong evidence (both epidemiological and molecular) for a causal relationship between tobacco smoke and lung cancer through direct smoking[10 11], with a less conclusive but growing body of evidence for environmental tobacco smoke (ETS)[12]. Lung carcinogenic substances have been identified in a number of occupational processes

and epidemiological evidence exists for an association between workers exposure to these substances and lung cancer development[13]. This association is particularly strong for "blue collar" work such as boiler making, building and construction (associated with asbestos and particulate matter exposure), jobs involving heavy vehicles (truck driving, forklift work, associated with polycyclic aromatic hydrocarbons and diesel exhaust), and mining, quarry and stone work (associated with crystalline silica).

There is also a group of people with lung cancer who have not been exposed to lung carcinogens from cigarette smoke or occupational process[14]. It is possible that this group of people may have been exposed to occupational carcinogens due to emissions of waste products from industry stacks/chimneys into the ambient air[15 16]. These emissions are particularly relevant to people residing in close proximity to polluting industry. The epidemiological evidence for a causal relationship between ambient carcinogens and lung cancer development is weaker than that for cigarette smoking and occupational exposure, and will be evaluated systematically in Chapter 2.

1.2. North Western Metropolitan Adelaide

The North Western suburbs of metropolitan Adelaide are comprised primarily of the Port Adelaide statistical local area (SLA), but also include parts of the Hindmarsh and Woodville SLA. The region identified for this research is approximately 10km by 15km, with an 88km^2 residential area and population of 100 000 (10% of metropolitan Adelaide population).

The NW suburbs of Adelaide are an historical area, first settled due to the availability of shipping ports along the Port River for the transport of goods into and out of Adelaide[2]. For this reason it has also been a focal point for industrial activity, with the highest concentration in South Australia of industry licensed to carry out "prescribed activities" by the Environmental Protection Authority (EPA) (Personal communication, Environmental Protection Authority of South Australia, 2003).

The SEIFA Index of Relative Socioeconomic Disadvantage is a measure used by the Australian Bureau of Statistics to summarise demographic variables such as poverty, income, education and housing status into one figure[1]. The Social Health Atlas shows that the North West are amongst the most disadvantaged in metropolitan Adelaide. The area also has a high concentration of public housing and unemployment[1].

The people of Port Adelaide have traditionally lived as a tight knit community. A book of oral histories from lifetime residents of the area paints a picture of a community determined to stand by one another, particularly during the depression years[17]. The book also documents the frustration residents feel towards polluting industry. Residents have formed community groups over the previous two decades in an effort to publicise their concerns regarding the health effects of industry in the area, particularly relating to respiratory health. Two reports have been published by members of these groups following residential surveys, case studies and collation of historical data[18] [19]. Although crude in design and primarily based on anecdotal evidence, both reports conclude that the public of Port Adelaide need to be better informed of the quality of the air they breathe, and of any new industrial developments or changes to licensing in the area. The groups also believe government legislation regarding air pollution emissions should be stringently

enforced. Finally, the groups publications request detailed investigations be undertaken into the health effects of residing in close proximity to industry, and subsequently living in an area of poor air quality.

1.2.1. Lung Cancer in the North West

Data published in the South Australian Health Atlas[1] indicated the NW suburbs to have the highest incidence of lung cancer (standardised for age and gender) in metropolitan Adelaide over the preceding 8 years (see Figure 1-1). When broken down to suburban levels, Osborne was found to have the second highest standardised incidence ratio for lung cancer in metropolitan Adelaide (211), more than twice that of metropolitan Adelaide as a whole, and more than 4 times that of more affluent Eastern suburbs (Belair – 30, Burnside – 38)[1].

1.2.2. Industry in the North West

The North West of Adelaide, in particular the area surrounding the Port River, was identified as an industrial site soon after the city of Adelaide was founded in 1836 (Figure 1-8). Initially the industry was focused on whaling (the Gulf of Saint Vincent is a breeding passage for Southern Right Wales), wool and wheat[2]. In 1856 the first wool stores were built on the corner of Lipson and Divett Streets by Elder Stirling and Co[20]. The 1880's saw a rapid increase in wool storage in the area, with some of these stores still used today by Quality Wool[2]. The area's first flour mill (Hart's Mill, later to become the Adelaide Milling Company) was established in 1855[2].

Figure 1-8: Aerial View of the Port River[21]



In the 1840's a smelter era began. The Adelaide Smelting Company began operations in 1849 on Newcastle St at Rosewater until 1851[2]. In 1861 the English and Australian Copper Company built a large smelter on the bank of the Pt River (St Vincent and Mundy Streets corner) that processed copper from mines in Burra[2]. When the Burra mine closed in 1877 the smelter continued, sourcing copper from other mines, but by 1912 smelting was phased out[2]. The Block 14 smelter works processed silver and lead from Broken Hill from 1894 to 1902[20].

In the late 1800's to early 1900's a number of fertilizer companies began operations in the North West. Three of these, Adelaide Chemical Works (formed in 1882 in Pt Adelaide), Adelaide Chemical and Fertilizer Company (a sulphuric acid plant established in 1900 in Pt Adelaide, known as TOP post 1906) and SA Fertilizer Company (1913, Birkenhead, known as Cresco Fertilizer Company after 1920) still exist today under the banner of Adelaide Wallaroo Fertilizers[22].

In the early 1900's the area was known for its ship building, with the first ship built at Osborne launched in 1920[22]. A paint manufacturer became operational in 1906 on Lipson St, Pt Adelaide, which made lead based paint until the 1960's, when it was renamed Dulux and became involved in car duco paint production[22].

The Pt Adelaide region supplied much of Adelaide with its first gas from gasworks at Rosewater (operational 1866 to the 1920's), Peterhead (1979) and Osborne (1928 to 1930, and 1939 to 1979[22]). By 1969 the states gas was supplied from Moomba so plants in the North West were shut down (other than Osborne which continued to supply gas to nearby industry)[22]. It was also a site for electricity generation, with the states first power station operational in Osborne in 1923[22]. An additional plant was built at the site in 1938, however both ceased operation when the Torrens Island Power Station (which remains in operation today) began generating power in 1967(Figure 1-9)[22].

***Figure 1-9: The Torrens Island Power Station*[23]**



A number of factories manufacturing building products have been situated in close proximity to the Port River. In 1891 a cement mix producer (CSR) began operations in Glanville and, other than an interruption due to an extensive fire in 1926, it remained working until 1991[20]. Adelaide Brighton Cement, one of the most recognisable industrial buildings in the region today, began manufacturing cement products in 1914 at its Birkenhead plant (Figure 1-10)[20]. ICI (now known as Penrice Soda Products) began manufacturing soda ash in 1940 and continues today at its Osborne site[2]. Asbestos Cement Ltd (part of the James Hardies Victorian company) manufactured asbestos sheets, roofing and pipes under the brand name Asbestolite from 1941 until it was phased out in the 1980's[24].

Figure 1-10: Aerial View of Adelaide Brighton Cement[25]



Whilst industry in the Pt Adelaide and Lefevre Peninsula region developed quickly, by the mid 1900's there were 2 other key industrial regions in the North West suburbs; Finsbury and Hendon. Finsbury began its industrial activity in 1941 manufacturing shell cases and fuses (munitions) for the war, under the name The Cheltenham Works in Woodville North[26]. By 1946 the factories were leased by private companies for engineering, automotive and whitegoods production (this included Kelvinator, Apac Industries, Firestone Tyre and Rubber Company), a number of which are still operational today[26]. Hendon was also involved with munitions production, but after the war in 1947 became a much smaller industrial area operated wholly by Phillips Electrical Industries[26].

Today there are 205 industries licensed to carry out 'prescribed activities' (permission to release a range of emissions into the air) in the North West Adelaide Lung Cancer Study geographic area. This is 33% of all licensed industry in metropolitan Adelaide, in an area where 10% of the population live. Many of these industries operate in close proximity to residential homes as is shown in Figure 1-10 where homes are directly across the road from industry. The majority of these industries undertake air-polluting activities (Environmental Protection Authority (EPA)). Licensed industry are allowed to carry out a variety of polluting activities and are required to regularly report their emissions to the South Australian EPA. As per the industrial history above, the majority of industry is clustered around the Port River. However, also as described, many of the industries operating in the region have since closed. In addition, clean air regulations introduced in 1972 and changes to Australian design rules in the 1970's[27] [28]mean it is likely that historical air quality was poorer than that of today.

Table 1-2 lists major industries located in the North West area, the proximity to which will be used to assess the residential exposure of study participants. Each was identified after research into the industrial history of the region, and was selected due to it being operational at the time relevant for exposures relating to contemporary lung cancer cases (15 to 30 years latency period[29]), and the high likelihood of each to have emitted lung carcinogens during its operations (as determined by an occupational hygiene panel comprised of three occupational hygienists with specific historical and contemporary knowledge of metropolitan Adelaide, the panel will be explained in more detail in the Methods Chapter).

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

Name	Location	Year Established	Year Closed	Type of industry	Potential Lung Carcinogens Emitted	Additional Information	Reference
Adelaide Brighton Cement	Charles St, Birkenhead	1914	N/A*	Cement production	Crystalline silica $PM_{2.5}$	Originally named Adelaide Cement Company, renamed in 1971	[20] [30]
ICI/Penrice Soda Products	Osborne	1940	N/A*	Soda products plant (produced soda ash)	Crystalline silica $PM_{2.5}$	Renamed Penrice Soda Products in 1987	[2] [31]
CSR	Glanville	1891	N/A*	Mineral building product manufacture	Crystalline silica $PM_{2.5}$	Fire in 1926 destroyed much of the plant, it was rebuilt soon after	[20] [32]

Name	Location	Year Established	Year Closed	Type of industry	Potential Lung Carcinogens Emitted	Additional Information	Reference
Torrens Island Power Station	Torrens Island	1967	N/A*	Electricity generation	PAH	Additional 3 units operational 1971	[22]
James Hardies – Asbestos Cement Pty Ltd	Birkenhead	1941	Phased out in early 1980's	Asbestos product manufacture (sheets, roofing, pipes)	asbestos	Initially owned jointly with Wunderlich Ltd who were bought out in 1960. Product brand name was Asbestolite.	[24]

Name	Location	Year Established	Year Closed	Type of industry	Potential Lung Carcinogens Emitted	Additional Information	Reference
Finsbury Industrial suburb	Woodville North	1941	N/A*	Prior to 1945 a government munitions factory, post 1946 area was private leased and home to a cluster of industry including engineering, automotive, household appliance & electrical goods factories	Diesel exhaust, PAH, $PM_{2.5}$	Initially known as “The Cheltenham Works”. 1945 change in industry type – see industry types column	[33] [26]

** N/A – not applicable as industry is still operational*

1.2.3. Ambient Air Quality in the NW

In the past decade ambient air quality monitoring has been regularly carried out in the North Western suburbs by the South Australian EPA (usually on a 6 day cycle)[34]. Monitoring stations for PM_{10} are located in Osborne and Port Adelaide. The National Environmental Protection Measure (NEPM) guideline indicates that more than 5 days per year of 24hr PM10 exceeding 50ug/m3 is unacceptable[35]. Between 1993 and 1999 the NEPM standard was never exceeded in Pt Adelaide, as opposed to Osborne where the standard was exceeded for 5 days in each of 1990 and 1993, and for 6 days in each of 1991, 1994, 1998 and 1999[34]. Other air pollutants have not been consistently monitored in the North West.

The EPA also has a van used for "hot-spot" monitoring. The location of this van is rotated depending on government and community concerns, complaints and requests. In 1996 the EPA van was rotated between 3 sites in the North Western suburbs for a total of 18 weeks (Site 1 – residential area, Site 2 – area containing cement works, Site 3 – area containing a soda plant and power generation plant). This monitoring was carried out in conjunction with the cross sectional survey discussed previously[3]. Nitrogen dioxide, sulphur dioxide and ozone 1 hour concentrations did not vary significantly between the 3 locations, and did not exceed NHMRC ambient air quality guidelines[3].

Whilst some monitoring has been carried out in the North West both regularly and sporadically, the resulting data can not be used to assess the residential exposure of incident lung cancer cases due to the lung cancer latency period of 15 to 30 years[29]. In addition, existing monitoring data has little relevance as it has not specifically

targeted potential lung carcinogens, nor has its location had a specific health focus. Given the ongoing collocation of a diverse range of industry and residential homes it is important, and relevant to a study of incident lung cancer in the region, to quantify current levels of airborne lung carcinogens in the area to be used as an indicator of future respiratory health risk.

2. Chapter 2 Review of the Literature

Chapter 1 described the high rate of lung cancer in the North West of metropolitan Adelaide, an area containing residential homes in close proximity to industry. Before conducting research to investigate the relationship between lung cancer and air pollution from industry, it is important to determine what other evidence for this relationship exists both in Australia and internationally. This chapter provides an overview of how substances are able to induce lung cancer, the evidence for air pollutants to be carcinogenic and the likelihood of these pollutants to be present in the North West of Adelaide. It also includes a systematic review investigating whether evidence of a causal relationship between air pollution and lung cancer can be concluded from previously published epidemiological studies (as published in Respirology[36]), and an evaluation of Australian research investigating lung cancer and air pollution. Finally, the aims, objectives and hypothesis for this study are presented.

2.1. Lung Cancer Histology

Lung cancer development results from a multistage process of mutations and morphological changes in the cells of the lung. When inhaled lung carcinogens are metabolised to become reactive carcinogenic metabolites. These metabolites are able to interact with and bind to DNA to form mutagenic DNA adducts[7]. Mutations leading to cancerous cells occur in two broadly classified types of genes, proto-oncogenes, and tumour suppressor genes[7]. Proto-oncogenes are a group of genes that promote cell growth and replication by producing proteins that initiate metabolic or transcriptional activity in the cell. The *ras* and *myc* families of proto-oncogenes have both been associated with lung cancer development. Tumour suppressor genes are those that regulate and restrain cell growth and replication by producing proteins that inhibit metabolic or transcriptional activity[7]. Mutations in *p53* (responsible for the production of a phosphoprotein that arrests the G1 phase of the cell cycle when DNA checking and repair occurs) and retinoblastoma (*rb*, responsible for production of a nuclear phosphoprotein involved with the cell cycle) tumour suppressor genes have been associated with lung cancer. Lung carcinogens are able to mutate proto-oncogenes or tumour suppressor genes to initiate uninhibited cell growth and proliferation, while preventing apoptosis (programmed cell death), therefore promoting tumour development in the cellular tissue of the lung[7].

2.1.1. Lung Cancer Classification

When lung cancer is diagnosed it is classified by the cell type and level of differentiation. This level of diagnosis is usually obtained by tumour biopsy and assists in determining the treatment and prognosis of the patient. Associations have been identified between specific types of lung cancer and sources of carcinogens (for example smoking with squamous cell carcinoma, and occupational exposures with adenocarcinomas)[6]. Table 2-1 describes the features of each cell type. Mixed tumours are also possible, but are usually classified according to the most dominant cell type in the mixture (as it most closely predicts patient outcome) and are rarely diagnosed except in autopsy.

Cellular differentiation is a measure of the distortion of tumour cells when compared to a non-cancerous cell of the same type. Two of the levels of differentiation are illustrated in Figure 2-1. A decrease in cellular differentiation indicates a highly developed tumour and hence a poor prognosis for the patient.

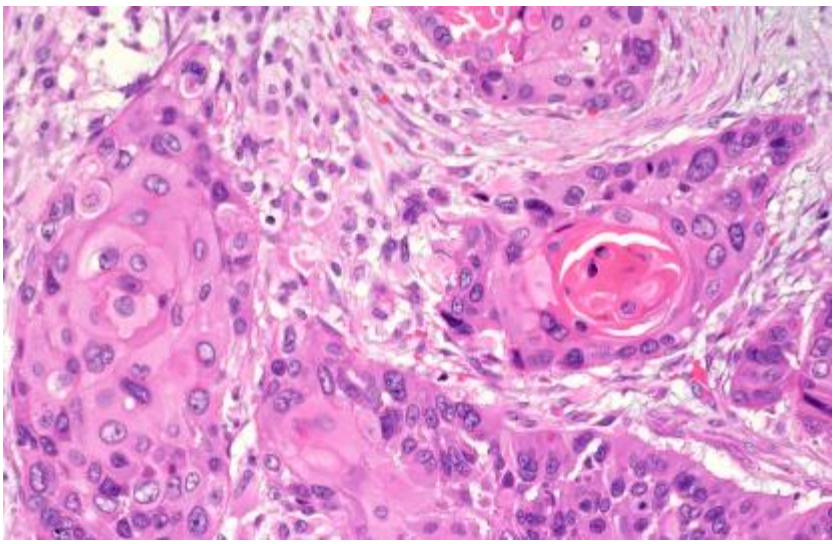
Table 2-1: Features of each Lung Cancer Cell Type

Adapted from Mosby's Crash Course –Respiratory Systems[6]

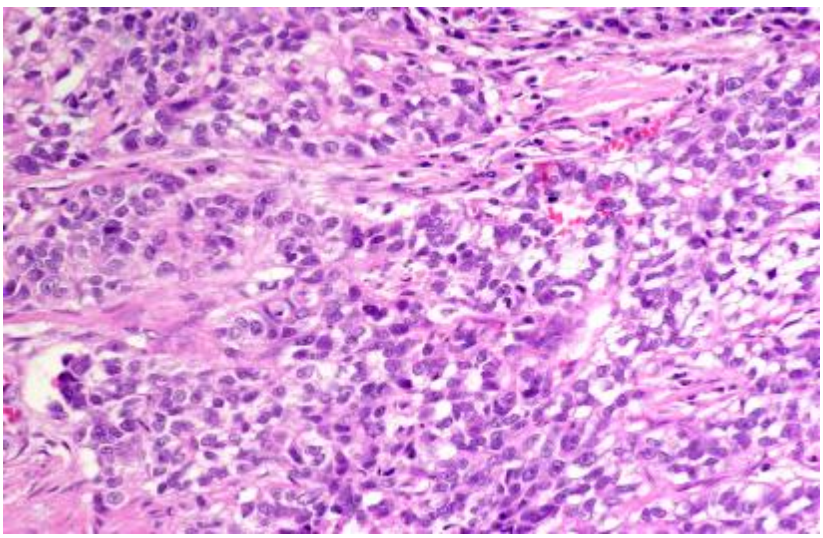
	Cell Types			
	Non-small-cell tumours			
	Squamous cell tumour	Adeno-carcinoma	Large cell	Small cell
Relative incidence (%)	52	13	5	30
Male (M) to Female (F) ratio	M>F	F>M	M>F	M>F
Location	Hilar	Peripheral	Peripheral/ central	Hilar
Smoking association	High	Low	High	Very High
Growth rate	Slow	Medium	Rapid	Very Rapid
Metastasis	Late	Intermediate	Early	Very Early

Figure 2-1: Two Levels of Tumour Differentiation

These high power histological photos with haematoxylin and eosin stain were provided by the Department of Pathology, University of Adelaide.



a) Well differentiated squamous cell carcinoma. Note the islands of large tumour cells with large nuclei (blue/purple), abundant eosinophilic (pink) cytoplasm and areas of keratinisation (deep pink round area).



b) Highly undifferentiated (or anaplastic) squamous cell carcinoma. Note the large tumour cells with large nuclei (blue/purple) and relatively little cytoplasm.

2.2. Lung Carcinogen Classifications

Substances are classified as carcinogenic based on evidence from molecular, animal and human research. Classifications from the International Agency for Research on Cancer (IARC) are convention internationally (Table 2-2)[37].

Table 2-2: Carcinogen Classifications Employed by IARC[37]

Category	Description
Group 1	The agent or mixture is carcinogenic to humans
Group 2A	The agent or mixture is probably carcinogenic to humans
Group 2B	The agent or mixture is possibly carcinogenic to humans
Group 3	The agent or mixture is not able to be classified according to its carcinogenicity
Group 4	The agent or mixture is probably not carcinogenic to humans

2.2.1. Lung Carcinogens

For this study we are interested in substances known to be (Group 1) or probably (Group 2A) carcinogenic to the lung or respiratory tract of humans. Carcinogens in these categories were selected to reduce contamination of exposure estimates with substances not likely to be carcinogenic, and because this study did not aim to identify new respiratory carcinogens. Table 2-3 lists lung carcinogens assigned one of these classifications and their sources (including potential sources in the North Western suburbs of Adelaide).

Table 2-3: Known (1) or Probable (2a) Respiratory Carcinogens and their Potential Sources[38 39]

Substance	Category	Source	NW Adelaide potential source
Asbestos	1	Construction work & maintenance, mechanical brake lining	Abandoned asbestos cement manufacturing factory
Crystalline silica	1	Mining, masonry, stonework, concrete & gypsum, pottery	Cement manufacturer
Polycyclic Aromatic Hydrocarbons	2a	Furnaces, aluminium industry, bitumen & asphalt, residential heating	Heavy vehicle traffic, Power station, Light industry
Diesel exhaust	2a	Trucking, combustion	Industrial vehicle traffic
Particulate matter	*	Welding, building products manufacture	Mineral building product manufacturer, light industry
Formaldehyde	2a[#]	Adhesive in manufacture of particle board, fibreboard & plywood, disinfectant and preservative	Industrial vehicles Asbestos cement manufacturer (converted to fibreboard in the 1980's)

Substance	Category	Source	NW Adelaide potential source
Arsenic	1	Alloying agent, herbicides, insecticides, wood preservative, mining	Historically – pesticide manufacturer and timber mill
Beryllium	1	Mining, refining and manufacture of ceramics, electronic and aerospace equipment	No
Nickel	1	Production of stainless steel, alloys, electroplating and battery manufacture	No
Cadmium	1	Electroplating, some plastics manufacturer, alloys and electrodes in batteries	No
Chromium 6	1	Production of stainless steel, chrome alloys and welding	Stainless steel welding in some industries
Radionuclides (Radon)	1	Uranium mining and processing	No

** - Whilst at the time of identifying carcinogens it was not identified as carcinogenic itself, components of Particulate Matter such as welding fumes and wood dust have been classified as carcinogenic, and it is able to act as an airborne carrier for a variety of substances including carcinogens*

 # - Formaldehyde is a respiratory carcinogen rather than being specifically related to lung cancer

2.3. The Origins of the Association between Air Pollution and Lung Cancer

Descriptive epidemiological studies specifically investigating a potential relationship between lung cancer and air pollution emerged in the literature in the 1950's. Initial studies were ecological and compared lung cancer rates between rural and urban populations, immigrants and non-immigrants and industrial and non-industrial regions[15]. Rural versus urban studies found smoking gradients of lung cancer were steeper in industrial urban areas compared to rural. Studies have found that the rates of lung cancer in migrants fell somewhere between the rates in their country of origin and their new country. In the latter studies, an increased lung cancer rate in migrants when in their new country may be attributed to occupational exposure (due to a higher proportion of migrants employed in blue collar work). Due to the limitations of the ecological study design, particularly a lack of confounder adjustment, such studies require cautious interpretation today. In 1978 Sir Richard Doll summarised that preliminary evidence for an association between lung cancer and ambient carcinogens did exist, and suggested a potential interaction effect between smoking and ambient carcinogens[40].

2.4. A review of the Epidemiological Evidence for a Causal Relationship between Environmental Exposure to Carcinogens (Air Pollution) and Lung Cancer

The aim of the following section is to systematically evaluate the strength of evidence presented in the medical literature in the past two decades for a causal relationship between exposure to air pollution and lung cancer development by application of the Bradford Hill criteria for causality[41].

Two previous reviews in 1983 and 1990 concluded that the effect of air pollution on lung cancer is greater than zero, but the epidemiological evidence was weak due to poor

confounder adjustment and studies of a descriptive nature[15 16]. The majority of studies at the time of publication for these reviews were ecological, both reviews briefly assessed the evidence from these studies, concluding that they demonstrated an association between lung cancer and air pollution, but did not adjust for the confounding nature of cigarette smoking. Methods of exposure assessment (both air pollution and for cigarette smoking and occupation as confounders) were criticised for lacking adequate detail. These reviews also highlight the inherent heterogeneity of both the air pollution exposure measurements and study outcomes.

In this review, "air pollution" is the generic term used to describe the risk factor of ambient exposure to potentially carcinogenic airborne substances. In the results section the methods used by each paper to quantify air pollution will be described. In addition "lung cancer" refers to the study health outcome of either primary lung cancer mortality or incidence, as diagnosed by a registered doctor or at autopsy.

2.4.1. Literature Review Methodology

A structured literature search was undertaken on MEDLINE and EMBASE databases using the following key words (EMBASE M-tags numbers in brackets): lung neoplasm (306) AND epidemiology (400) AND human (888) AND air pollution AND NOT molec*. A handsearch of reference lists was also undertaken.

Literature identified in the primary search was then culled based on the following inclusion criteria; post 1982 case control or cohort study that had described its study population, measured ambient environmental factors and considered the confounding effects of both tobacco smoke and occupational exposure. This criteria ensured that the

final set of studies were of an analytical design, and had all attempted to adjust for important confounders in their analysis.

The method of environmental exposure classification was described, and the literature systematically evaluated in accordance with the seven relevant Bradford Hill criteria for causality[41] (Biological Plausibility and Coherence were combined as is currently recommended[42]). "Experimental evidence" was excluded as the epidemiological focus of this review would not have captured evidence for either of these criteria.

2.4.2. Results of the Literature Review

Fourteen papers met all of the search criteria, four cohort[43-46] and ten case control studies[47-56]. Two of the papers were reports of the same cohort, at seven[46] and 16 years[44] of follow-up. Table 2-4 is a summary of these papers.

Table 2-4: Adjustments for the Confounding Effects of Smoking and Occupation

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Vena[57]	1982	Case control	1957-1965	Residential exposure Smoking Occupation	Primary lung cancer incidence	Logistic regression
Brown et al[48]	1983	Case control	1974-1977	Residential exposure Smoking Occupation	Primary lung cancer mortality	Logistic regression
Pershagen[54]	1985	Case control	1961-1979	Residence Smoking Occupation	Primary lung cancer mortality	Not indicated

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Jedrychowski et al[49]	1990	Case control	1980-1985	Residential exposure Smoking Occupation Socioeconomic status	Primary lung cancer mortality	Unconditional logistic regression
Katsouyanni et al[51]	1991	Case control	1987-1989	Residential exposure Smoking Occupation Marital status Socioeconomic status	Primary lung cancer incidence	Logistic regression

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Jockel et al[50]	1992	Case control	-	Indoor and outdoor residential air pollution Smoking Passive smoking Occupation Diet Leisure activities	Primary lung cancer incidence	Unconditional logistic regression
Barbone et al[47]	1995	Case control	1979-1981 & 1985-1986	Last residence Smoking Occupation Social status	Primary lung cancer mortality	Conditional logistic regression

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Pawlega et al[53]	1997	Case control	1992-1994	Residential exposure Smoking Occupation Education Vodka consumption Diet	Primary lung cancer incidence	Unconditional logistic regression

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Tousey et al[55]	1999	Case control	1993-1996	Residential exposure Smoking Passive smoking Occupation Diet Medical history Life style	Primary lung cancer incidence	Logistic regression
Nyberg et al[52]	2000	Case control	1985-1990	Residential exposure Smoking Occupation Diet	Primary lung cancer incidence	Unconditional logistic regression

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Dockery et al[45]	1993	Cohort	1975-1991	Residential exposure Smoking Occupation Socioeconomic status Body mass index	Mortality Primary lung cancer mortality Cardiopulmonary mortality	Cox proportional-hazards model
Pope et al[46]	1995	Cohort	1982-1988	Residential exposure Smoking Occupation Alcohol intake Body mass index	Mortality Primary lung cancer mortality Cardiopulmonary mortality	Cox proportional-hazards model

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Beeson et al[43]	1998	Cohort	1977-1992	Residential exposure Smoking Passive smoking Occupation Diet Alcohol intake Family history of lung cancer	Primary lung cancer incidence	Cox proportional-hazards model

Paper	Year of publication	Study design	Time period	Risk factors examined	Outcomes measured	Analytic method
Pope et al[44]	2002	Cohort	1982-1998	Residential exposure (air pollution) Smoking Occupation Socioeconomic status Alcohol intake Diet Body mass index	Mortality Primary lung cancer mortality Cardiopulmonary mortality	Cox proportional-hazards model

2.4.2.1. Environmental Exposure Classification

Eleven of the fourteen studies used a direct method to quantify environmental exposure, assigning each subject the result of their nearest air sampling station, or using multiple air sampling stations to create a map overlay that joins areas of similar air quality into categories (an isopleth map). None of these studies measured all known or potential lung carcinogens, instead using indicators such as particulates[43-45 47 49 50 53 57] or sulfur dioxide[43 45 48-50 53]. The remaining three studies used an indirect exposure classification method, measuring residential proximity to industry as a proxy for exposure[52 54 55].

Both the direct and indirect method of exposure quantification mentioned above lack validity if the latency period is not considered. Eight of ten retrospective (case control) studies attempted to take the 10 to 30 year latency period into account using historical air quality measurements[47 49-51 53 57], extrapolating current air quality data based on changes in industrial practice and traffic conditions[52], or using undisturbed soil sample [48]. The four prospective (cohort) studies monitored air quality for the duration of the cohort[43-46]. The two studies[54 55] relying purely on current data did not discuss this methodological flaw in their papers.

2.4.2.2. Strength of Association

What is the magnitude of the RR or OR?

Of the 14 studies reviewed, after adjustment for potential confounders, relative risks (RR) or odds ratios (OR) for the association between environmental exposure and lung cancer ranged from 0.28[53] (protective) to 5.2[43] (both significant, $p<0.05$) (see Figure 2-2 and Figure 2-3). Of the studies investigated, eight demonstrated a significant positive effect of

poor air quality or close proximity to industry on lung cancer development in at least one subgroup[43 44 47-49 53 58].

As Figure 2-2 and Figure 2-3 illustrate, there is a high degree of heterogeneity both between and within studies. A formal forest plot was carried out for the case control studies (Figure 2-2) but could not be carried out for cohort studies due to the unavailability of the required data. A test of homogeneity for the case control studies showed that the studies are not homogeneous and therefore a pooled estimate of odds ratio is not meaningful (assessed using Mantal-Haenszel test). The likely explanation for this is the high degree of diversity in assessment of exposure to both air pollution and confounding factors (tobacco smoke and occupation, and potential differential relationships between lung cancer and air pollution amongst population subgroups. The highest RR's were found when place of residence approximately 30 years prior to diagnosis was used to classify environmental exposure [48] and in a prospective study where air quality had been monitored over 15 years (both periods of time within the known lung cancer latency period[43]). Pawlega et al[53] is the only study to report a protective effect of poor air quality. This anomaly is potentially a function of the method used by Pawlega et al to adjust for confounders (see 'Specificity') and uncertainty as to the reference city having "good" air quality.

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

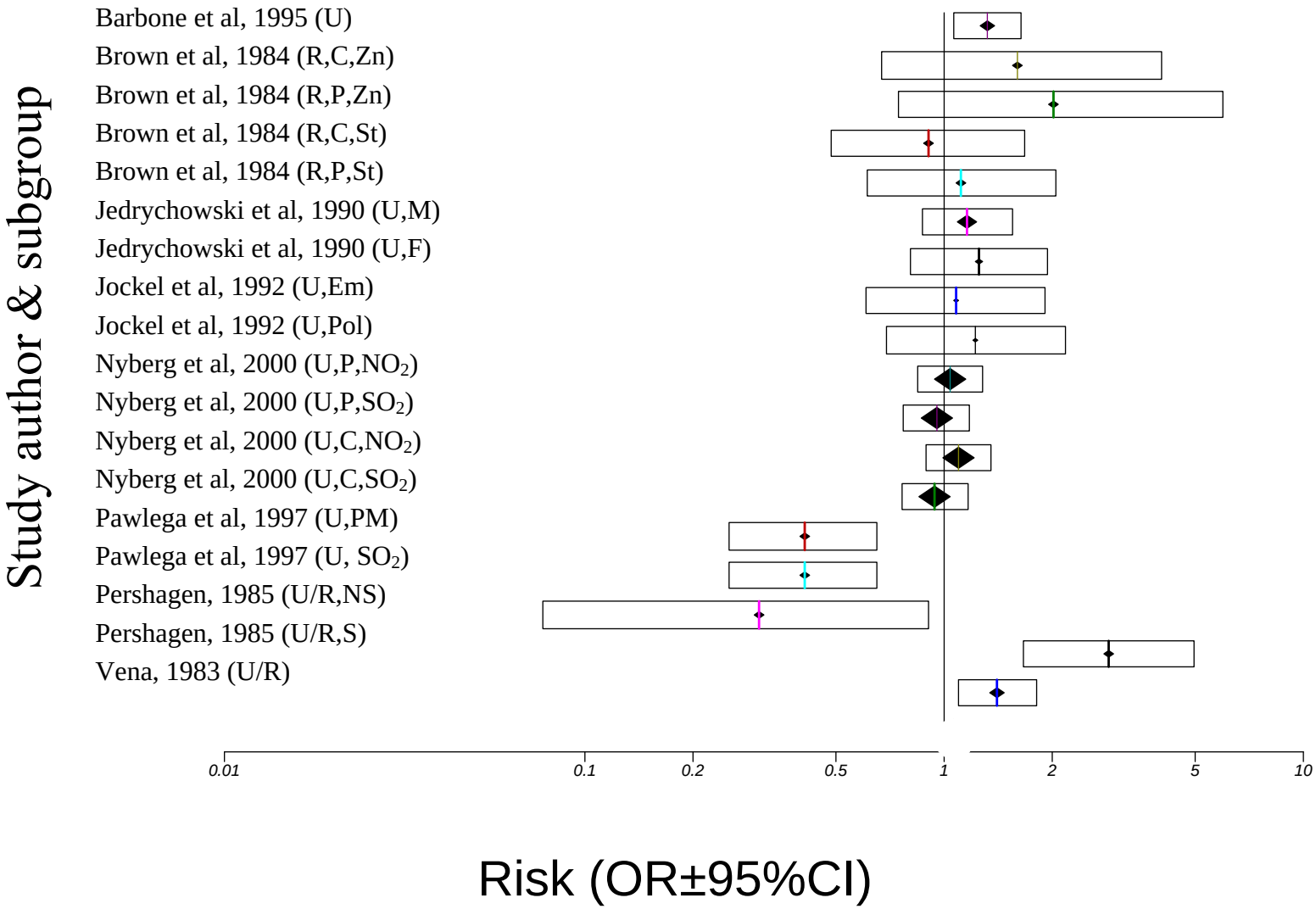
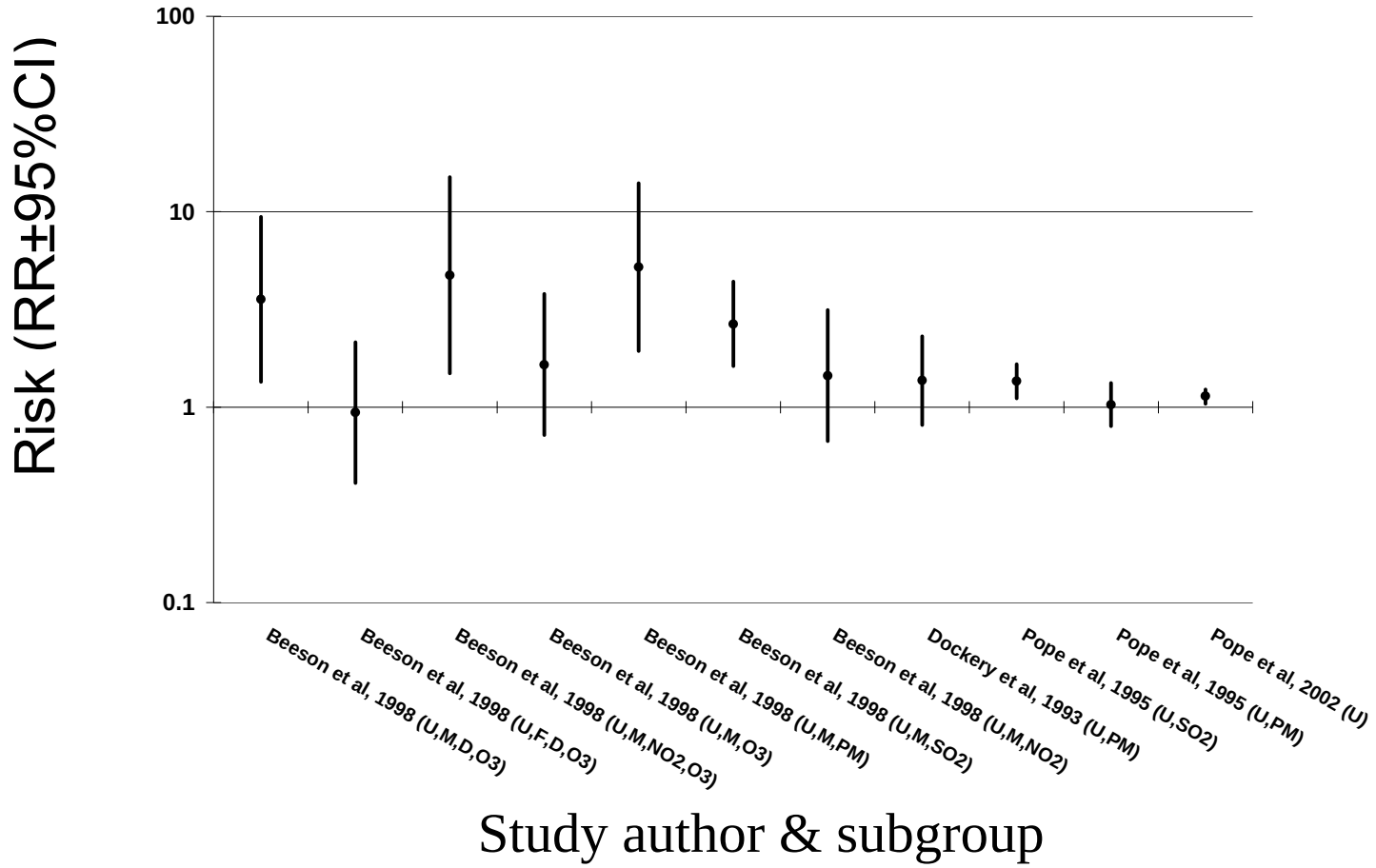


Figure 2-3: Strength of Association - Results from Cohort Studies



Legend for Figure 2-2 and Figure 2-3

Subgroups		Environmental Exposure Assessment	
U	Urban based study	Zn	Proximity to Zinc smelter
R	Rural based study	St	Proximity to Steel plant
F	Females only	Em	Emission based index
M	Males only	Pol	Pollution based index
S	Smokers only	PM	Particulate matter concentration
NS	Non smokers only	SO2	Sulphur Dioxide concentration
C	Current residence only	O3	Ozone concentration
P	Past residence (1950)	NO2	Nitrogen Dioxide concentration
NO	No occupational exposure only	D	Duration of exposure

2.4.2.3. Consistency

Are the findings similar across different studies?

Eight studies (57%) found a significant positive association between their measure of air pollution and lung cancer (Figure 2-2), including one of the three studies utilizing proximity to industry, and two of the three cohort studies. With respect to specific pollutants, effects of sulfate and particulate deposition were each specifically documented in three studies; however these factors were not individually measured and analyzed in all of the studies discussed. There appeared to be no association between sample size and magnitude or significance of results.

Of the six studies not reporting a relationship between air pollution and lung cancer: one found a protective effect explained in 'Strength of Association' and 'Specificity'[53]; one inadequately adjusted for smoking and occupation[57]; and one assigned environmental exposure broadly (by city)[45]. Hence it is possible studies finding no significant effect may have done so due to poor exposure classification of either the study factor or potential confounders.

2.4.2.4. Specificity and confounder adjustment

Does the risk factor only cause that disease?

No, air pollution is known to trigger a range of respiratory symptoms including asthma[59] and chronic obstructive airways disorder[60], so it is not specific for lung cancer.

Is the risk factor a unique cause of the disease, and how have studies dealt with potential confounders?

No, other risk factors also cause lung cancer. In this case it is vital that studies identify, measure and adjust for alternative risk factors, particularly if they are also associated with exposure to air pollution, and hence could have a confounding effect on results.

The two key identified confounders of the relationship between lung cancer and air pollution are tobacco smoke and occupational exposure. All fourteen studies investigated the effects of these factors to a varying degree as described in the following.

(i) Tobacco smoke:

Tobacco smoke exposure (directly or passively) was strongly linked to lung cancer development in 1964[10]. Since then, more detailed evidence that pack years[61] (a pack year is equivalent to smoking a pack (20) of cigarettes per day for 1 year), age commenced[62], time since ceased[11], presence of a filter[63] and tar content[64] are all contributing risk factors for lung cancer, highlighting the importance of using these factors to adjust for an effect of smoking on lung cancer development.

All of the studies collected detailed information on tobacco smoking history, but the majority neglected to adjust for this detail in their analysis. Three studies used information beyond a form of pack years or cigarettes per day or year categories to adjust for smoking in their analysis[44 49 52].

Most studies grouped cigarette consumption information into broad categories, despite evidence that a difference in cigarettes smoked per day of as little as five can significantly alter the RR for lung cancer[65]. The broadest categories were used by Vena[57], less than 40, or greater than or equal to 40 pack-years. This lack of precision in adjusting for tobacco smoke exposure is likely to result in smoking misclassification, as a subject who has smoked the equivalent of one pack year of cigarettes may be placed in the same category as a subject with 39 pack years.

A meta-analysis in 2001 investigating the relationship between lung cancer and environmental tobacco smoke (ETS) found an “abundance” of consistent evidence that non smokers exposed to ETS had an elevated risk of developing lung cancer[12].

Four of the fourteen studies evaluated in this review measured exposure to ETS in some way[43 44 46 55], and of these three included it as a variable in the analysis[43 44 46].

(ii) Occupation:

Numerous occupations have been identified as being likely to expose employees to lung carcinogens[13]. Occupational exposure was documented by job title and procedures, and/or self reported exposure to a list of known lung carcinogens

In the majority of studies measurement of occupational exposure included the collection of detailed information such as job title, place of work and in some instances workplace tasks. However all measured factors were not always used to adjust for occupation in the analysis (Table 2-4). Data used in the analysis was converted to categories, either by exposure duration or exposure likelihood. This is best exemplified by Pawlega et al[53], who classified occupational exposure by questioning exposure to a range of substances, some of which are not known lung carcinogens (CO_2, oil), and then categorized this exposure as <20 or ≥20 years duration, regardless of exposure intensity. This misclassification resulted in inadequate adjustment for occupational exposure as subjects exposed to substances not known to be carcinogenic would have been given a similar or higher exposure score to a subject exposed to known carcinogens.

The most adequate measurement and adjustment were done by Jockel et al[50] and Nyberg et al[52]. Jockel et al[50] assigned weighting to different levels of exposure that were determined by an occupational hygiene panel who had been provided with job titles and a carcinogenic substance checklist. Nyberg et al[52] collected details on

employer, workplace and tasks undertaken which were analyzed by a Job Exposure Matrix and then quantified by an occupational hygiene panel for diesel, combustion products and asbestos exposure.

A factor not considered by any of these studies was time since exposure (the latency period).

(iii) Other risk factors/confounders:

Dietary intake of beta carotene has been reviewed as a risk factor for lung cancer[66 67], with inconsistent findings between studies. Results range from a protective relationship to a causative effect in high dose. Recent biochemical studies indicate anti-carcinogenic properties of beta-carotene, but its oxidized products have the opposite effect.

A 2001 review of epidemiological studies[68] found the evidence "suggestive" of an association between lung cancer and alcohol, but unable to demonstrate a causal relationship. In-vitro, ethanol may facilitate the action of other carcinogens (i.e. from tobacco smoke) in their entry in to cells and subsequent inhibition of DNA repair and/or tumor promotion. However confounding by tobacco smoke makes the clinical significance unclear.

Six of the studies reviewed collected data on beta-carotene intake[43 44 52 53 55] and/or alcohol consumption[43 46 53]. Four studies included this information as a variable in their reported analysis[43 44 46 53].

The ability to allow for potential confounding by different risk factors has been variable across these studies. Jedrychowski et al[49], Nyberg et al[52] and Pope et al[44] were best able to adjust for cigarette smoking, whilst Barbone et al[47], Jockel et al[50] and Nyberg et al[52] most thoroughly adjusted for occupational exposure.

2.4.2.5. Temporality

Did the exposure occur prior to disease onset?

The time between exposure to lung carcinogens and lung cancer development varies for different carcinogens, is partially dependent on the concentration of exposure, and is documented to have a range of 10 to 30 years[29]. Latency is due to the time taken for accumulation of multiple mutations and lung cancer's often late diagnosis (diagnosis is rare until patient is symptomatic) hence it is unlikely that recent exposure (<10yrs) is responsible for a recently diagnosed tumor[69].

In all of the studies it was assumed exposure to air pollution occurred prior to diagnosis, but for this to hold true it would be necessary to gather evidence of historical place of residence and hence historical exposure of subjects. It is not possible to demonstrate temporality with a case control study design. The four reports of cohorts documented residence throughout their follow up period[43-46].

2.4.2.6. Dose Response

Dose the RR or OR increase with an increase in exposure to the risk factor?

Five studies reported investigating a dose response relationship between lung cancer and environmental exposure.

Both Barbone et al[47] and Jedrychowski et al[49] reported a positive relationship between lung cancer and three increasing levels of air pollution indicators (respectively, *particulate deposition* - sampled daily at 28 locations, categories of <0.175, 0.176 to 0.298, and >0.298 g/m^2/day were used in the analysis, and *SO_2* and *total suspended particulate* - sampled daily, 20 locations, eight years, categories reported as high, medium or low). Nyberg et al[52] reported there to be no significant dose response between five concentration categories of NO_2 or SO_2 and lung cancer, and Katsouyanni et al[51] found a dose response in current or former smokers only. In contrast, Pawlega et al[53] were able to demonstrate a significant negative relationship between lung cancer development and both TSP (total suspended particulate) and SO_2.

2.4.2.7. Biological Plausibility/Coherence

Does the relationship concur with current knowledge of biological mechanisms?

Table 2-3 lists substances with the potential to be airborne in suburban/industrial areas that are known or reasonably anticipated to be lung carcinogens according to the 9th Report on Carcinogens 2000 published by the United States Dept of Health and Human Services[39]. These substances can be produced during various industrial process' (Table 2-3), with potential for exposure by nearby residents. The studies in this review were not designed to provide biological evidence for a relationship between lung cancer and air pollution, and did not report any industries likely to emit lung carcinogens. Epidemiological studies investigating the relationship between air pollution and short term respiratory health effects (such as asthma) provide evidence to support the theory for a biological mechanism between air quality and the long term health effect of lung cancer.

2.4.2.8. Analogy

Is the relationship similar to others that are known to be causal?

Analogies to the relationship between lung cancer and air pollution can be drawn from the relationship between lung cancer and other risk factors. For example the previously discussed relationship between lung cancer and tobacco smoke (See section 2.4.2.4). Alternatively, analogy can be drawn from other cancer types with known environmental risk factors. For example the relationship between bladder cancer and chlorine concentration in drinking water has been well-documented[70]. None of the epidemiological studies in this review provided information on any relationships between a disease and exposure that may be analogous to that of lung cancer and air quality.

2.4.3. Discussion of the Literature Review Findings

The evidence for a causal relationship between lung cancer and air pollution is inconsistent. Twelve studies were identified in this review that had not been included in previous reviews of this nature[15 16]. Approximately half of the studies (8 of 14) demonstrated a significant positive association between their measure of environmental exposure and lung cancer, although within each of these studies significance was inconsistent between subgroups, different methods of exposure classification and sample size.

The Bradford Hill criteria for causality were first documented in the Proceedings of the Royal Society of Medicine in 1965[41]. In the decades since, the nine criteria have been widely utilized[71] and recommended for use to systematically assess causality in

cancer epidemiology[42]. Versions of the criteria have been utilised to establish a causal relationship between lung cancer and cigarette smoking[10], but to our knowledge have not specifically been applied to explore the existence of a causal relationship between lung cancer and exposure to air pollution.

This review has evaluated the positive and negative methodological traits of studies investigating the relationship between lung cancer and air pollution. Barbone et al[47], Jockel et al[50] and Nyberg et al[52] were the strongest retrospective studies, the Pope et al studies[44 46] reported the strongest prospective. Features of these stronger study designs were thorough measurement and analysis of exposure (both confounders and environmental exposure), an attempt or ability to generate a dose response relationship, and demonstration of temporality. Of these five stronger studies three reported a significant positive relationship between their measure of air pollution and lung cancer[44 46 47], Barbone et al[47] also demonstrating a strong dose response relationship. The American Cancer Society cohorts[44 46] were able to demonstrate an increasing RR associated with PM2.5 with an increasing cohort follow up period, likely to be a function of the lung cancer latency period. Negative results were not associated with studies of smaller samples; Nyberg et al[52] sample size of 1042 cases and 2364 controls.

The inconsistency among the well-designed studies may be attributed to the different methods employed to quantify environmental exposure. As yet there is no established "gold standard" for environmental exposure quantification. There has been discussion as to the validity of using air quality concentrations taken from sampling stations and applying them to all nearby areas, a method implemented by 11 of the

reviewed studies. There is little biological evidence that air quality at monitoring stations, often kilometres away from study subjects, are relevant measures of subject exposure, particularly as they fail to consider wind direction and strength[72]. In addition, grouping large residential areas into "exposed" or "not exposed" does not account for the likely variation in pollutant concentration that can occur over as little as 500 metres[72]. It is likely that this method will result in exposure misclassification, diluting the true relationship between lung cancer and air pollution.

This review may be limited by publication bias. The majority of papers reviewed presented significant tobacco smoking and occupational exposure results in addition to their air quality data. This would potentially reduce the occurrence of publication bias due to each study finding a significant relationship between at least one exposure variable (i.e. smoking, occupation) and lung cancer. Additionally, only papers reported in peer reviewed journals were reviewed, excluding government reports. A meta-analysis was not undertaken for this review due to heterogeneity of study designs, subgroups analysed and exposure assessment methodology.

This review found the evidence for causality to be modest, with intermediate consistency of findings between studies, limited number of studies reporting evidence for dose response (although these few studies presented a strong dose response over numerous categories) and only crude adjustment for important potential confounders. Studies with improved individual exposure assessment and quantification are required to clarify the small effect of air pollution given the relatively large effects of tobacco smoking and occupational carcinogen exposure.

2.5. Air Pollution and Lung Cancer in Australia

There have not been any published reports of case control or cohort studies investigating the relationship between air pollution and lung cancer development within Australia. Existing studies have had a descriptive design. A 1988 study by Freeman and Cattell[73] attempted to estimate the number of environmental exposure attributed lung cancers in Sydney per year. The study involved monitoring ambient concentrations of PAH (as an indication of combustion and a surrogate for other carcinogens) and assessing records from the NSW State Pollution Control Commission to estimate region based benzo(a)pyrene exposure concentrations. Subsequently, US EPA data on lung cancer deaths per year per ng/m^3 benzo(a)pyrene was used to conclude that air pollution in Sydney has the potential to cause an estimated 31 of the over 1000 lung cancer deaths per year[73].

Epidemiological studies have been conducted to describe asbestos related lung cancers in the area surrounding the Wittenoom crocidolite mine, Western Australia. Of 122 mesothelioma cases in Wittenoom (1979 to 1994) 34 were residents or visitors to the town who were not employed in mining, milling or mine transport positions[74], hence were unlikely to have had occupational related lung cancer. It has also been estimated that the nearby Pilbara Aboriginal region has one of the highest population based rates of mesothelioma recorded. Whilst mesothelioma in this population has not been investigated in a structured way, case studies in the area have generated the hypothesis that exposure to asbestos was due to residence both near the Wittenoom mine and near roads where trucks carry asbestos from the mine[75].

Hence, although there have been fourteen case control or cohort studies investigating the relationship between lung cancer and air pollution internationally, evidence in Australia is deficient. The two studies in Western Australia[74 75] are unable to conclusively attribute lung cancer incidence to air pollution exposure as they did not investigate the confounding nature of cigarette smoking or occupational exposure. There are no published Australian case control or cohort studies designed specifically to investigate the lung cancer and air pollution relationship.

2.6. Aims and Hypothesis

The aims, objectives and hypothesis of the present study are twofold, relating to the primary epidemiological case control study investigating incident lung cancer in the North West region, and the secondary investigation of contemporary air quality in the region as an indicator of future respiratory health risk.

Aims

1. a) To determine the geographical relationship between place of residence of lung cancer cases and controls with potential industrial related sources of lung carcinogens in the North Western suburbs of metropolitan Adelaide.

   b) To assess the relative contribution of smoking and occupational exposure, and socioeconomic status, participation in hobbies related to carcinogen exposure and family history, to lung cancer incidence in the North West of metropolitan Adelaide

2. To monitor contemporary ambient concentration of lung carcinogens at various sites in the North Western suburbs of metropolitan Adelaide, and to compare these concentrations between sites, to a control site outside of the North Western suburbs, and to national and international (where available) health exposure based guidelines.

Objectives

1. a) To systematically assess the literature for evidence of a causal relationship between ambient lung carcinogen exposure and lung cancer.

   b) To evaluate published literature to determine the most valid and reliable method of assessing and quantifying lung carcinogen exposure through residential proximity to industry, occupation, smoking and hobby participation, and to implement these methods to assess the lifetime lung carcinogen exposure of lung cancer patients and control subjects.

2. To determine the most suitable method of monitoring ambient concentrations of asbestos, crystalline silica, formaldehyde, polycyclic aromatic hydrocarbons and diesel exhaust, and to carry out this monitoring at 4 sites within the North Western suburbs and 1 control site outside of the North West.

Hypothesis

1. Incident cases of lung cancer in the North West of Adelaide are more likely to have lived in close proximity to sources of lung carcinogens than control subjects, after controlling for smoking and occupational exposure

2. Concentrations of ambient lung carcinogens will be higher at sites within the North Western suburbs than at the controls site. However, contemporary concentrations of carcinogens in the North West will not exceed national health exposure based guidelines due to the emission regulations imposed[27] and the closure of polluting industry in previous decades.

3. Chapter 3 Methodology

3.1. Study Design

A case control study design was employed to investigate the relationship between lung cancer and air pollution. This was the most suitable study design as it could investigate retrospective exposures of current lung cancer cases, and be conducted over a relatively short period of time (compared to a cohort design).

3.1.1. Cases

3.1.1.1. Sample

3.1.1.1.1. Inclusion Criteria

Cases were primary lung cancer patients who had been diagnosed during the study recruitment period (April 1999 to July 2002) and had been reported to either the South Australian Cancer Registry or The Queen Elizabeth Hospital pathology department. They were also required to be residing within the study's geographical area (defined as postcodes 5007 to 5023, inclusive) at the time of lung cancer diagnosis.

Lung cancer has a short survival rate, with prognosis often only 3 months[6]. There is also some indication that certain types of lung cancer, and hence the cancer growth rate, are related to specific exposures (for example cigarette smoking is strongly associated with the very rapid growing small cell lung cancer[6]). To reduce the possibility of selection bias being introduced (by excluding deceased cases, a group with a high rate of small cell cancer), if a potential case had passed away between diagnosis and recruitment or was too unwell to take

part, the Next of Kin (NOK) of the patient (aged over 18 years, as listed in their medical records) was recruited to take part in the study on their behalf. The process of recruitment and participation was identical for cases and NOK.

3.1.1.1.2. Exclusion Criteria

Cases were excluded if their lung cancer was secondary to another site. Cases were unable to take part if a suitable (known to the patient) and willing doctor was not available to recruit them, or, in the situation of a deceased case, if a suitable (over 18 years of age and of sound mind) NOK was unavailable or uncontactable.

3.1.1.2. Sampling Frame

Potential cases were identified via two sources:

1. The South Australian Cancer Registry. The registry provided the names of primary lung cancer patients to the hospitals from which they were diagnosed, which were in turn passed onto the diagnosing doctor or the researchers involved with the study (variation due to different ethics requirements at each hospital). Approval to gain access to the Cancer Registry was given by Prof David Roder and Dr Colin Luke, State Cancer Registry, Department of Human Services, South Australia. Due to compulsory reporting by pathology laboratories, medical records departments of hospitals, radiotherapy departments, oncologists and Births, Deaths and Marriages[76], use of the Cancer Registry data ensured the sample was complete. In addition, the lag time between diagnosis and registration was approximately 3 months (among the most

efficient in Australia)[76], reducing the likelihood of patients passing away before recruitment.

2. Department of Pathology, The Queen Elizabeth Hospital. The names and details of lung cancer patients diagnosed though Pathology at The Queen Elizabeth Hospital were obtained on a regular basis. The Queen Elizabeth Hospital was the only public hospital within the study area. This source provided an opportunity to recruit recently diagnosed patients.

3.1.2. Controls

3.1.2.1. Sample

3.1.2.1.1. Inclusion Criteria

Controls were residents of the study's geographical area (postcodes 5007 to 5023), listed on the South Australian State Electoral Roll (SASER).

3.1.2.1.2. Exclusion Criteria

Controls were excluded if they had been diagnosed with primary lung cancer prior to April 1999, if they were deceased (due to unavailability of NOK contact data on the electoral roll, see Section 3.1.3 for further discussion on use of deceased controls) or if they had moved out of the study area more than 12 months ago.

3.1.2.2. Sampling Frame

Population based controls were used. Potential controls were identified though SASER. SASER provided an electronic copy of people listed on the Electoral Roll who resided in postcodes 5007 to 5023 (inclusive) at the time of obtaining the list (January 2000). The electoral roll estimated that 90% of the eligible residential population were enrolled to vote (personal communication, Jane Peace, Research Officer, State Electoral Office). The eligible residential population consists of those aged over 18 years who had lived in the same place for over 1 month, were of sound mind, and were Australian citizens (or were British citizens enrolled to vote prior to January 1984). Permission to access the electoral roll was granted by Mr Laurie Waters, Director, State Electoral Commission. The use of population-based controls from the most thorough population based database available ensured our sample was representative of the population in the study geographical area.

3.1.2.2.1. Selection

Random numbers were generated with the current date as the seed using the STATA statistical program[77]. Figure 3-1 is the programming used. If a control declined to participate or was unable to be contacted a replacement control (with same age group and gender) was randomly selected using the same STATA program. This process of reselection continued until three matched controls had agreed to participate per case. Available data (age, gender, address) on non-participating controls was recorded.

Figure 3-1: Stata Do File used for Generation of Random Numbers

```
Use "c\electoral1.dta" *

Local x=date("$S_DATE","dmy")

Set seed 'x'

For num 1/99: gen ranomX=round(N*uniform()+1,1)

Save "random'x'.dta"

List
```

**File named "electoral1.dta" contains the number of people in each age/gender electoral roll data set.*

3.1.3. Matching

Controls were matched to subjects for age and sex. These were both known and clearly demonstrated risk factors for lung cancer[29] and were available to us on the electoral roll prior to attempted recruitment of each subject.

Deceased controls were not matched to deceased cases due to evidence in the literature for moderate to good agreement between subjects and their NOK[78]. The literature indicates that whilst agreement varied with the level of detail requested[79], Kappa values for smoking and occupation details range from 0.55 to 0.93[78]. Published research reporting the ability of a proxy respondent to recall lifetime residences (as required for this study) was not found. Hence, particularly due to the lack of research on NOK recollection of residence, a substudy was undertaken to investigate the extent of any differential responses of NOK of living controls and controls themselves (See Section 3.8 for more information about the substudy).

3.1.4. Subject Recruitment

The method of subject recruitment is described in Figure 3-2 to Figure 3-4. As of mid 2001 the 'part a' step of Figure 3-4 was omitted (to be explained in Section 3.3.4). Copies of all case and control information letters are provided in Appendix 1 to Appendix 6.

Attempts were made to recruit all cases as soon as possible after diagnosis to reduce recall bias (differential recall of exposure related life events between cases and controls).

Non-English speaking subjects were able to participate in the study with the assistance of an interpreter or relative (acting as an interpreter) to avoid response bias towards English speaking members of the community.

Efforts made to enhance subject participation included:

- Increasing doctor awareness of the study through regular presentations of recruitment rates, articles published in "The Pulse" (internal North West Adelaide Health Service newsletter) and when recruitment was close to completion, flyers providing the number of patients left to recruit and an encouraging message (Appendix 8).
- Increasing general public awareness of the study through the print, radio and television media (see example in Appendix 9).

Figure 3-2: Flow Chart of Lung Cancer Patient Recruitment Protocol

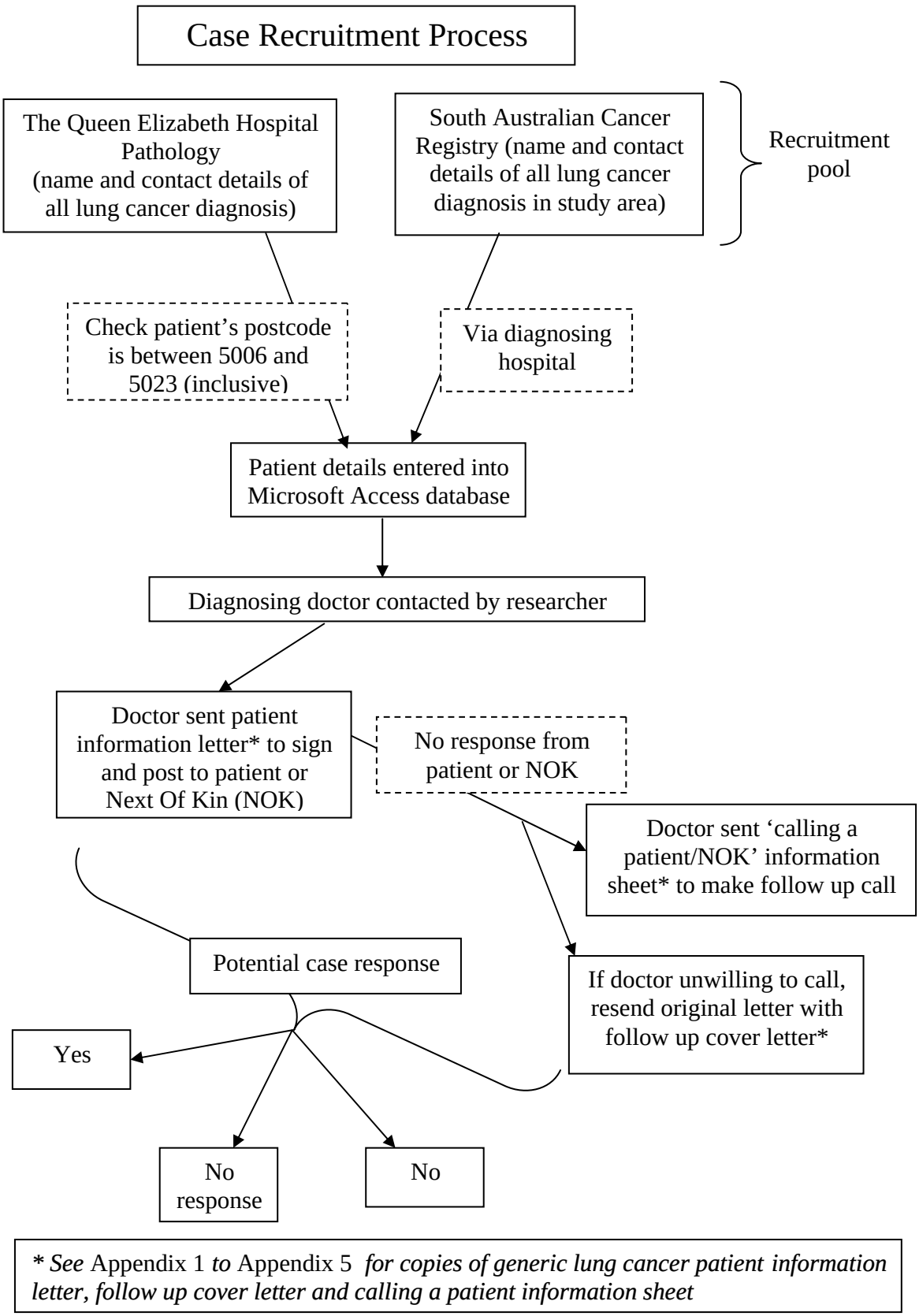
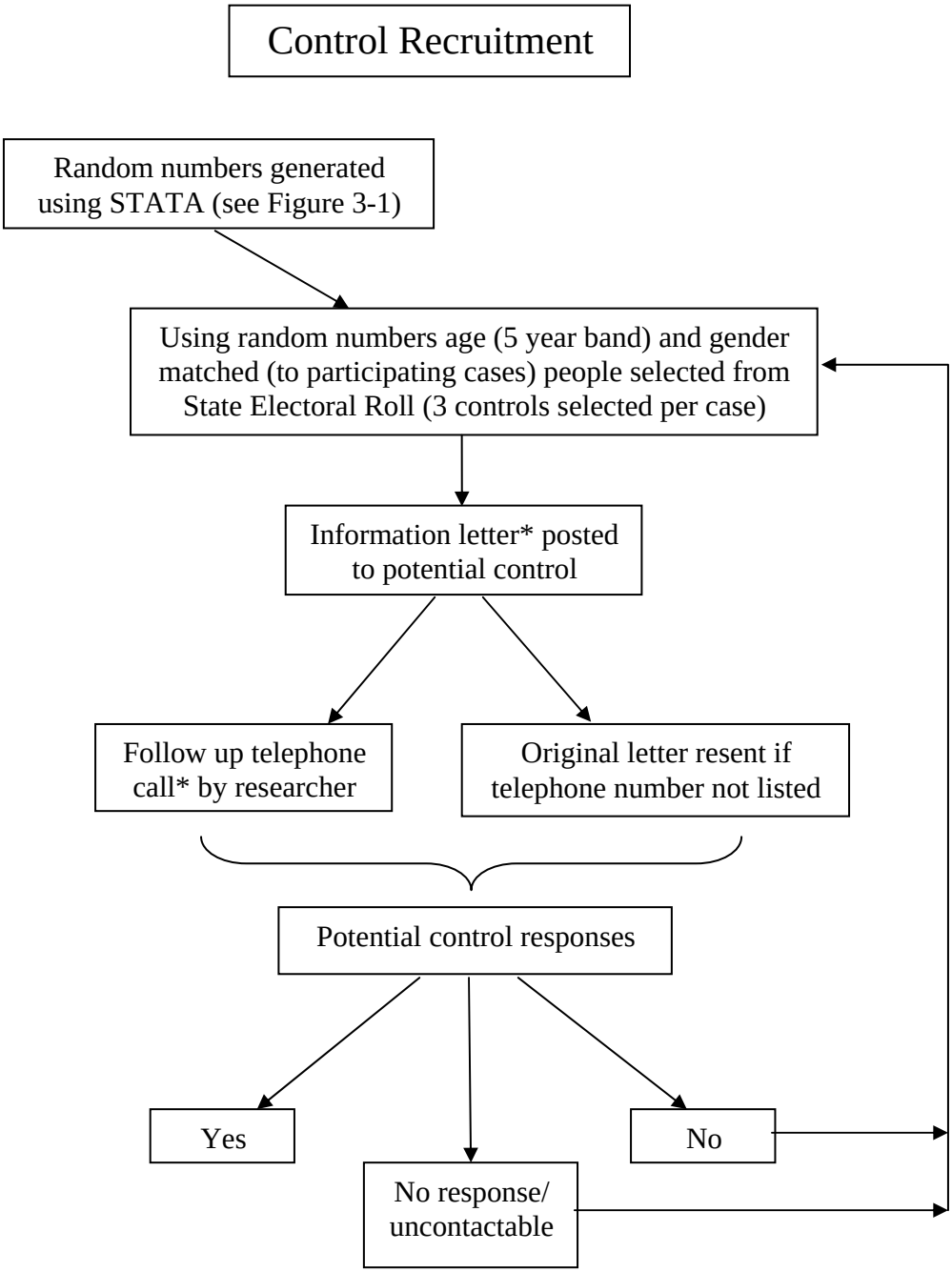
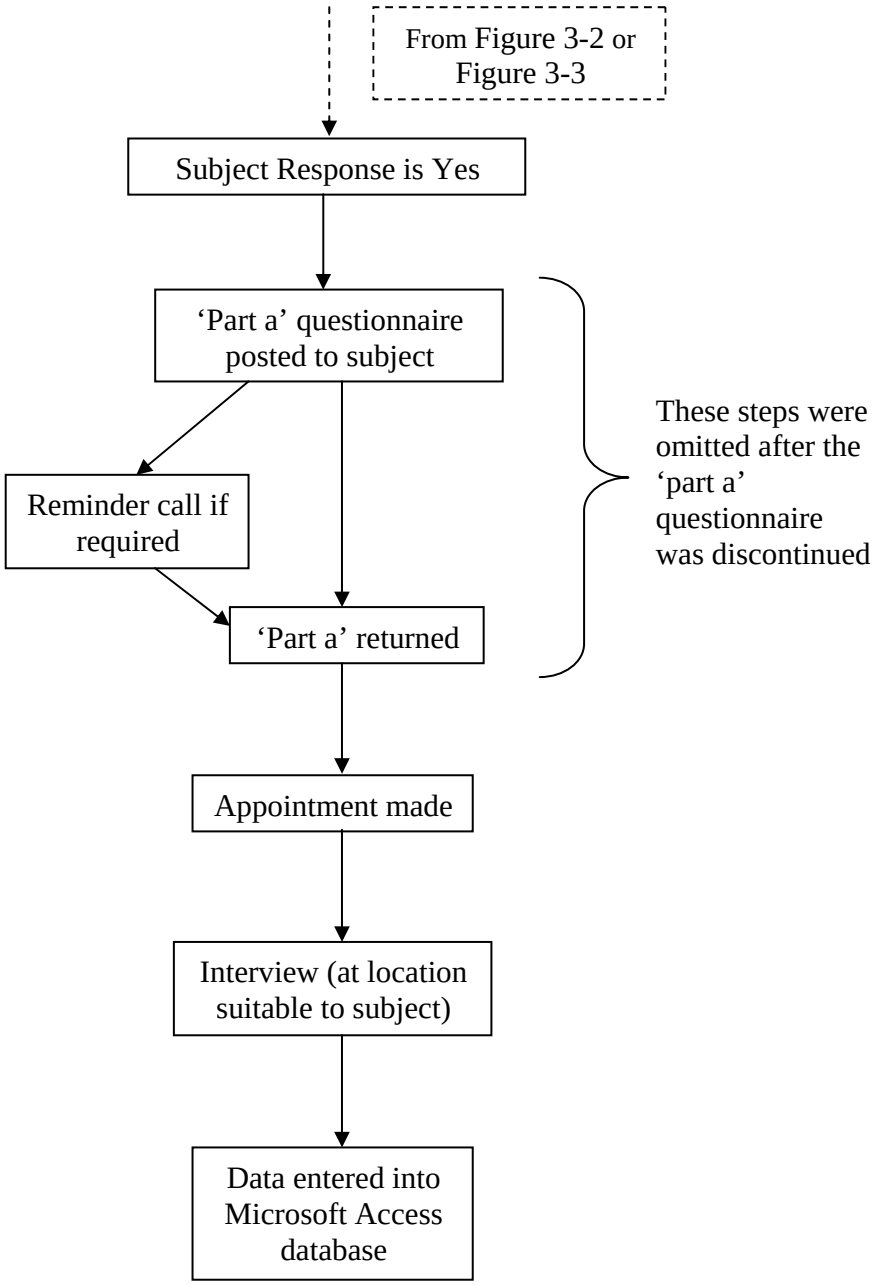


Figure 3-3: Flow Chart of Control Recruitment Protocol



** See* Appendix 6 *and* Appendix 7 *for copies of control information letter and script for control follow up phone calls*

Figure 3-4: Flowchart of Subject Participation Protocol



3.2. Ethics Approval

Ethics approval was obtained from the Research and Ethics Committees of the following metropolitan public and private hospitals (Appendix 10 contains letters of ethics approval). Annual reviews were submitted to the committees for re-approval where required.

- North West Adelaide Health Service (The Queen Elizabeth Hospital and Lyell McEwin Health Service)
- Royal Adelaide Hospital
- Adelaide Community Healthcare Alliance (Ashford Community Hospital, Western Community Hospital, The Memorial Hospital, Flinders Private Hospital)
- The Repatriation General Hospital
- Flinders Medical Centre
- Modbury Public Hospital

Approval was also gained from Calvary Hospital, Burnside War Memorial Hospital and Wakefield Hospital; however no subjects were recruited from them.

3.2.1. Informed Consent

Information regarding the study was supplied to subjects in the form of an information letter (Appendix 1 to Appendix 5). Informed consent was gained at the interview or, in the case of telephone interview, by post, using a standard consent form developed by the Research and Ethics Committee of The Queen Elizabeth Hospital (Appendix 11).

3.3. The Design and Development of a Questionnaire to Investigate Lung Carcinogen Exposure in a Case Control Study

3.3.1. Identification of Potential Confounders

Adjustment in the analysis for potential confounders was an important component of this case control study, and hence exposures to potential confounders, and the risk factor in question, were assessed retrospectively by a structured questionnaire.

Table 3-1 lists potential risk factors for lung cancer development, the evidence for their association with lung cancer, their potential for confounding and their inclusion or exclusion status for this study.

Table 3-1: Lung Cancer Risk Factors

Risk Factor	Association with lung cancer	Confounder?*	Included in this study?
Occupational exposure	A minimum of 10 substances found in the workplace are known to be lung carcinogens[38]	Y	Y
Tobacco Smoking	Evidence for this association has existed since 1985[10]. Recent studies indicate significant OR's of 23.9 (males) and 8.7 (females), with elevated OR's for both dose and duration[80]	Y	Y
Environmental tobacco smoke (ETS)	2001 meta-analysis of 43 studies found significant RR of 1.29 in non smoking wives of smokers[12]	Y	Y

Risk Factor	Association with lung cancer	Confounder?*	Included in this study?
Hobbies	No specific studies have been conducted to assess the relationship between exposure to carcinogens through hobby participation and lung cancer. However, a number of hobbies exist that are closely related to occupations known to involve exposure to lung carcinogens (for example car mechanical work and home renovations). Many older people in the North West of Adelaide built their own homes whilst asbestos was still widely used.	Inconclusive	Y
Family history	Genetic susceptibility may act as an independent or effect modifying risk factor for lung cancer[81]	Y	Y
Socioeconomic status	Review concludes excess risk of lung cancer in men in low socioeconomic groups[82]	Y	Y
Diet	Inconsistent findings indicate β-carotene to be protective in low dose, but causative when taken in high dose by cigarette smokers[66 67]	N	N

Risk Factor	Association with lung cancer	Confounder?*	Included in this study?
Alcohol consumption	Review of studies "suggestive" of relationship with lung cancer, but inconclusive, partly due to strong confounding by cigarette smoking[68]	Inconclusive	N

** To be classified as a confounder the risk factor must be associated with both lung cancer and residing in close proximity to industry in areas of low air quality. Residential areas in close proximity to industry are usually also low socioeconomic areas and this is true of the North Western suburbs of Adelaide[1]. People living in low socioeconomic areas are more likely to have a high prevalence of cigarette smoking[1], and occupation is considered one of the components of socioeconomic status[83], hence both are associated with residing near industry.*

3.3.2. Format of Questionnaire

The purpose of the questionnaire was to collect valid and reliable retrospective data from subjects on their lifetime exposure to ambient pollution from industrial sources and the confounders identified in Table 3-1.

Subjects' lifetime event histories were collected using an event history calendar. This method has been used previously to enhance recall of events related to a variety of exposures[84-87]. Its reliability has been shown to be good for long term events[88].

To develop the question format, previous questionnaires administered to assess exposure in other cancer studies were obtained from within Australia and internationally, and reviewed for validity and reliability (see Table 3-2). The most comprehensive questionnaire was of German origin developed by Ahrens and Merletti[13]. This questionnaire has been used in Germany to investigate associations between lung cancer and occupations[89] (particularly welding)[90], family history of lung cancer[81], tobacco smoking[80 91] and ETS exposure[92 93].

Table 3-2: Assessment of Questionnaires

Questionnaire	Origin	Validity	Reliability	Level of completeness*	Notes
Ahrens et al[13]	Germany	Yes	Yes	High	High level of detail, very thorough
Gun et al[94]	University of Adelaide	No	No	Medium to High	Used specifically in South Australia, therefore designed for similar study population to this study
Armstrong et al[95]	Australian National University	No	No	Medium	Use of an event history calendar

** Level of completeness refers to the studies ability to gather detailed information on each relevant lung cancer risk factor*

Due to the complete nature of the Ahrens et al[13] questionnaire and its demonstrated reliability, and the structural organisation of Armstrong et al[95] in relation to the event history calendar, a combination of the two was utilised; the format and question wording of Armstrong et al[95], with additional questions (reworded to be in a similar format) as used by Ahrens et al[13]. Subjects were only required to recall the occupation, smoking status or residence undergone for the majority (greater than 6 months) of each year as per Ahrens et al[13] and Armstrong et al[95]. The questionnaire was highly structured to minimise interviewer bias. The final version of the questionnaire used and the data collection booklet can be found in Appendix 13 and Appendix 14.

3.3.3. Pilot of Questionnaire

The original questionnaire was piloted on five subjects (3 cases and 2 controls). At the completion of pilot interviews, subjects were asked if there were any questions they had difficulty understanding or answering. Subject internal consistency was checked at face value, for instance, did the residential address agree with the workplace (was it in the same city?), and was found to be accurate. The interviewer also evaluated subject response time and subjects' ability to answer each question; finding that they had little difficulty.

A member of the occupational hygiene panel also reviewed occupational data collected during the pilot study. The composition and purpose of the occupational hygiene panel will be discussed in detail in Section 3.6. Briefly, the panel comprised 3 occupational hygienists with over 60 years cumulative experience assessing and measuring workplace exposure, with particular experience in the North West suburbs of Adelaide.

3.3.4. Method of Data Collection

Data was collected using a two step process. Step 1 involved subjects filling out a lifetime questionnaire (Part a) of basic data (job title, and residential address per year) in their own time (see Appendix 12). The purpose of this step was to reduce the time taken for the in person interview to be carried out. It also provided subjects with the opportunity to discuss their history with family members, or to look up personal records. This step was removed approximately one third through the recruitment process due to subjects having difficulty filling in the form without being stepped through it by an interviewer and hence attempting to withdraw from the study. For the remaining two thirds of the study 'part a' was replaced by a verbal request at the time the interview appointment was scheduled to "before the interview it would help if you tried to think about the places you have lived and the jobs that you have had over your lifetime, and the years you did these, maybe even writing down some notes".

Step 2 of data collection was an in-person interview conducted at a time and location (ie home, work, café, hospital office) convenient to the subject. Data collection involved a detailed lifetime calendar history of occupation, tobacco smoking and residence in calendar format, with additional questions on hobbies, family history and socioeconomic status (not calendar format) – see Appendix 14. The calendar format allowed for cross-reference of lifetime events when subjects were having difficulty recalling dates (For example in 1975 you were living at 10 Smith St, where did you work at that time?), as per Belli et al[96].

3.3.5. Interviewer Training

A pool of four interview staff interviewed all of the participating subjects. It was not practically feasible for interviewers to be blinded to the case or control status of each subject, due to the obvious ill health of the cases and the use of case NOK. Thus, it was important that each interview was conducted to the same standard to reduce interviewer bias (potential for differential probing of cases and controls). Prior to their first independent interview all interviewers undertook training involving watching other interviews take place, interview role-playing and gradually taking on sections of the interview under the supervision of an already trained interviewer. Following this, regular formal and informal meetings were held to discuss interviewing methods and any difficulties with interviews, and joint interviews were held to ensure interviews were carried out to a similar standard. Efforts were also made to ensure each interviewer interviewed a range of both cases and controls.

3.4. Environmental Exposure Assessment and Quantification

An indirect method of assessing residential exposure was used as suitable air quality monitoring data (historical monitoring of lung carcinogens throughout the study area) was unavailable for the direct method. The literature indicates that in the absence of suitable air quality data, a modelling equation representing the relationship between pollution levels and distance from industry is an acceptable surrogate[72 97 98] (Table 3-3). A modified version of the Gaussian model was used for this equation as it is considered the most representative[99]. The Gaussian model also provides the greatest variation in exposure scores of those reviewed (see Figure 3-5). Detailed historical industry information required for extensive Gaussian modelling (ie historical emission data) was unavailable, hence a segment of the Gaussian

model that represents the relationship between distance and exposure was extracted, and the relationship of exposure with duration of residence and downwind frequency incorporated[72] to arrive at the equation for residential exposure that was calculated per exposure source (Figure 3-6).

Table 3-3: Studies using dispersion modelling to determine the relationship between proximity to industry and adverse health effects

Study	Validated against ambient monitoring of:	Use of Distance in Model	Additional Factors	Study's Assessment of Model Used
Williams and Ogsten, 2002 [72]	Copper, Arsenic	Exposure inversely proportional to distance (exposure = 1/distance)	Downwind frequency	Distance negatively correlated with ambient copper concentration ($p \leq 0.05$). Concentric circles around a source an inadequate method. Wind speed not significant when included in model.

Study	Validated against ambient monitoring of:	Use of Distance in Model	Additional Factors	Study's Assessment of Model Used
Pless- Mulloli et al, 2000 [97]	Nitrogen dioxide, benzene	Three geographical exposure zones assigned based on exposure being inversely proportional to distance (exposure = 1/distance) Gaussian model (equation not reported)	Wind speed In Gaussian model (used for validation) – downwind frequency, stack height & diameter, wind speed, emission release rate, gas exit temperature & velocity	Proximity to industry (3 zones) is a defensible surrogate for community exposure when validated against a Gaussian model and contemporary ambient monitoring.

Study	Validated against ambient monitoring of:	Use of Distance in Model	Additional Factors	Study's Assessment of Model Used
Rogers et al, 1999[98]	Sulphur dioxide	Exposure inversely proportional to distance multiplied by 2pi divided by 16 (1/[distance*(2π/16)]) (derived from Gaussian model)	Downwind frequency, stack height, wind speed, emission release rate	The model is a good predictor of SO_2 concentration. 2π/16 is used as is the angular width of a standard wind rose sector of 22.5° (22.5° = 2π/16 radians)

Figure 3-5: Graphical Representation of the Relationship between Environmental Exposure and Proximity to Industry from the Literature

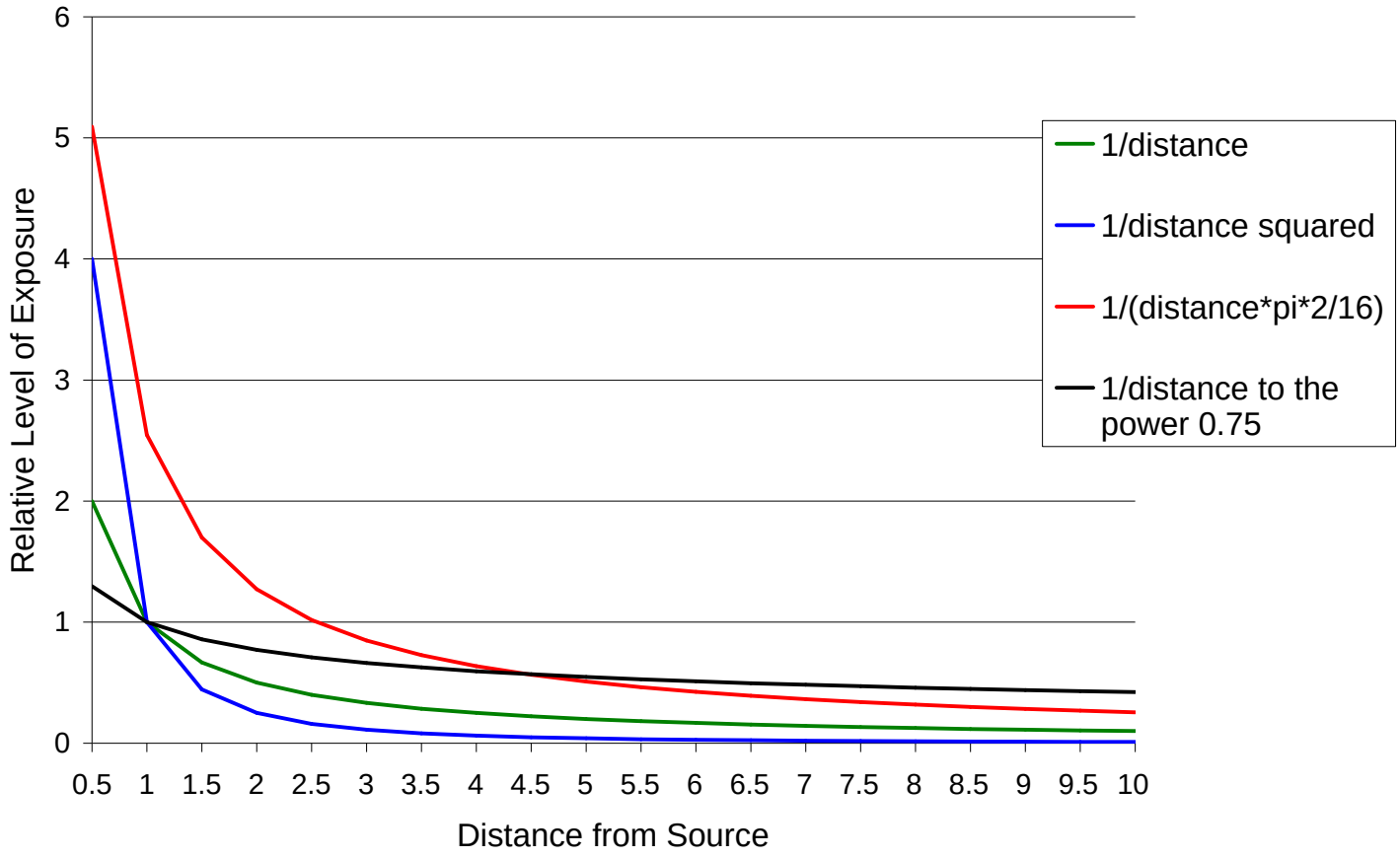


Figure 3-6: Equation utilised to represent residential exposure to a point source

$$\text{Exposure}_{(\text{source})} = \frac{\text{Duration (yrs)} * \text{Downwind frequency}}{\text{Distance}_{(\text{from source})} * (2\pi/16)}$$

As per Brown et al[48], exposure to multiple sources of industry and exposure over multiple episodes of time were considered additive, allowing the calculation of an overall score.

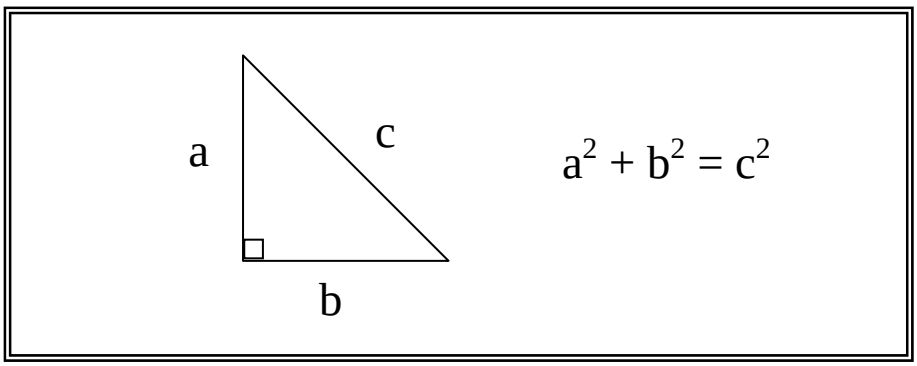
3.4.1.1. Calculation of Distance from Industry within the Study Geographical Area

All reported subject addresses within the study area (North Western suburbs of Adelaide) were assigned easting (x) and northing (y) coordinates using a Geographical Information System (GIS supplied by the Port Adelaide Enfield City Council and the Charles Sturt City Council) to provide a comparable numerical classification of their geographic position. Where subjects only reported a fragment of their address (ie street name and suburb, or suburb alone) the average x and y co-ordinate of the respective street or suburb was assigned to them. Similarly, the 6 selected industries in the region (as discussed in Chapter 1) were also assigned the x and y coordinates of the centre of their operations (See Table 3-4). The distance of each residence from each factory was then calculated using Pythagoras theorem of right angle triangles, that is, the sum of the squares of the length of the two shortest sides of the triangle is equal to the square of the longest side (Figure 3-7).

Table 3-4: X and Y Coordinates for the 6 Key Industries in the North West

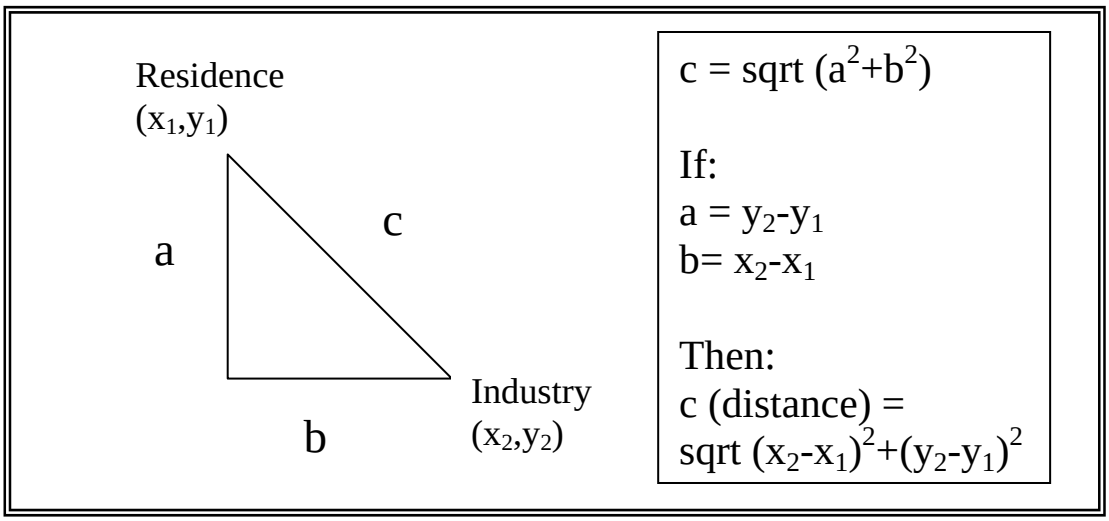
Industry Name	X coordinate	y coordinate
Adelaide Brighton Cement	271 666	6 142 473
Penrice Soda Products	271 979	6 146 273
CSR	270 949	6 141 432
Torrens Island Power Station	273 323	6 145 412
James Hardies Asbestos Cement	271 393	6 143 507
Finsbury Industrial Suburb	276 418	6 138 397

Figure 3-7: Pythagorus Theorem of a Right Angle Triangle



Thus, the distance of a given residence with coordinates (x_1, y_1) from industry (x_2, y_2) was the square root of $(x_2-x_1)^2+(y_2-y_1)^2$ (Figure 3-8). Due to the use of easting and northing for the x and y coordinates, the units of this distance was kilometres.

Figure 3-8: Application of Pythagoras Theory



sqrt = Square Root

3.4.1.2. Calculation of Angle of each Residence from each Industry

The angle of each residence (θ) from each industry was calculated for use in subsequent steps to assess the frequency of wind directed across the industry toward the residence. The methodology for this calculation was determined with assistance from Dr David Simon, Manager, Port Pirie Lead Investigation Group, Environmental Health Branch, Department of Human Services, South Australia.

Steps in angle calculation:

1. Assume residence coordinates (x_1, y_1) and industry coordinates (x_2, y_2)

2. Zero the industry:

   New coordinates - Industry (0,0)

   Residence (X, Y) where X= x_2-x_1 and Y= y_2-y_1 AND Y=sin(α), X=cos(α)

3. Calculate the angle in radians:

   Arctan (X/Y) = γ radians (ie Arctan ($\cos(\alpha)/\sin(\alpha)$))

4. Convert to a mapping plane:

   As the angle is based on a Cartesian plane (units are radians) not a mapping plane (units are degrees), to know which of the four quadrants the vector is in, the sign of X and Y were used:

   If both X and Y positive, do nothing

   If X is negative, add π

   If X is positive AND Y is negative, add 2π

   (where, π=3.14159265)

5. Convert radians to degrees:

   Degrees = γ *($180/\pi$)

6. Rotate 180 degrees to determine the direction (θ) the wind must be from to blow over both the industry and the residence

3.4.1.3. Calculation of Exposure Based on Wind Direction

The Bureau of Meteorology (BOM) supplied wind directional data. Three BOM monitoring sites within metropolitan Adelaide were available for data collection; Adelaide Airport, Parafield Airport, and the RAAF base (Salisbury). The Adelaide Airport site was selected as it has a similar location relative to the ocean as the North Western suburbs and is only just

outside the Southern boundary of the study area, hence would best reflect North West Adelaide weather patterns.

Two alternative sets of data for Adelaide Airport were provided for our use; (a) 8 recordings (3 hourly) per day from 1955 to 2002, directional data in 16 categories (ie 22, 45, 68 degrees from North) and (b) 48 recordings (half hourly) per day from 1992 to 2002, directional data to the nearest 10 degrees (ie 10, 20, 30 degrees from North).

The half-hourly data (b) was used due to the increase in precision for angle and time it provided (due to variable wind patterns over the day). With this improved precision came a loss of monitoring duration (37 years), but upon consultation with BOM 10 years of data was determined to be a good representative sample, incorporating a full range of weather patterns.

The percentage of time the wind blew over an industry and residence was calculated from the data using the following steps:

1. Removal of data relating to "calm" weather conditions where there is no wind (0^o wind direction and 0 knots) and removal of incorrect data (non multiples of 10 equating to <0.05% of the data set at various times during the 10 years of monitoring)

2. Frequency counts for each of the 10^o wind direction categories were calculated using a Microsoft Access database (See Table 3-5). Total counts equals 154 864

3. Sum the number of times the wind blows between +/- 11.25º for each multiple of 10º. (+/- 11.25º was chosen to align with the final exposure equation with wind-rose sector of 22.5º, see Section 3.4). ie Sum for 50º equals sum of the frequency counts for 40º, 50º and 60º (due to rounding this gives us the number of times the wind blows from ≥ 35º to <65º, ie +/-15º; it was not possible to calculate precisely 11.25º due to the 10º increments of the data).

4. Calculate the percentage of time the wind blows in each +/- 15º segment by dividing each sum in (3) by the total (154 864) and multiplying by 100% (See Table 3-5)

5. Round residential angle data, as calculated in 3.4.1.2 to nearest 10º (using same method BOM uses for wind direction data rounding, ≥5 rounds up, <5 rounds down)

6. Assign the percentage score for each wind direction angle to the matching residential addresses angle in Microsoft Access database.

3.4.1.4. Calculation of a Final Exposure Score

The final exposure equation was derived from Gaussian plumage modelling as described in Section 3.4. Data calculated by the methodology in Sections 3.4.1.1 to 3.4.1.3 were used in the equation.

Table 3-5: Calculation of the Percentage of Time the Wind Blows ± 15˚ around each Angle from North in 10˚ Increments

Wind direction (degrees from North)	Count of times wind blows at this angle	Count of times the wind blows ±15% around the angle	Percent of time wind blows ±15% around the angle
10	4992	14634	9.00
20	5690	17130	10.53
30	6448	19498	11.99
40	7360	20233	12.44
50	6425	16813	10.33
60	3028	11801	7.25
70	2348	7546	4.64
80	2170	6568	4.04
90	2050	6446	3.96
100	2226	7253	4.46
110	2977	9017	5.54
120	3814	11312	6.95
130	4521	12486	7.68
140	4151	13691	8.42
150	5019	14987	9.21
160	5817	16249	9.99
170	5413	15877	9.76

Wind direction (degrees from North)	Count of times wind blows at this angle	Count of times the wind blows ±15% around the angle	Percent of time wind blows ±15% around the angle
180	4647	13794	8.48
190	3734	12483	7.67
200	4102	14322	8.80
210	6486	19142	11.77
220	8554	24222	14.89
230	9182	24638	15.14
240	6902	21080	12.96
250	4996	15940	9.80
260	4042	12791	7.86
270	3753	10706	6.58
280	2911	9348	5.75
290	2684	7894	4.85
300	2299	7358	4.52
310	2375	6899	4.24
320	2225	6957	4.28
330	2357	6945	4.27
340	2363	7571	4.65
350	2851	9166	5.63
360	3952	11795	7.25

3.4.1.5. Validity

The validity of using proximity to industry as a measure of exposure was introduced in Section 3.4. Whilst the use of actual air monitoring data is a more valid method of exposure assessment[100], in its absence a dispersion model for the relationship between distance from industry and exposure is a defensible surrogate[97 100].

3.4.1.6. Reliability

This method of quantification of residential exposure within the North Western suburbs was reliable as was based purely on mathematical calculations.

3.4.2. Exposure Assessment Outside of the Study Area

3.4.2.1. Definition of Exposed

Residential exposure outside of the North Western suburbs of Adelaide was also assessed using proximity to industry. This could not be measured as precisely as residence within the North West due to the unavailability of Graphical Information System (GIS) data and comprehensive historical industrial records. Initially subjects were asked to recall the name, type and location of industry near their home. An early validation check of a sample for the industries recalled indicated very low and inconsistent recall accuracy. Hence, records of current licensed industry (industry type and location) were obtained from the Environmental Protection Authority (or its equivalent) in each state. The occupational hygiene panel (to be described in 3.6.1, briefly, a group of occupational hygienists with knowledge and experience of occupational exposures in Australia) identified industry types likely to emit lung

carcinogens (See Table 3-6). Subjects were then considered exposed if they resided in the same suburb as a lung carcinogen emitting industry. Years of exposure and number of factories/industry exposed to were used to quantify exposure (Exposure is equal to duration multiplied by number of industry).

Residential exposure scores for residences outside of Australia were not calculated due to resource limitations (inaccessibility of industrial information for other countries and the potential for bias due to differences in industry licensing policy and pollutant monitoring).

Table 3-6: List of Industry Types Identified by the Occupational Hygiene Panel as Likely to Emit Lung Carcinogens

Industry Type
Brukunga Mine Site
Bulk Shipping Facility
Cement Works
Ceramic Works
Chemical Works
Coal Processing
Crushing
Extractive Industries
Fibreboard/Chipboard
Ferrous and Non-ferrous Metal Melting

Industry Type
Fuel Burning exceeding 500 kilowatts : to bake or dry any substance that on heating releases dust or air impurities
Fuel Burning exceeding 500 kilowatts : to stove enamel
Fuel Burning: rate of heat release exceeding 5 megawatts
Glass Manufacturing
Hot Mix Asphalt Preparation
Maritime Construction
Metal Coating
Metallurgical Works
Mineral Wool/Ceramic Fibre
Oil Refinery
Petroleum Production/Works
Power Station
Primary Metallurgical
Scrap Metal Recovery
Surface Coating - Powder Coating
Surface Coating: hot dip galvanising
Surface Coating: metal finishing
Surface Coating: spray painting
Wood Preservation Works

3.4.2.2. Validity

The validity of the residential exposure score for residences outside of the study area (but within Australia) was compromised by the use of contemporary rather than historical local industry. This was unavoidable as thorough historical records of licensed industry were not available or obtainable. This reduced validity was likely to mean an underestimation of residential exposure for previous residence outside of the NW suburbs due to reductions in industry numbers and emissions over previous decades.

3.4.2.3. Reliability

This method of quantification of residential exposure within the North Western suburbs was reliable as was based on mathematical calculations, hence could be easily repeated.

3.4.2.4. Inclusion in Analysis

Residential exposure outside of the study area was quantified as duration of time residing in the same suburb as an EPA licensed and potentially lung carcinogen emitting industry. Exposure to multiple industries over multiple periods of time was considered additive[101].

3.5. Tobacco Exposure Quantification

3.5.1. Direct Smoking

Smoking dose and duration are the two important determinants of lung cancer risk[11 102 103]. Hence it was decided ab initio that pack years of cigarette smoking (a combined measure of dose and duration) would be used as a combined measure of dose and duration of smoking. Table 3-7 indicates the tobacco smoking data collected in this study and the justification of its inclusion in the analysis.

Table 3-7: Tobacco Smoking - Data collected and its Inclusion in the Analysis

Collected Data	Included in Analysis?	Justification of Inclusion/Exclusion
Pack years	Yes	Pack years is a commonly used combined measure of cigarettes per day and smoking duration. It has been used in the majority of studies investigating the relationship between lung cancer and air pollution to adjust for the confounding effects of smoking[36].
Cigarettes per day	Yes (in contributing the to the calculation of pack years)	Overwhelming dose response evidence for number of cigarettes smoked per day to increase RR for lung cancer [11 102]
Duration	Yes (in contributing the to the calculation of pack years)	Strong dose response relationship evident, likely to be greater than that of cigarettes per day. Original estimates in 1978 were for a quadratic relationship (ie incidence is related to duration to the power 4[40]
Year commenced	N	Significant increase in RR for lung cancer when start smoking at a young age[11], however it is unlikely the study will have enough power to investigate its relationship with lung cancer.

Year ceased	N	Dose response effect, as time since ceased increases, RR of lung cancer decreases (but not to non smoker level)[11], however it is unlikely the study will have enough power to investigate its relationship with lung cancer.
Number of smoking periods	N	This information is gained automatically when other smoking data is collected; there is no evidence that the number of smoking periods significantly effects lung cancer risk.
Tar level	N	Excluded due to missing data, particularly from Next of Kin.
Inhalation level	N	Closely associated with Tar Level (proposed compensatory effect, decrease tar level, increase inhalation[104]), therefore can not be used alone
Butt length	N	Missing data

3.5.1.1. Cigars and Tobacco Pipes

Due to the low number of subjects (n=20) reporting use of cigars or a tobacco pipe for 6 months or longer, dose information was converted to number of cigarettes and combined with cigarette data in the analysis as per Table 3-7, using a previously reported method[105]. Of the 13 studies in the systematic literature review (see Chapter 2)[36], two reported including pipe or cigarette smoking as a yes/no variable in their analysis[46 55] and one study[50] converted cigars and tobacco into cigarettes but did not describe their method of conversion.

3.5.2. Environmental Tobacco Smoking

Exposure to environmental tobacco smoke (ETS) was reported separately for "at work" and "at home". Based on a meta-analysis by Taylor et al[12] ETS exposure variables for duration and dose were assessed pre-hoc to be relevant to the study analysis (see Table 3-8). However, in this study duration (years of regular – most days – exposure to cigarette smokers, separate work and home variable) was used alone due to the perceived unreliability of dose recall (hours and number of smokers exposed to per day), and missing data relating to dose recall.

Table 3-8: Environmental Tobacco Smoke - Data Collected and its Inclusion in the Analysis

Location	Data Collected	Format of data for analysis		Stepwise analysis (for at work and at home separately)
		Binomial	Continuous	
At Home	Year exposure began Year exposure ceased Number of people exposed to Hours exposed per week	Exposed at all, Y/N	Number of years exposed	Continuous – number of people exposed to multiplied by number of years
At Work	Year exposure began Year exposure ceased Number of people exposed to Hours exposed per day	Exposed at all, Y/N	Number of years exposed	

3.5.3. Reliability

Scores were easily repeated, as were mathematical functions.

3.5.4. Validity

All scores were justified by evidence from the literature (see justification of inclusion/exclusion and of categories).

3.6. Occupational Exposure Assessment and Quantification

A panel of occupational hygienists were used to rate occupational exposure in this community based study. The literature indicates that in the absence of detailed work records (as would be used in a work based case control study), utilising an experienced occupational hygiene panel to assess detailed subject recalled information on work role and activities is the gold standard for community based studies[106].

3.6.1. The Occupational Hygiene Panel

The hygiene panel comprised three occupational hygienists selected due to their experience in measuring workplace exposure in suburban Adelaide and their familiarity with current occupational exposure literature. All have been members of a previous South Australian panel investigating workplace exposures relating to lung cancer[94]. The panel members were as follows:

Member 1:

Seventeen years of professional experience covering consulting activities with government agencies and private industries, for both small and large industry. This work has included the evaluation of workplace exposures.

President and full member of the Australian Institute of Occupational Hygienists.

Certified in comprehensive industrial hygiene by the American Board of Industrial Hygiene.

Member 2:

Twenty years of professional experience covering consulting activities with government agencies and private industries, for both small and large industry. This work has included the evaluation of workplace exposures.

Full member of the Australian Institute of Occupational Hygienists.

Certified in comprehensive industrial hygiene by the American Board of Industrial Hygiene.

Member 3:

Twenty-five years of professional experience covering consulting activities with government agencies and private industries, for both small and large industry. This work has included the evaluation of workplace exposures.

Full member of the Australian Institute of Occupational Hygienists.

Each panel member was provided with a typed report of self reported occupation and task information per job for each subject (example in Appendix 15). Panel members were blinded to the case or control status of each subject.

3.6.2. Occupational Data Collected from Subjects for Exposure Assessment

Detailed information on all jobs held in the subjects' lifetime was collected. This format and content of this section of the questionnaire was based on that of Ahrens et al[13] described previously.

3.6.3. Levels of Exposure Assessed

Quantifying occupational exposure is not commonly implemented when the purpose of data collection is confounder adjustment. However we felt that it was important to include detailed confounder adjustment in this study. Of the studies meeting the criteria for the systematic literature review (Chapter 2), only one assigned scores to quantify hygiene panel assessed occupational exposure[50]. Their method was adapted for use in this study. The Jockel et al[50] method involved a hygiene panel classifying occupational exposure for each subject to one of five categories (none, low level, medium level, high level, suspected). These categories were based on the German TRK (TRK is an acronym in German meaning the allowable concentration of each carcinogen in the workplace, Jockel, personal communication, 2001). Subsequently, weightings were assigned to each category based on their percentage of the TRK. Weightings were then multiplied by the number of years exposed to derive a final index of exposure[50].

3.6.4. Levels of Exposure

The four levels of exposure in this study were based on percentages of the current health related occupational exposure guidelines obtained from the National Occupational Health and Safety Council (NOHSC – an expert working group of hygienists and medical professionals)[107] (Table 3-9). The NOHSC guidelines are based on the best available technical data from Australia and overseas, applying molecular, animal and human studies to the decision making process. The guidelines "represent airborne concentrations of individual chemical substances that … should neither impair the health of nor cause undue discomfort to nearly all workers", and are enforced in workplaces throughout Australia[107]. At the time of exposure assessment there was not an Australian guideline for diesel exhaust exposure, hence for this study the American guideline was utilised[108]. This is a feasible option as the majority of Australian guidelines closely reflect those in America as they are based on similar exposure studies. Radionuclide exposure does not fall under the NOHSC banner, instead its workplace exposure guideline is sourced from the NHMRC & the Australian Radiation Laboratory[109]. This guideline is a measure of annual exposure rather than 8-hour average.

Table 3-9: Contemporary Health Based Daily (8hr) Occupational Exposure Guidelines

(Source is National Occupational Health and Safety Council[107] unless otherwise specified)

Carcinogen	**Exposure Standard**
Asbestos	0.1 fibre per ml of air
Formaldehyde	1 ppm
Crystalline Silica	0.2 mg/m^3
Fine Particulate	5 mg/m^3 (based on welding fumes, most common)
PAH	0.2 mg/m^3 (surrogate measure, coal tar pitch volatiles)
Diesel Exhaust	0.5 mg/m^3 (surrogate measure, elemental carbon, this standard is from America[108])
Arsenic	0.05 mg/m^3
Beryllium	0.002 mg/m^3
Nickel	1 mg/m^3 (metal and nickel sulphide fumes), 0.1 mg/m^3 (soluble)
Cadmium	0.01 mg/m^3
Chromium 6	0.05 mg/m^3
Radionuclides (ie Radon)	20mSv/annum (no daily guidelines, created by NHMRC & Australian Radiation Laboratory[109])

Definitions of 'High', 'Medium', 'Low' and 'Very low' exposure were determined pre-hoc in consultation initially with the members of the hygiene panel, and finally with the occupational hygienist community (see Appendix 17). As there are no levels of carcinogen exposure considered "safe"[107], it was possible to assign scores to subjects who were exposed to concentrations less than the relevant exposure guideline. The percentages of the exposure guidelines assigned to each exposure level are indicated in Table 3-10.

Table 3-10: Percentage of Exposure Guidelines Assigned to Each Level of Exposure (Average Daily Exposure)

Exposure level	Assigned % of health based exposure guideline	Basis of decision	Source of decision
High	≥ 100%	Respiratory exposure above the guideline has been demonstrated to have adverse health effects	Hygiene panel members
Medium	≥ 42% and < 100%	Previous studies have not specified exposure so precisely so could not be relied on as a precedent, hygiene panel suggested 4 potential levels but could not agree on one	Survey of 22 members of the Australian Institute of Occupational Hygienists (Appendix 17)
Low	≥ 5% and < 42%		

Exposure level	Assigned % of health based exposure guideline	Basis of decision	Source of decision
Very Low	>0% and <5%	After the panel assessed a sample of 20 jobs for exposure it was determined that the category of low was too broad and a very low category was required for those with definite but very little exposure. Following this decision the first jobs assessed were revisited.	Hygiene panel members

3.6.5. Occupational Hygiene Panel Output

Members of the hygiene panel were asked to determine each subject's exposure to a list of known carcinogens (Table 3-9). This was done per job for each subject in a three-step process:

1. Individually assess the likelihood of exposure per carcinogen as "probable", "possible" or "unlikely".
2. In the case of "probable" exposure, assess the level of exposure as "high", "medium", "low" or "very low".

3. Reach a consensus at a face to face meeting on both the likelihood and level of exposure. The consensus was not an average of their individual exposure perceptions, rather it was a level that all three members agree was the most likely, based on their differing level of experience and expertise.

The exposure decisions made by panel members were based on their experience visiting workplaces and measuring exposure, and contemporary workplace exposure literature.

3.6.6. Inclusion in Analysis

Occupational exposure was included in the analysis as a Dose Year score for each carcinogen, and then repeated for the number of years of probable exposure to each carcinogen

3.6.7. Quantification of Exposure Levels in the Analysis

Section 3.6.3 describes the methods available to quantify occupational exposure and concludes a Gold standard methodology has not been identified, however Jockel et al[50] was selected as the most comprehensive methodology.

As per the methodology of Jockel et al[50] each level of exposure was assigned a weighting score based on their assigned percentage of the exposure guidelines (Table 3-11). The score assigned to "possible" exposure was determined pre hoc in consultation with the hygiene panel. When assessing exposure, the panel views "possible" exposure as being between "very low" and "unlikely", hence a score of the mean of these was assigned.

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

Level of exposure	Score
High	10
Medium	7.1
Low	2.35
Very Low	.25
Possible	.125
Unlikely	0

3.6.7.1. Calculation of Dose Years

Dose years per carcinogen were used to provide an overall exposure score per carcinogen for each subject as per Figure 3-9.

Figure 3-9: Method Utilised to Calculate Occupational Dose Years per Carcinogen

Dose year (per carcinogen, per job)[50] =

Score (per carcinogen, per job) * Years exposed (per carcinogen, per job)

Total dose years (per carcinogen)[48 50] =

Σ Dose years (per carcinogen, per job)

3.6.8. Reliability

Siemiatycki et al have demonstrated the reliability of hygiene panel exposure assessment[110]. A two-member hygiene panel assessed exposure to 196 jobs in 1988 and again four years later. The agreement between their individual assessments was good (Kappa = 0.7) and the agreement between their consensus exposure assessments was high (Kappa = 0.8). This indicates strong levels of reliability are attainable when using a group of occupational hygienists to assess exposure.

In addition, thirty job summaries in this study (selected to obtain a range of exposures) were redistributed to the panel for reassessment of exposure. The panel were blinded to this reassessment.

Agreement between initial evaluation and retest and agreement between individual panel members and each member with the consensus decision were determined using the Kappa statistic.

The scoring system for the final exposure score was based on mathematics so was reliable.

3.6.9. Validity

The relative validity of each method of exposure assessment has been assessed previously by comparing exposure score output of each of the three methods. McGuire and collegues[106] reviewed 13 studies and found that, when hygiene panel is considered the gold standard, Job Exposure Matrices (JEM's) have comparatively poor specificity, and self-reports comparatively poor sensitivity. For example, when self reported exposure was compared with hygiene panel assessment in a 1988 study, workers were only able to

report 2.6% of chemical agents evaluated as likely exposures by the hygiene panel (poor sensitivity)[111].

A 1998 review of occupational exposure assessment in community-based studies did not suggest alternate methods of quantifying levels of occupational exposure to the method described here[106].

There is not a demonstrated valid method available to score occupational exposures for community based epidemiological studies. The strengths of this method were described in Section 3.6.7. It is not possible to determine validity of results for this community-based study as actual exposure measurements were unavailable.

3.7. Quantification of Other Potential Confounders

3.7.1. Hobbies

Three hobbies were identified pre hoc by the hygiene panel as likely to involve exposure to specific lung carcinogens (see Table 3-12). Subjects were asked to recall their involvement with the each listed hobby and the duration of this involvement. Exposure scores were then generated as the duration of exposure to each hobby in years.

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

	Hobby	Carcinogen exposure
1	Mechanical Repairs	Possible Asbestos
		Possible Polycyclic Aromatic Hydrocarbons
2	House Renovations/Building	Possible Silica
	Construction	Possible Asbestos
3	Pottery Work/Sculpting	Possible Silica

3.7.2. Socioeconomic Status

Low socioeconomic status (SES) has been associated with lung cancer in published reviews[82]. Utilising the same method as the National Health Survey[4], SES was quantified by education (age left school, highest level of school completed – yes or no, and highest education qualification completed). This SES data did not undergo conversion prior to analysis as per the National Health Survey[4].

3.7.3. Family History

It has been demonstrated that having a first degree relative (parent or sibling) who has been diagnosed with lung cancer elevates the odds ratio for lung cancer after adjusting for the tobacco smoking history of both the lung cancer patient and family members[81].

In this study, scores for subjects with a family history of primary lung cancer were generated based on the number of first degree family members (parents or siblings), as per the methodology of Bromen et al[81]. For example, a subject with a parent and a sister with a reported primary lung cancer diagnosis would be assigned a score of 2.

3.8. Substudy: A Comparison of the Responses from Controls and their Next of Kin (NOK)

3.8.1. Sample

A subgroup of control subjects and their NOK were asked to participate in a sub-study to compare the recall of lifetime smoking, occupation and residences of the NOK with the control. Controls were asked to nominate the NOK listed on their medical records, as per the NOK recruited for deceased cases. The NOK was contacted by telephone to obtain consent to take part, and to arrange a meeting time. A modified questionnaire (see description in Section 3.8.2) was then administered to both the control and their NOK at the same time in separate rooms. Both the control and NOK were advised not to consult one another about the contents of the questionnaire, but to complete it separately in the presence of a researcher.

3.8.2. The Tool

The questionnaire used for this sub-study was a modification of that referred to as the "Part a Questionnaire" in the main study (see Appendix 18). The modifications were the addition of cigarette smoking history (when started, when stopped, number smoked per day) and listing of the industry worked in and tasks, in addition to job title. It also included an example of a completed questionnaire to assist with completion. NOK were not required to fill out the questionnaire for the lifetime of the control, only the previous 15 to 30 years reflecting the 15 to 30 year latency period for lung cancer[29]. This reduced the burden of participation for the NOK.

3.8.3. Classification

Data collected from the NOK was quantified in the following ways:

Smoking

Cigarette smoking was classified by pack years categorised as per the main study.

Occupation

Information collected on occupational history (job title, industry worked in, main tasks undertaken) was sent to the panel of occupational hygienists for exposure classification. The panel were blinded as to the control or NOK source of information. Job title and industry were taken into account to determine likelihood of exposure to a list of lung carcinogens supplied. Control and NOK exposure scores were calculated and categorised (as per occupational exposure quantification previously described in Section 3.6.7).

Residence

Residential responses were used to determine an exposure score for each of the 6 factories as per the modified Gaussian exposure equation utilised in the main study (as described in Section 3.4).

3.8.4. Substudy Analysis

Categorical data was analysed using the Kappa Statistic (k) for inter-rater agreement (as per Nelson et al[78]). This method measured agreement after taking into account agreement by chance. Kappa values were interpreted according to Altman, 1991[112] (Table 3-13):

Table 3-13: Interpretation of the Kappa Statistic

Value of kappa (k)	Strength of Agreement
<0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very Good

3.9. Statistics

3.9.1. Sample Size Calculation

This case control study aimed to detect a doubling of lung cancer risk (ie odds ratio = 2), in keeping with the variations in lung cancer incidence within the region of interest[1]. If 25% of lung cancer cases in the Osborne region have been exposed to excessive levels of carcinogenic pollution compared to 15% of controls, and required power is 80%, at a significance level of 0.05 two-sided, and using a control to case ratio of 3:1 then 140 cases and 420 controls were required[113].

3.9.2. Data Entry and Storage

Data was entered and stored in a Microsoft Access database with password protection. Prior to use data was systematically checked for errors. Paper copies of data were stored in a locked filing cabinet in a locked room

There were some missing data and relevant sample sizes are provided for each statistical analysis in the Results Chapter (Chapter 4). In general any subject with a missing data point was excluded from that portion of the statistical analysis.

3.9.3. Analysis

Data was exported from the Access database into STATA[77] and the Statistical Package for Social Sciences (SPSS)[114] statistical packages using Stat-transfer[115].

Analysis took place as a 5-stage process:

1. Comparison of participants and non-participants

Basic demographics of participants and non-participants were compared. Student's t-tests were used for continuous variables, and chi-squared tests for categorical data.

2. Comparison of cases and controls for basic demographic factors

Basic demographics of cases and controls were compared. Student's t-tests were used for continuous variables, and chi-squared tests for categorical data.

3. Comparison of cases and controls for individual study factors (Univariate analysis)

The purpose of this analysis was to investigate the relationship between each study factor in isolation with the study outcome (lung cancer). Data for each variable was assessed for normality using the Shapiro-Wilks test. If data was normal ($p>0.05$) it was analysed using a 2-sided Student's t-test. For data not fitting a normal curve the mean ranks were compared using the Mann-Whitney U test. Categorical data was assessed using chi-squared tests.

4. Determining candidate variables for the final conditional logistic regression model (Bivariate analysis)

Each study factor was entered separately into a conditional logistic regression model.

The Odds Ratio (OR) for each variable was calculated after adjustment for matching (cases and controls were matched for gender and 5-year age band).

Continuous variables were first divided into quartiles. In some instances, due to the skewed nature of the variable, some were dichotomised.

5. Final conditional logistic regression model (Multivariate analysis)

Variables with a p-value less than or equal to 0.1 in the previous analysis were included in the final multivariate analysis. This was designed to ensure that variables even of a marginal significance had a chance to partake in the final model. A multivariate model was run for residential exposure to each of the 6 industry and the composite score, including potential confounders identified in (4).

Agreement between members of the occupational hygiene panel and the occupational hygiene panel test/retest data were analysed as per Section 3.6.8. Agreement between NOK and controls in the substudy were analysed as per Section 3.8.4.

3.10. Distribution of Case Control Study Results

All participating subjects were sent a one-page summary of the results and conclusions drawn from this study (Appendix 19). The public was informed through the media. The ethics committees of hospitals participating in subject recruitment were also sent a summary of the study results.

3.11. Ambient Air Sampling Methodology

A global literature search and research of local industrial activity were undertaken to identify a list of carcinogens, potentially associated with industrial sources in the NW area, to be included for environmental sampling (Table 3-14). In addition similar monitoring of particulate matter with a mass median equivalent aerodynamic diameter of 2.5μm ($PM_{2.5}$), and short term monitoring of ultrafine particulate matter occurred. Fine and ultrafine particulate matter have not been classified as carcinogenic, but are useful indicators of pollution levels, and are able to act as carriers for carcinogenic substances[44].

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

Carcinogen	Potential Source
Asbestos	Abandoned asbestos cement manufacturing factory
Crystalline Silica	Cement manufacturer
Formaldehyde	Foundries, industrial vehicles
Polycyclic Aromatic Hydrocarbons (PAH)	Industrial vehicle traffic, power station, fuel depots
Diesel Exhaust	Industrial vehicle traffic

** known to be carcinogenic*

*** probably carcinogenic*

3.11.1. Monitoring Locations

Five locations were selected to be monitoring sites based on their proximity to industry or to a major traffic intersection, and on lung cancer mortality figures (Figure 3-10 site numbers correspond to the list of sites below). These sites were readily accessible to our vehicles transporting the monitoring equipment and appeared secure from vandalism and tampering.

The five site locations selected for sampling were:

1. Osborne – residential area closely adjacent to an industrial area (including a soda ash production plant), equipment located on private property
2. Birkenhead – residential area very closely adjacent to industrial area (including a cement works) with high volume of heavy vehicle traffic, equipment located on private property (see Figure 3-11)
3. Pt Adelaide – high volume, heavy vehicle traffic intersection with some nearby residences, equipment located on council owned fenced property
4. Mile End – high volume traffic intersection, away from North West industrial area, equipment located in monitoring cage owned by the Environmental Protection Authority (See Figure 3-12)
5. Kidman Park – control residential area with little industry and no heavy vehicle traffic, equipment located on private property

Precise monitoring locations were chosen based on criteria in the Guide for the Siting of Sampling units developed by the Committee on Methods for Examination from the Air Standards Association of Australia[116]. The criteria include such things as distance from trees, height above ground and clear sky angle.

Figure 3-10: Location of Air Monitoring Sampling Sites within the North West of Adelaide

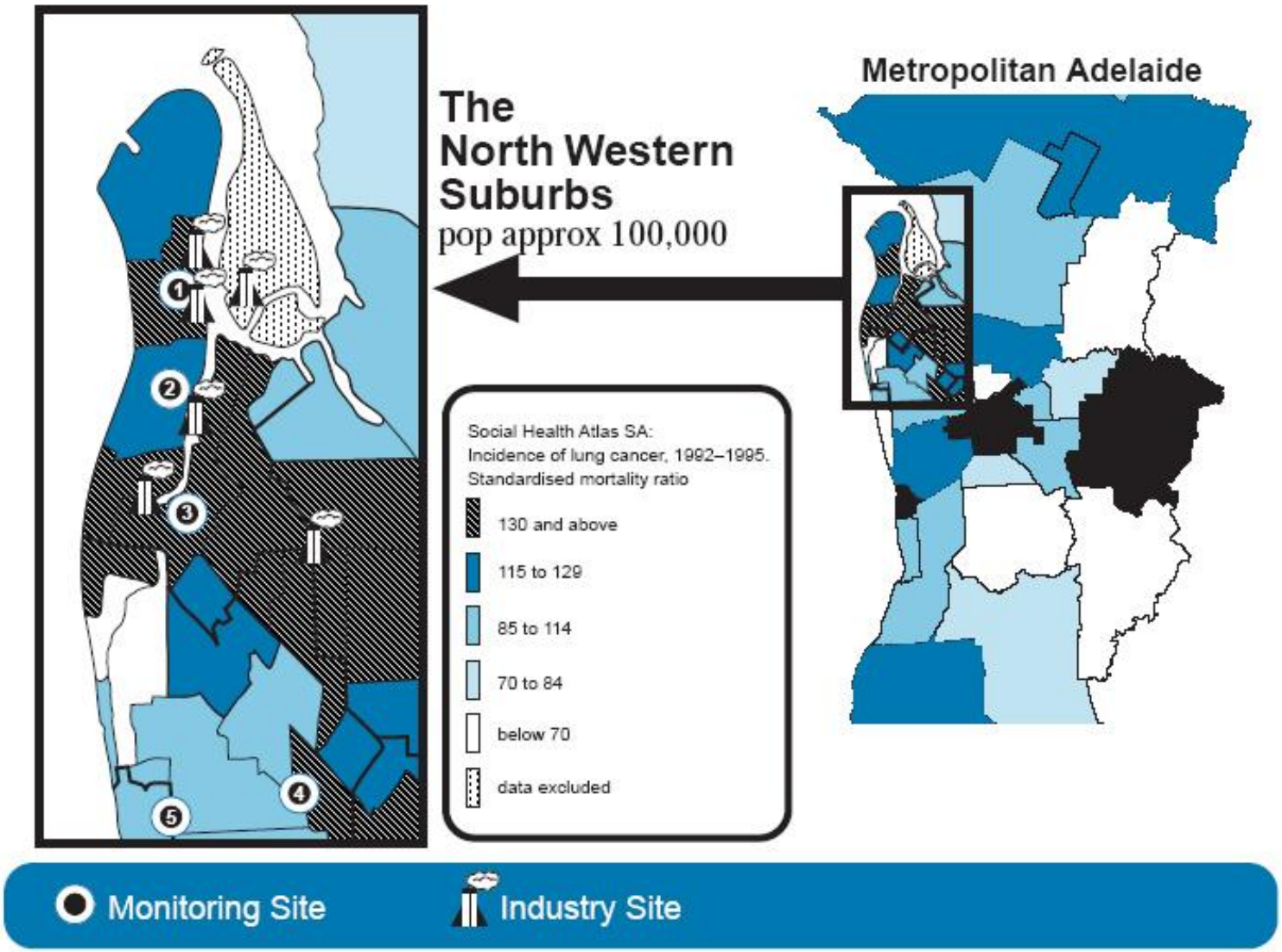


Figure 3-11: Photograph of Monitoring Site 2 - Birkenhead



Figure 3-12: Photograph of Monitoring Site 4 - Mile End (in Environmental Protection Authority Cage)



3.11.2. Sampling Duration and Timing

Air sampling was predominantly carried out in March 2002. This period was considered “mid season” and was chosen to avoid temperature extremes and increase likelihood of dry conditions (metropolitan Adelaide had been in drought conditions for approximately 6 weeks prior to this). The sampling is representative of typical conditions rather than worst-case scenario.

3.11.3. Field Work

SKC PCXR universal air sampling pumps were used for low flowrate measurements of asbestos, crystalline silica and diesel exhaust particulate. External high capacity 6V lead acid batteries were fitted to each pump. Prior to sampling all pumps were calibrated at 2.0 L/min, except for respirable crystalline silica, which was 1.9 L/min. Flowrates were checked at the end of each sampling interval.

Asbestos:

Airborne asbestos was sampled using 25 mm *Nuclepore* 0.8 µm polycarbonate filters and anti-static cowls[117], with subsequent scanning electron microscopy (SEM) by the Centre for Electron Microscopy and Microstructure Analysis, University of Adelaide. Following sampling, the filters were removed from the holders and a quadrant cut from the filter using a razor blade. The filter quadrants were mounted on SEM stubs using carbon tabs. The mounted samples were evaporatively coated with carbon. The carbon coating is approximately 30 nm thick.

Samples were examined using a Philips XL30 field emission gun SEM fitted with an EDAX energy-dispersive spectrometer. The microscope was operated at an accelerating voltage of 20 kV with the spot size set to 3. Non-overlapping regions (10244 μm^2) of the filters were examined in a grid pattern. Particles were identified using back-scattered electron (BSE) imaging mode in order to distinguish inorganic particles from organic material.

An estimate of the number of asbestos particles on a given filter was obtained by searching 20 regions for particles with a fibrous morphology and determining the elemental composition of these particles using EDAX spectroscopy[118].

Respirable Crystalline Silica:

Respirable crystalline silica was sampled using 25 mm *Nuclepore* 0.8 µm polycarbonate filters in miniature cyclones[119]. Quartz content was determined by MPL Laboratories, using an in house infrared spectroscopic method (WILAB 4.0) adapted from NIOSH Method 7603[120].

The crystalline silica content of asbestos SEM samples (see above) was also estimated using automated particle counting software (iDXac) from 4 regions of each filter. The iDXac software was set to detect all particles with dimensions over 0.5 µm in size in BSE images.

Formaldehyde:

Formaldehyde was sampled using 2,4-dinitrophenylhydrazine-coated silica gel passive samplers with an effective sampling rate of 25 ml/minute. Samples were analysed by HPLC with UV detection[121].

Polycyclic Aromatic Hydrocarbons (PAH):

Inhalable PAHs were sampled using the EHL sampler[122 123]. Analysis was conducted by the BHP Environmental Health Laboratory, using in house methods (EHL 9 GC/MS for PAH).

Diesel Exhaust Particulate:

Diesel exhaust particulate was monitored using 37 mm quartz filters, in accordance with NIOSH Method 5040[124]. Analysis was conducted by Alan Rogers OH&S Pty Ltd, at the University of Sydney.

Fine Particulate ($PM_{2.5}$) by Dust Trak™:

$PM_{2.5}$ levels were sampled using a TSI Instruments Dust Trak™ with 2.5μm inlet. The Dust Trak™ determines $PM_{2.5}$ concentration using light scattering detection. Concentration data, recorded at 1min intervals, were periodically downloaded to a laptop computer at the site. Environmental enclosures (Dust Trak™ Environmental Enclosure Model 8520-1) were used for fixed monitoring locations.

$PM_{2.5}$ by Tapered Element Oscillating Microbalance (TEOM):

$PM_{2.5}$ sampling at the Osborne site (1) was also carried out using a Tapered Element Oscillating Microbalance in a caravan located in the driveway of the residence. A Ruprecht and Patashnick Series 1400A ambient particulate monitor was used. Total flow was 16.67l/min, with a sample flow of 3l/min. The sample inlet and filter were maintained at 50C. Correction was made for semi volatiles and daily temperature variation. A similar TEOM unit was located at an EPA reference site approximately 6 km west of the Adelaide central business district.

Ultrafine Particulate:

Short term sampling of ultrafine particles was carried out with a TSI Instruments P-Trak™ which counts particles between 0.02 and 1μm. The P-Trak™ predominately measures diesel exhaust and combustion sources[125]. The P-Trak sampling was undertaken in 15 sites (in addition to the 5 key sites) for short (5 to 15 mins) periods both within and external to the study area.

3.11.4. Meteorological Measurements

The prevailing weather conditions at Site 5 were recorded using a portable weather station (Model Number 102083, Climatronics Corporation, Bohemia, NY), [supplied by MEA instruments; Datalogging was with a Unidata Australia Starlogger Model 6004C]. The Bureau of Meteorology supplied other meteorological data relevant to the sampling period.

3.11.5. Air Quality Monitoring Analysis

Air quality monitoring results were compared to the relevant National Environmental Protection Guideline[35], or the 8hr occupational exposure standard where a community ambient standard was unavailable[107].

4. Chapter 4 Results

The following chapter is a detailed description and analysis of the data collected for the case control study. It begins with a description of the participating subjects and study participation rates, second is an analysis of 2 aspects of the study design (hygiene panel agreement and next of kin agreement), third is a univariate analysis of the exposure scores in relation to case or control status, fourth bivariate analysis of exposure scores with adjustment for age and gender matching, and concludes with the final multivariate logistic regression model.

4.1. Sample Demographics

4.1.1. Study Participants

Control subjects were matched to cases by both age and gender, therefore, as expected, cases and controls did not differ significantly with regard to either age or gender (Table 4-1).

Table 4-1: Age and Gender of Study Participants

Variable	Cases (n = 142)	Controls (n=415)	Test	P-value
Age - mean yrs ± SD	72.77 ± 10.36	73.39 ± 10.23	T-test	0.5407
Gender - %M/F	69.7 / 30.3	69.9 / 30.1	Pearsons	0.971

4.1.2. Participants versus Non-participants

The purpose of the following analysis is to demonstrate that the study sample is representative of the study population (that participating cases are an accurate representative sample of lung cancer cases diagnosed within the study area during the recruitment period, and that participating controls are representative of the general population within the study area). This was accomplished by comparing non-participants to participants for available sample demographics, and comparing the control sample with demographics previously collected within the study area (for example census information). In this section eligible subjects are classified as either participants, non participants (those who responded to the invitation to take part but declined) or uncontactable subjects (see footer (*) of Table 4-2).

4.1.2.1. Cases

One hundred and forty-two cases participated in the study, 76 (54%) of these were the NOK of a deceased lung cancer patient (Table 4-2). The participation rates of lung cancer patients and patients' NOK were almost identical. Seventy-four percent (142 of 192) of contactable cases took part in the study.

Table 4-2: Case Participation Rates

	Alive (n=111)		Dead (n=130)		All (n=241)	
	n	%	n	%	n	%
Yes	66	59	76	58	142	59
No	23	21	27	21	50	21
Uncontactable*	22	20	27	21	49	20
Total	111	100	130	100	241	100

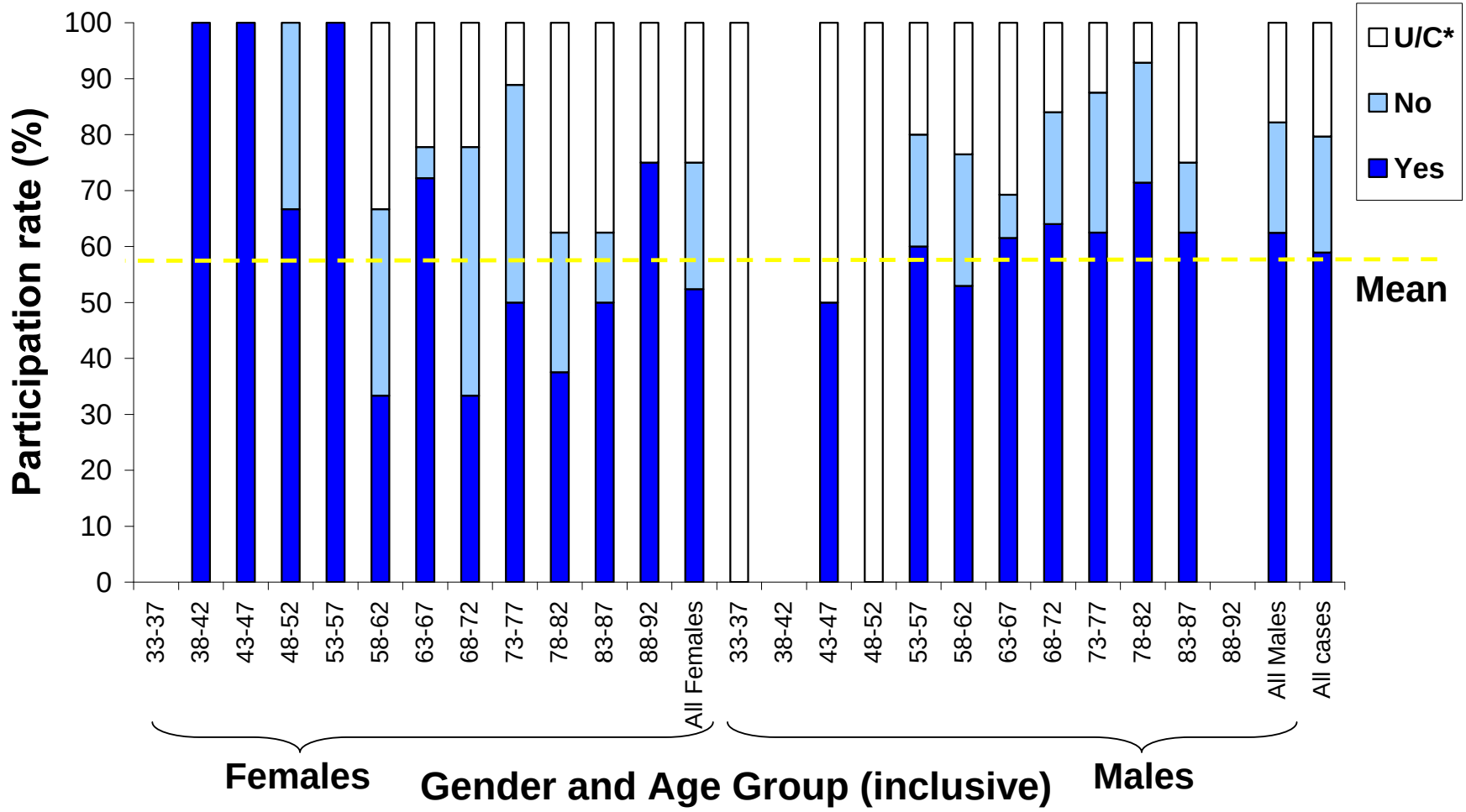
**Cases were deemed uncontactable if:*

A response was not received from them after 2 information letters had been posted and 3 attempts had been made to contact them by phone

A suitable (treating) and willing doctor could not be found to contact them

In the instance of deceased cases, there was not an appropriate NOK (age greater than or equal to 18 years) listed on their medical records, or the listed NOK was uncontactable.

Figure 4-1: Case Participation Rates by Gender and Age Group



** U/C = uncontactable*

4.1.2.1.1. Differential Participation Rate for Age and Gender

Figure 4-1 is a graphical representation of participation rates for cases sub grouped by age and gender. There were no differences in the overall participation rates between males and females. Females aged between 38 and 47 years (inclusive) were the group most likely to participate in the study, with those aged 68 to 87 years (inclusive) least likely.

4.1.2.1.2. Distance from Industry

There was no significant difference in the distance participating cases lived from each of the major industry at the time of recruitment, or in the distance from their nearest industry, compared to non participating cases (Table 4-3).

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

Industry	Participants (n=142)			Non participants (n=88)			Significance (Mann Whitney U)
	Median (kms)	Min	Max	Median (kms)	Min	Max	
ABC	4.762	0.411	10.836	4.887	0.569	1.0561	.434
CSR	4.637	0.295	9.817	4.911	0.732	9.568	.259
Fins	4.060	0.385	10.781	3.929	0.967	9.818	.905
Hardies	5.605	0.270	11.873	5.748	0.631	11.605	.361
PSP	8.147	0.370	14.641	7.937	0.454	14.358	.412
Pwr St	7.328	1.654	13.882	6.840	1.593	13.568	.574

** Key to Industry names: ABC – Adelaide Brighton Cement, CSR - Sugar Refinery, PSP – Penrice Soda Products, Hardies – James Hardies Asbestos Products, Pwr St – Torrens Island Power Station, Fins – Finsbury industrial suburb. For map of industry location see Figure 1-1.*

4.1.2.2. Controls

415 controls participated in the study. The control participation rate was lower than that for cases (47% vs 59%). 60% of contactable controls took part in the study (Table 4-4). A significantly higher proportion of cases participated than controls (Chi-squared = 12.316 on 1 degree of freedom, $p<0.001$).

Table 4-4: Control Participation Rates

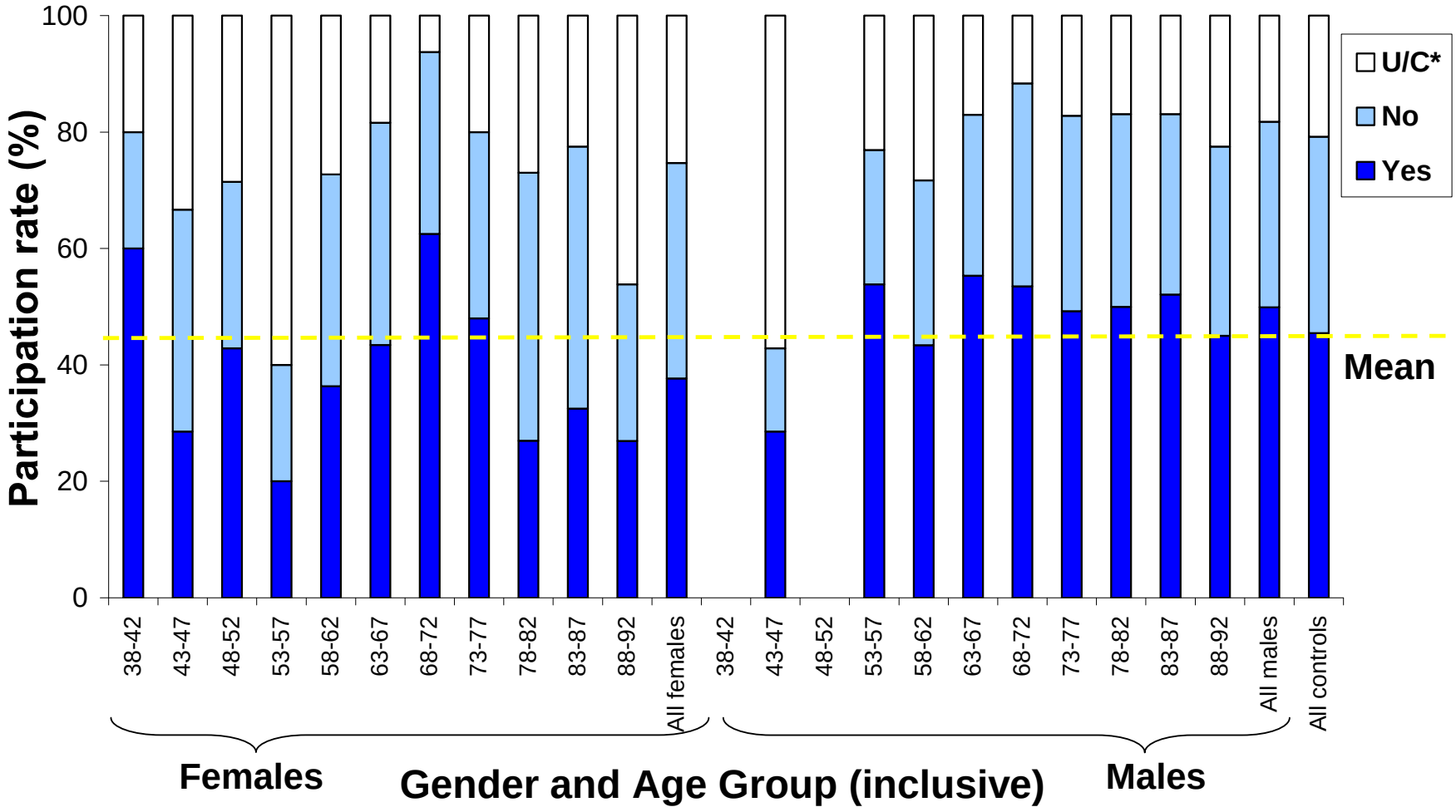
	All (n=880)	
	n	%
Yes	415	47
No	275	31
Uncontactable*	190	22
Total	880	100

** Controls were deemed uncontactable if a response was not received from them after the initial information letter and 1 follow up letter were sent, and 3 attempts to contact by phone had been made, or if they were deceased.*

4.1.2.2.1. Differential Response Rate for Age and Gender

Figure 4-2 is a graphical representation of participation rates for control subjects sub grouped by age and gender. Male control subjects were more likely to participate than females, and had similar participation rates across the age categories. Due to the gender and age matching to cases when selecting controls, this differential participation had no influence on the gender mix of the final sample.

Figure 4-2: Control Participation Rates by Gender and Age Group



** U/C = uncontactable*

4.1.2.3. Distance from Industry

There was no significant difference in distance of current residence from Adelaide Brighton Cement, James Hardies, Penrice Soda Products and the Torrens Island Power Station between participating and non participating control subjects (who responded). Participating control subjects resided significantly closer to CSR (difference of 0.665km, p=0.007) and significantly further from Finsbury (difference of 1.567km, p<0.001) than non-participating controls (Table 4-5), however participation controls did not live significantly closer to their nearest industry than non participants (Mann Whitney U test p=0.598).

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

Industry	Participants (n=415)			Non participants (n=396)			Significance (Mann Whitney U)
	Median (kms)	Min	Max	Median (kms)	Min	Max	
ABC	4.788	0.273	10.992	5.670	0.251	10.654	.064
CSR	**4.696**	**0.330**	**10.062**	**5.361**	**0.430**	**10.343**	**.007**
Fins	**5.545**	**0.257**	**11.422**	**3.978**	**0.113**	**11.094**	**<0.001**
Hardies	5.610	0.147	12.034	6.700	0.394	11.702	.060
PSP	8.153	0.344	14.790	8.660	0.411	14.443	.203
Pwr St	7.471	1.640	14.001	7.598	1.560	13.631	.529

** Key to Industry names: ABC – Adelaide Brighton Cement, CSR - Sugar Refinery, PSP – Penrice Soda Products, Hardies – James Hardies Asbestos Products, Pwr St – Torrens Island Power Station, Fins – Finsbury industrial suburb. For map of industry location see Figure 1-1.*

4.1.3. Occupational Hygiene Panel Agreement

The three member panel of occupational hygienists assessed exposure to a list of lung carcinogens for each occupation recalled by study subjects. Each panel member assessed the exposure individually and then reached a consensus decision with the other members of the group. Table 4-6 indicates the level of agreement between the three panel members, and then between each panel member and the consensus decision. Agreement between the panel members was moderate (Kappa statistic 0.41-0.6), and agreement between each individual panel member and the consensus rating was good (Kappa statistic 0.61-0.8) for the majority of panel members and variables.

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

(Total number of assessments were 13 136 i.e. scores from each rater and the consensus for 3284 jobs)

	Agreement between:			
Material	Raters 1, 2 and 3	Rater 1 and Consensus	Rater 2 and Consensus	Rater 3 and Consensus
Asbestos	0.50	0.62	0.68	0.79
Formaldehyde	0.35	0.48	0.53	0.73
PAH	0.49	0.66	0.71	0.72
Diesel Exhaust	0.53	0.66	0.70	0.75
Crystalline Silica	0.49	0.66	0.69	0.74
PM2.5	0.40	0.60	0.58	0.68

Weighted kappa was used to indicate reliability for 30 pairs of test-retest data. Panel members differed considerably in their reliability (Table 4-7). Reliability for exposure score was generally moderate with only exposure to diesel exhaust having good reliability. The Kappa results were affected by the lack of variation between exposure scores for each subject that meant expected agreement was very high for each exposure assessment.

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

Material	Rater 1	Rater 2	Rater 3	Consensus
Asbestos	0.148	0.551	0.531	0.710
Formaldehyde	0.783	0.464	0.310	0.000
PAH	0.083	0.471	0.435	0.348
Diesel Exhaust	0.836	0.507	0.688	0.550
Crystalline Silica	0.513	0.366	- 0.091	0.429
PM2.5	0.526	0.000	0.786	0.634

4.1.4. Next of Kin Agreement

Reliability for the smoking (pack year categories) and occupational (weighted dose for each carcinogen) exposure scores was perfect (Kappa = 1.00, n=5 pairs), whilst that for residential exposure (using modified Gaussian equation) was very good (ICC = 0.93, n=5 pairs).

4.2. Univariate Analysis

The purpose of this analysis is to investigate the relationship between each study variable with the study outcome (lung cancer), in isolation. In each case variables were categorised to give more meaningful presentation (for the majority of the variables the raw data did not follow a normal distribution and was skewed towards no exposure).

4.2.1. Socio-economic Status

Cases were significantly ($p \leq 0.034$) more likely to leave school at a younger age than controls, however there was also a trend ($p \leq 0.054$) for cases to be more likely to have completed their schooling than controls (Table 4-8). This seemingly contradictory result is likely to be due to the phrasing of the question about finishing school; "Did you finish the highest level of school available to you?" Although it can not be determined from the data, it is possible that controls had a higher level of schooling available to them than cases, hence even though they did not 'finish' school by our definition; they still stayed at school to a later age then cases. The majority of both cases (68%) and controls (59%) did not have qualifications higher than a secondary school certificate and there was no significant difference between cases and controls for this variable ($p=0.497$).

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

Variable	Cases (n=142)		Controls (n=415)		Significance
	n	%	n	%	(Chi square)
Age left school					**0.034**
<14 years	33	24	68	16	
14-15 years	75	55	218	53	
>15 years	29	21	129	31	
Total	137	100	415	100	
Highest level of school completed					**.054**
Yes	106	80	293	72	
No	26	20	115	28	
Total	132	100	408	100	

Variable	Cases (n=142)		Controls (n=415)		Significance
	n	%	n	%	(Chi square)
Highest qualification					.497
Secondary school or less	96	70	246	59	
Nursing	2	1	4	1	
Teaching	1	1	8	2	
Trade certificate/ Apprenticeship	31	22	89	21	
Technicians Certificate/ Advanced certificate	3	2	14	3	
Other Certificate	2	1	18	4	
Associate Diploma	0	0	5	1	
Undergraduate Diploma	0	0	3	1	
Bachelor Degree	2	1	4	1	
Post graduate Diploma	0	0	1	0	
Master Degree/Doctorate	0	0	4	1	
Other	5	4	19	5	
Total	142	100	415	100	

4.2.2. Residential Exposure within the Study Area

Residential exposure (a function of distance from industry, downwind frequency and duration of residence) to each of the six individual industries and to a composite exposure score (sum of residential scores to each individual industry) in the study area were not significantly related to being a case or control (Table 4-9). Only exposure to the power station approached significance (p=0.07), with controls having a higher residential proximity score.

Table 4-9: A Comparison between Cases and Controls of Residential Scores[#] for each Identified Industry

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
ABC					0.144
<1.0	64	45	142	34	
1.0 – 1.4	23	16	83	20	
1.5 – 2.9	26	18	90	22	
3.0+	29	20	100	24	
Total	142	100	415	100	
CSR					0.128
<1.0	59	42	133	32	
1.0 – 1.4	26	18	76	18	
1.5 – 2.9	23	16	98	24	
3.0+	34	24	108	26	
Total	142	100	415	100	

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Fins					0.308
<1.0	44	31	101	24	
1.0 – 1.4	24	17	82	20	
1.5 – 2.9	38	27	135	33	
3.0+	36	25	97	23	
Total	142	100	415	100	
Hardies					0.198
<1.0	74	52	182	44	
1.0 – 1.4	21	15	68	16	
1.5 – 2.9	17	12	78	19	
3.0+	30	21	87	21	
Total	142	100	415	100	
PSP					0.351
<1.0	88	62	228	55	
1.0 – 1.4	17	12	62	15	
1.5 – 2.9	20	14	55	13	
3.0+	17	12	70	17	
Total	142	100	415	100	

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Pwr St					0.070
<1.0	79	56	193	47	
1.0 – 1.4	19	13	74	18	
1.5 – 2.9	33	23	88	21	
3.0+	11	8	60	14	
Total	142	100	415	100	
All sites[‡]					0.276
<6.0	48	34	117	28	
6.0 – 7.9	25	18	62	15	
8.0 – 17.9	43	30	131	32	
18.0+	26	18	105	25	
Total	142	100	415	100	

[#] *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

** Key to Industry names: ABC – Adelaide Brighton Cement, CSR - Sugar Refinery, PSP – Penrice Soda Products, Hardies – James Hardies Asbestos Products, Pwr St – Torrens Island Power Station, Fins – Finsbury industrial suburb. For map of industry location see Figure 1-1.*

[‡] *The composite score equal to the sum of residential scores for each industry*

4.2.3. Residential Exposure outside of the Study Area

There was no significant difference between cases and controls for residential exposure outside of the study area (Table 4-10).

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

	Cases		Controls		Significance
		%		%	Mann-Whitney U)
Exposure Duration					.844
No exposure	2	1	97	7	
≤ 10 years	4	4	11	7	
>10 years	6	5	07	6	
Total	42	00	15	00	

** Residential exposure outside of the NW of Adelaide is defined as the numbers of years spent residing within Australia in the same suburb as an industry licensed by local environmental protection authorities to emit airborne pollutants.*

4.2.4. Cigarette Smoking

Cases were significantly more likely to be cigarette smokers than control subjects (Table 4-11). Cases smoked more cigarettes per day on average (8 vs 18, $p<0.001$), smoked for a longer period of time (21 vs 48yrs, $p<0.001$), started smoking at a younger age (17 vs 18yrs old, $p=0.013$) and ceased smoking at an older age (53 vs 63yrs old, $p<0.001$), culminating in a higher median number of pack years in cases than controls (by 27.5 pack years, $p<0.001$).

Table 4-11: Comparison of the Cigarette Smoking Habits of Cases and Controls ‡

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Smoking duration					**<0.001**
Non smoker	9	6	146	35	
≤ 30 years	18	13	111	27	
>30 – 49 years	51	36	103	25	
49+ years	64	45	55	13	
Total	142	100	415	100	
Cigarettes per day					**<0.001**
Non smoker	17	12	150	36	
<10	16	11	66	16	
10-19	44	31	95	23	
20+	65	46	104	25	
Total	142	100	415	100	

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Pack-years smoked					**<0.001**
0	17	12	150	36	
<10	12	8	51	12	
10-19	9	6	50	12	
20-29	16	11	48	12	
30-39	20	14	31	7	
40+	68	48	85	20	
Total	142	100	415	100	
Number smoking episodes‡					**<0.001**
0	17	12	150	36	
1	47	33	106	26	
2+	78	55	159	38	
Total	142	100	415	100	

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Smokers only	n=133		n=269		Student's t-test
Age commenced					**0.013**
<15 years	34	25	37	14	
15-19 years	66	50	149	55	
20+ years	33	25	83	31	
Total	133	100	269	100	
Age ceased					**<0.001**
<40 years	9	7	51	19	
40-49 years	11	8	50	19	
50-59 years	23	17	62	23	
60+ years	90	68	106	39	
Total	133	100	269	100	

** Smoking is defined as having smoked ³ 1 cigarette per day for a continuous period of ³6 months*

‡ To be defined as a separate smoking episode smoking must have ceased for ³6 months prior to commencing again

4.2.5. Environmental Tobacco Smoke (ETS)

Cases were exposed to ETS in their home for significantly longer than controls (11 years, see Table 4-12). There was no difference between cases and controls for the duration of exposure to ETS at work.

Table 4-12: Environmental Tobacco Smoke (ETS) Exposure by Cases and Controls

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
ETS at home					**0.006**
0 years	16	11	52	13	
<20 years	20	14	78	19	
20-39 years	44	31	169	41	
40+ years	62	44	116	28	
Total	142	100	415	100	
ETS at work					0.396
0 years	34	24	80	19	
<20 years	35	25	110	27	
20-39 years	36	25	130	31	
40+ years	37	26	95	23	
Total	142	100	415	100	

4.2.6. Occupational Exposure to Lung Carcinogens

Eight control subjects were excluded from this analysis as the occupational hygiene panel could not reach consensus on their exposure scores and hence featured missing data. Substances to which few subjects (less than five) had been possibly or probably exposed were excluded from this analysis (Radon, Chromium 6, Cadmium, Nickel, Beryllium and Arsenic).

Initially occupational exposure to individual lung carcinogens was assessed using the Jockel equation methodology (see Methods, Chapter 3). This method assigns weightings to the hygiene panel exposure scores and combines them with duration of exposure to generate an occupational exposure score for each identified carcinogen. There was no significant difference in carcinogen exposure between cases and controls using this method (Table 4-13) potentially due to the small number of exposed subjects in both the case and control groups, and the wide range of exposure scores generated by the Jockel equation method.

Subsequently exposure was assessed using a simpler method to reduce the variation in exposure scores. The number of years of probable or possible exposure alone (also as deemed by the occupational hygiene panel) was used to quantify occupational exposure. This second method of assessment also found no significant difference between occupational exposure for cases and control subjects for each of the lung carcinogens tested (Table 4-14).

Table 4-13: Occupational Exposure to each Lung Carcinogen for Cases and Controls - Jockel equation method*(units are exposure years)

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Asbestos					0.180
0	79	56	203	50	
<5	38	27	135	33	
5-9.9	11	8	18	4	
10+	14	10	51	13	
Total	142	101	407	100	
Crystalline Silica					0.364
0	72	51	230	57	
<5	49	35	135	33	
5-9.9	15	11	26	6	
10+	6	4	16	4	
Total	142	101	407	100	
Formaldehyde					0.668
0	116	82	327	80	
<5	25	18	71	18	
5-9.9	1	1	6	1	
10+	0	0	3	1	
Total	142	101	407	100	

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
PAH					0.421
0	64	45	154	38	
<5	55	39	175	43	
5-9.9	18	13	66	16	
10+	5	4	12	3	
Total	142	101	407	100	
Diesel					0.797
0	98	69	282	69	
<5	35	25	90	22	
5-9.9	8	6	32	8	
10+	1	1	3	1	
Total	142	101	407	100	
PM2.5					0.139
0	123	87	336	83	
<5	11	8	49	12	
5-9.9	1	1	11	3	
10+	7	5	11	3	
Total	142	101	407	101	

** Jockel equation method – exposure levels assessed by the occupational hygiene panel were weighted according to Jockel et al [50] and multiplied by duration of exposure. Units of the scores generated are exposure years.*

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

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Asbestos					0.101
None	79	56	203	50	
1 – 9 years	17	12	81	20	
10+ years	46	32	123	30	
Total	142	100	407	100	
Crystalline silica					0.141
None	72	51	230	57	
1 – 9 years	20	14	69	17	
10+ years	50	35	108	27	
Total	142	100	407	100	
Formaldehyde					0.690
None	116	82	327	80	
1 – 9 years	13	9	47	12	
10+ years	13	9	33	8	
Total	142	100	407	100	

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
PAH					0.146
None	64	45	154	38	
1 – 9 years	23	16	95	23	
10+ years	55	39	158	39	
Total	142	100	407	100	
Diesel exhaust					0.708
None	98	69	282	69	
1 – 9 years	20	14	48	12	
10+ years	24	17	77	19	
Total	142	100	407	100	
PM2.5					0.296
None	123	87	336	83	
1 – 9 years	7	5	37	9	
10+ years	12	8	34	8	
Total	142	100	407	100	

4.2.7. Hobbies

Cases were significantly (p=0.015) more likely to participate in pottery as a hobby than controls (Table 4-15). There was also a trend evident for cases to be more likely to participate in house renovating as a hobby than controls (p=0.077).

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

	Cases		Controls		Significance
	n	%	n	%	(Mann-Whitney U)
Mechanics					1.000
No	124	87	363	87	
Yes	18	13	52	13	
Total	142	100	415	100	
Home renovation					0.077
No	113	80	298	72	
Yes	29	20	117	28	
Total	142	100	415	100	
Pottery					**0.015**
No	135	95	410	99	
Yes	7	5	5	1	
Total	142	100	415	100	

4.2.8. Family History of Lung Cancer

There was a trend evident for cases to be more likely than controls to have an immediate family member who had been diagnosed with lung cancer (p=0.095, Table 4-16).

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

	Cases		Controls		Significance
	n	%	n	%	(Chi square)
Family member with lung cancer*					0.095
No	124	87	382	92	
Yes	18	13	33	8	
Total	142	100	415	100	

** Direct blood related family member – parent or sibling only*

4.3. Bivariate Analysis

The bivariate analysis was undertaken to determine factors for the final logistic regression model. The bivariate analysis investigates the relationship between each study factor in isolation with the study outcome (lung cancer). The OR for each variable was calculated after adjustment for matching; those with $p \leq 0.1$ were considered eligible factors for the final model.

4.3.1. Subject Demographics

After adjustment for matching, age and gender were not associated with an increase in lung cancer risk (Table 4-17). This is to be expected as this was a matched case control study where controls were matched to cases by gender and 5 year age band. Age and gender will not be used as factors in the final multivariate analysis.

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

Sample size – n=142 (cases), 415 (controls)
Bold text indicates p £ 0.1

Variable	OR	SE	95% CI	Significance (conditional logistic regression)
Age (yrs)	0.96	0.04	0.88-1.10	0.37
Gender				
Female	1.0			
Male	1.42	1.30	.24-8.48	0.70

4.3.2. Socio-economic Status

Leaving school when aged 14 years or less, finishing secondary school, and not earning a qualification beyond a secondary school or a trade certificate are associated with an increased risk of lung cancer (Table 4-18). As determined by these 3 factors, low socioeconomic status increases lung cancer risk. As discussed in 1.3.1, age left school is the more valid measure of SES for this study and hence will be representing SES in the multivariate analysis.

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

Sample size – n=142 (cases), 415 (controls)

Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
Age left school			
>14 years	1.0		
14-15 years	**1.58**	**0.96-2.60**	**0.070**
<14 years	**2.12**	**1.18-3.81**	**0.012**
Highest level of SS reached			
No	1.0		
Yes	**0.59**	**0.37-0.96**	**0.035**
Highest qualification			
Secondary school or less	1.0		
Trade certificate	0.83	0.50-1.38	0.477
Other qualification	**0.44**	**0.23-0.83**	**0.011**

4.3.3. Residential Exposure

Table 4-19 indicates a high residential exposure score (a function of distance from industry, downwind frequency and duration of residence) for each of the industry considered, and for the composite residential exposure score (sum of scores for each industry) are significantly negatively associated with lung cancer development. Therefore each of the individual residential exposure scores and composite score are eligible factors for the final multivariate analysis.

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

Sample size – n=142 (cases), 415 (controls),

Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
ABC			
<1.0	1.0		
1.0-1.4	**0.59**	**0.34-1.05**	**0.072**
1.5-2.9	**0.64**	**0.37-1.08**	**0.096**
3.0+	**0.59**	**0.35-0.99**	**0.045**
CSR			
<1.0	1.0		
1.0-1.4	0.75	0.44-1.30	0.304
1.5-2.9	**0.51**	**0.29-0.91**	**0.022**
3.0+	0.67	0.41-1.11	0.118
PSP			
<1.0	1.0		
1.0-1.4	0.71	0.39-1.27	0.247
1.5-2.9	0.99	0.55-1.75	0.960
3.0+	**0.58**	**0.32-1.05**	**0.071**

Variable	OR	95% CI	Significance (conditional logistic regression)
Hardies			
<1.0	1.0		
1.0-1.4	0.76	0.43-1.33	0.336
1.5-2.9	**0.54**	**0.30-0.96**	**0.037**
3.0+	0.82	0.49-1.37	0.446
Pwr St			
<1.0	1.0		
1.0-1.4	0.66	0.37-1.16	0.145
1.5-2.9	0.93	0.57-1.51	0.773
3.0+	**0.39**	**0.19-0.80**	**0.010**
Fins			
<1.0	1.0		
1.0-1.4	0.63	0.35-1.13	0.120
1.5-2.9	**0.64**	**0.39-1.07**	**0.087**
3.0+	0.84	0.50-1.43	0.522

Variable	OR	95% CI	Significance (conditional logistic regression)
All industry[†]			
<6.0	1.0		
6.0-7.9	0.94	0.53-1.66	0.828
8.0-17.9	0.80	0.49-1.29	0.359
>18.0	**0.57**	**0.33-1.00**	**0.050**

[#] *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

** Key to Industry names: ABC – Adelaide Brighton Cement, CSR - Sugar Refinery, PSP – Penrice Soda Products, Hardies – James Hardies Asbestos Products, Pwr St – Torrens Island Power Station, Fins – Finsbury industrial suburb. For map of industry location see Figure 1-1*

[†] *All industry is a composite score comprising the sum of the residential score for each industry*

Exposure to industry during periods of residence outside of the study area (defined as duration of residence in a suburb that also contains industry licensed to emit airborne pollutants) is not a significant risk factor for lung cancer and hence is not an eligible candidate for the final multivariate model (Table 4-20).

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

Sample size – n=142 (cases), 415 (controls)

Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
No exposure	1.0		
≤ 10 yrs	0.82	0.50-1.34	0.43
>10 yrs	0.99	0.62-1.57	0.93

** Residential exposure outside of the NW of Adelaide is defined as the numbers of years spent residing within Australia in the same suburb as an industry licensed by local environmental protection authorities to emit airborne pollutants.*

4.3.4. Cigarette Smoking

The OR's for all measures of direct smoking were significantly elevated in an exponential dose response manner (Table 4-21). This indicates an increase risk of lung cancer with increased duration and consumption of cigarettes. The only diversion from the dose response relationship was in those smoking 10 to 19 pack years, where the OR was not significantly elevated.

Pack years of cigarette smoking is conventionally used to quantify cigarette smoking and takes into consideration both duration and consumption of cigarettes. Hence pack years will be used to represent cigarette smoking in the final multivariate analysis.

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

Sample size – n=142 (cases), 415 (controls,)Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
Duration (yrs)			
Nonsmoker	1.0		
<31	**2.77**	**1.15-6.67**	**0.023**
31-48	**8.47**	**3.72-19.27**	**0.000**
48+	**29.84**	**12.44-71.62**	**0.000**
Ave cigs/day			
Nonsmoker	1.0		
<11	**2.82**	**1.43-5.56**	**0.003**
11- 20	**4.69**	**2.51-8.77**	**0.000**
21+	**6.36**	**3.32-12.17**	**0.000**
Pack yrs			
Nonsmoker	1.0		
<10	**2.43**	**1.06-5.55**	**0.035**
10-19	1.69	0.07-4.05	0.243
20-29	**3.43**	**1.59-7.44**	**0.002**
30-39	**6.33**	**2.83-14.16**	**<0.001**
40+	**8.46**	**4.39-16.30**	**<0.001**

4.3.5. Environmental Tobacco Smoke (ETS)

The OR for exposure to ETS at work for between 21 and 39 years (inclusive) was the only ETS variable with $p<0.1$ ($p=0.067$) and hence is the only eligible factor for the final multivariate analysis (Table 4-22).

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

Sample size – n=142 (cases), 415 (controls)

Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
ETS at home (yrs)			
0 years	1.00		
<20 years	0.81	0.38-1.73	0.594
20-39 years	0.79	0.41-1.51	0.478
40+ years	1.63	0.87-3.05	0.129
ETS at work (yrs)			
0 years	1.0		
<21 years	0.77	0.45-1.34	0.364
21 -39 years	**0.58**	**0.32-1.04**	**0.067**
40+ years	0.90	0.50-1.63	0.739

4.3.6. Occupational Exposure to Lung Carcinogens

Probable or possible occupational exposure to asbestos, formaldehyde, PAH, diesel exhaust or PM2.5 for greater than 1 year does not significantly elevate lung cancer risk (Table 4-23). However crystalline silica exposure for greater than or equal to 1 year does elevate risk of lung cancer ($p \leq 0.1$), so is an eligible factor for the final multivariate analysis.

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

Sample size – n=142 (cases), 415 (controls)
Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
Asbestos			
0 years	1.0		
1+ years	0.80	0.52-1.23	0.310
Crystalline Silica			
0 years	**1.0**		
1+ years	**1.45**	**0.93-2.26**	**0.097**
Formaldehyde			
0 years	1.0		
1+ years	0.95	0.58-1.56	0.849

Variable	OR	95% CI	Significance (conditional logistic regression)
PAH			
0 years	1.0		
1+ years	0.73	0.47-1.14	0.162
Diesel exhaust			
0 years	1.0		
1+ years	1.06	0.67-1.67	0.812
PM2.5			
0 years	1.0		
1+ years	0.73	0.41-1.30	0.282

4.3.7. Hobbies

Duration of participation in pottery as a hobby was associated with a significantly elevated risk of lung cancer ($p = 0.013$, Table 4-24). There is a trend towards a protective effect of duration of hobby participation in house renovations for lung cancer ($p = 0.053$). Participation in mechanical related hobbies has no effect on lung cancer risk. Hence only duration of participation in pottery and house renovations are eligible for the final multivariate model.

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

Sample size – n=142 (cases), 415 (controls)

Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
Mechanical			
No	1.0		
Yes	1.06	0.58-1.94	0.852
Pottery			
No	**1.0**		
Yes	**4.84**	**1.40-16.68**	**0.013**
Renovations			
No	**1.0**		
Yes	**0.63**	**0.39-1.01**	**0.053**

4.3.8. Family History of Lung Cancer

Lung cancer risk is not significantly elevated by one or more immediate family members (sibling or parent) having been diagnosed with lung cancer, hence family history is not an eligible factor for the final analysis (Table 4-25).

Table 4-25: Bivariate Analysis - Odds Ratio for the Number of Family Members* who have been Diagnosed with Lung Cancer with Adjustment for Matching

Sample size – n=142 (cases), 415 (controls)
Bold text indicates p £ 0.1

Variable	OR	95% CI	Significance (conditional logistic regression)
Family history			
No	1.0		
Yes	1.58	0.35-1.16	0.140

** A family member is defined as a direct blood relative – either parent or sibling.*

4.4. Multivariate Analysis

Factors with $p \leq 0.1$ in the bivariate analysis were systematically entered into a logistic regression model. As per the bivariate analysis, data was categorised. A multivariate model was run for residential exposure to each of the 6 industry and the composite scores, each with the potential confounders identified in the bivariate analysis. In the following tables a factor with OR significantly greater than 1 is associated with an elevated risk of lung cancer. A map providing the location of each of the 6 industries can be found in Figure 1-1.

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.54	1.08-5.97	0.033
10-19	1.69	0.69-4.15	0.253
20-29	3.06	1.36-6.91	0.007
30-39	7.50	3.15-17.82	<0.001
40+	9.18	4.56-18.49	<0.001
Age left school			
>14 years	1.00		
14 years	1.67	0.96-2.92	0.070
<14 years	2.30	1.17-4.53	0.016
Residential exposure			
<1.0	1.00		
1.0-1.4	0.56	0.29-1.07	0.079
1.5-2.9	0.78	0.43-1.43	0.422
3.0+	0.56	0.31-1.02	0.059

* *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.32	0.99-5.44	0.053
10-19	1.72	0.70-4.21	0.235
20-29	3.01	1.34-6.77	0.008
30-39	6.99	2.97-16.44	<0.001
40+	8.65	4.35-17.20	<0.001
Age left school			
>14 years	1.00		
14 years	1.64	0.94-2.87	0.081
<14 years	2.35	1.20-4.59	0.013
Residential exposure			
<1.0	1.00		
1.0-1.4	0.80	0.43-1.49	0.475
1.5-2.9	0.59	0.31-1.13	0.110
3.0+	0.69	0.39-1.23	0.211

* *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls), Bold indicates residential exposure p≤0.05

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.39	1.03-5.59	0.044
10-19	1.71	0.69-4.25	0.250
20-29	3.18	1.43-7.11	0.005
30-39	7.37	3.08-17.60	<0.001
40+	9.25	4.62-18.55	<0.001
Age left school			
>14 years	1.00		
14 years	1.76	1.00-3.11	0.051
<14 years	2.52	1.29-4.95	0.007
Residential exposure			
<1.0	1.00		
1.0-1.4	**0.47**	**0.24-0.94**	**0.034**
1.5-2.9	0.64	0.36-1.15	0.139
3.0+	0.77	0.42-1.41	0.388

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.32	0.989-5.47	0.053
10-19	1.70	0.69-4.20	0.249
20-29	2.98	1.33-6.71	0.008
30-39	7.18	3.03-17.02	<0.001
40+	8.81	4.37-17.76	<0.001
Age left school			
>14 years	1.00		
14 years	1.68	0.96-2.92	0.068
<14 years	2.46	1.26-4.82	0.008
Residential exposure			
<1.0	1.00		
1.0-1.4	.99	0.50-1.92	0.965
1.5-2.9	.92	0.48-1.77	0.797
3.0+	.66	0.34-1.27	0.213

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.36	1.01-5.52	0.047
10-19	1.71	0.70-4.18	0.241
20-29	3.03	1.35-6.79	0.007
30-39	7.10	3.02-16.71	<0.001
40+	8.40	4.22-16.71	<0.001
Age left school			
>14 years	1.00		
14 years	1.65	0.95-2.88	0.074
<14 years	2.32	1.19-4.54	0.014
Residential exposure			
<1.0	1.00		
1.0-1.4	0.80	0.41-1.56	0.515
1.5-2.9	0.65	0.35-1.23	0.186
3.0+	0.87	0.48-1.56	0.633

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls), Bold indicates residential exposure p≤0.05

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.43	1.02-5.76	0.043
10-19	1.53	0.61-3.84	0.363
20-29	3.28	1.45-7.38	0.004
30-39	7.36	3.09-17.52	<0.001
40+	8.86	4.39-17.87	<0.001
Age left school			
>14 years	1.00		
14 years	1.63	0.93-2.85	0.085
<14 years	2.45	1.24-4.83	0.009
Residential exposure			
<1.0	1.00		
1.0-1.4	0.64	0.34-1.23	0.179
1.5-2.9	1.04	0.59-1.81	0.897
3.0+	**0.37**	**0.16-0.83**	**0.016**

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.43	1.03-5.69	0.042
10-19	1.70	0.69-4.22	0.249
20-29	2.98	1.33-6.67	0.008
30-39	7.36	3.11-17.40	<0.001
40+	9.13	4.54-18.34	<0.001
Age left school			
>14 years	1.00		
14 years	1. 73	0.99-3.02	0.056
<14 years	2.53	1.28-4.98	0.007
Residential exposure			
<1.0	1.00		
<6.0	1.00	0.51-1.92	0.992
6.0 – 7.9	0.86	0.49-1.51	0.602
8.0 – 17.9	0.53	0.28-1.01	0.054

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

† The composite score is the sum of the residential exposure score to each industry

The final model is represented by Table 4-28 and Table 4-31. Pack years of cigarette smoking and age left school are significant positive risk factors for lung cancer. Residential exposure (a function of distance from industry, downwind frequency and duration of residence) to both the Power Station and Finsbury were significantly negatively associated with lung cancer for exposure scores greater than or equal to 3, or 1 to 1.4 respectively. Throughout each model 10 to 19 pack years of cigarette smoking lacked a significant association with lung cancer, even through surrounding categories formed a dose response relationship.

4.5. Post hoc Analysis

Due to participating controls living closer to industry than non participating controls we decided, post hoc, to investigate the effect of adjusting control residential scores to compensate for response bias.

The mean distance from each industry was calculated as the average residential distance from industry for all control subjects approached at the time of recruitment. We then calculated the percent difference between this mean and the distance from each industry for participating subjects as follows:

$$\text{Percentage change} = \frac{100\,(D_{(m)} - D_{(p)})}{D_{(p)}}$$

Where – $D_{(p)}$ = Distance participating controls live from industry

$D_{(m)}$ = Mean distance from industry for participating and non participating controls

This percentage change was then used to adjust the distance from industry for all residential addresses for control subjects from each respective industry, and the adjusted distance then used in the residential exposure equations to derive an adjusted exposure score.

4.5.1. Post hoc Multivariate Analysis

Table 4-33 to Table 4-39 are the results of the multivariate analysis using an adjusted residential exposure score for each industry and the composite score. In each table an OR greater the 1 is associated with an elevated risk of lung cancer.

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.41	1.03-5.65	0.042
10-19	1.72	0.70-4.21	0.236
20-29	3.11	1.38-6.99	0.006
30-39	7.28	3.10-17.13	<0.001
40+	8.85	4.44-17.64	<0.001
Age left school			
>14 years	1.00		
14 years	1.66	0.96-2.89	0.071
<14 years	2.41	1.23-4.71	0.010
Residential exposure			
<1.0	1.00		
1.0-1.4	0.81	0.43-1.54	0.526
1.5-2.9	0.95	0.52-1.72	0.862
3.0+	0.76	0.41-1.38	0.364

***** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.27	0.97-5.32	0.060
10-19	1.72	0.70-4.22	0.233
20-29	3.04	1.35-6.83	0.007
30-39	7.08	3.01-16.64	<0.001
40+	8.62	4.34-17.13	<0.001
Age left school			
>14 years	1.00		
14 years	1.64	0.94-2.87	0.081
<14 years	2.36	1.21-4.61	0.012
Residential exposure			
<1.0	1.00		
1.0-1.4	0.92	0.49-1.72	0.795
1.5-2.9	0.70	0.37-1.32	0.270
3.0+	0.83	0.47-1.47	0.521

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.34	1.00-5.51	0.051
10-19	1.67	0.67-4.15	0.272
20-29	3.09	1.38-6.89	0.006
30-39	7.99	3.31-19.29	<0.001
40+	9.01	4.48-18.10	<0.001
Age left school			
>14 years	1.00		
14 years	1.80	1.02-3.18	0.044
<14 years	2.60	1.32-5.15	0.006
Residential exposure			
<1.0	1.00		
1.0-1.4	0.71	0.34-1.46	0.346
1.5-2.9	0.48	0.26-0.86	0.014
3.0+	0.59	0.32-1.07	0.084

***** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)

Table 4-36: Post hoc Multivariate Analysis - Significant Factors (p≤0.05) and Adjusted Residential Exposure* to James Hardies

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.38	1.02-5.54	0.044
10-19	1.71	0.70-4.19	0.239
20-29	3.06	1.37-6.84	0.006
30-39	7.25	3.08-17.04	<0.001
40+	8.60	4.32-17.13	<0.001
Age left school			
>14 years	1.00		
14 years	1.67	0.96-2.90	0.068
<14 years	2.40	1.23-4.69	0.010
Residential exposure			
<1.0	1.00		
1.0-1.4	0.94	0.49-1.82	0.858
1.5-2.9	0.80	0.42-1.52	0.497
3.0+	0.96	0.53-1.73	0.893

** Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

Table 4-37: Post hoc Multivariate Analysis - Significant Factors (p≤0.05) and Adjusted Residential Exposure* to Penrice Soda Products

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.39	1.02-5.64	0.046
10-19	1.74	0.70-4.30	0.231
20-29	3.08	1.36-6.95	0.007
30-39	7.36	3.11-17.38	<0.001
40+	9.06	4.48-18.29	<0.001
Age left school			
>14 years	1.00		
14 years	1.68	0.97-2.93	0.066
<14 years	2.48	1.27-4.84	0.008
Residential exposure			
<1.0	1.00		
1.0-1.4	1.14	0.58-2.25	0.700
1.5-2.9	0.91	0.47-1.74	0.768
3.0+	0.69	0.35-1.34	0.269

* *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.46	1.04-5.83	0.041
10-19	1.57	0.63-3.94	0.332
20-29	3.25	1.44-7.33	0.004
30-39	7.40	3.10-17.65	<0.001
40+	8.92	4.42-18.02	<0.001
Age left school			
>14 years	1.00		
14 years	1.64	0.94-2.86	0.082
<14 years	2.43	1.24-4.77	0.010
Residential exposure			
<1.0	1.00		
1.0-1.4	0.62	0.33-1.18	0.146
1.5-2.9	1.02	0.58-1.77	0.951
3.0+	0.38	0.17-0.88	0.023

* *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

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

Sample size – n=142 (cases), 415 (controls)

Variable	OR	95% CI	Significance
Cigarette smoking (pack yrs)			
0	1.00		
<10	2.39	1.02-5.60	0.045
10-19	1.81	0.73-4.46	0.199
20-29	3.00	1.33-6.73	0.008
30-39	7.34	3.10-17.35	<0.001
40+	9.21	4.59-18.48	<0.001
Age left school			
>14 years	1.00		
14 years	1.72	0.98-3.00	0.059
<14 years	2.56	1.30-5.04	0.007
Residential exposure			
<1.0	1.00		
<6.0	1.37	0.71-2.63	0.343
6.0 – 7.9	0.82	0.47-1.42	0.483
8.0 – 17.9	0.62	0.33-1.18	0.147

* *Residential Score is the modified Gaussian plumage modelling equation: Residential score = Duration of residence (yrs) * Downwind frequency / Distance (km) * (2π/16)*

† The composite score is the sum of the residential exposure score to each industry

Adjusting the residential exposure scores for each industry and composite score to compensate post hoc for potential response bias did not alter the significant results in the final multivariate model. Residential exposure to Finsbury and the Power Station remained significantly negatively associated with lung cancer, and pack years of cigarette smoking and age left school positively associated.

4.6. Air Quality Monitoring

Table 4-40 illustrates the ambient air concentrations of the carcinogens under investigation. The only detectable asbestos was found at Site 4 (busy metropolitan traffic intersection), all other values being less than the detection limit for the SEM method and well below the 8 hour occupational exposure standard (no community standard available). Similarly, respirable crystalline silica levels were less than the limit of detection using infrared spectroscopy. However, when particles greater than 0.5 microns were examined using SEM, the highest values of crystalline silica (quartz) were found at Sites 1 and 2 (in close proximity to industrial sites). Formaldehyde levels were well below national and international criteria. Concentrations of PAH including naphthalene were very low and in particular benzo-a-pyrene was not detected in any of the samples. Acenaphthene, fluorene, phenanthrene, benz(a)anthracene and chrysene were detected in small amounts. Apart from naphthalene, no PAH's were detected at the control site (5). As expected, the diesel exhaust particulates concentrations as expressed as elemental carbon were higher at sites 3 and 4, reflecting the higher density of diesel powered vehicle traffic.

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

Substance	Units	Site						Standard
		1	2	3	4	5 (Control)	EPA reference site	
Asbestos[a]	fibres/ml	<0.0002	<0.0002	<0.0002	0.00035	<0.0002		0.1[b]
Crystalline Silica[a]	µg/m^3 [c]	<0.5	<0.5	<0.5	<0.5	<0.5		200[b]
	particles/m^3 [d,e]	52709	29934	14069	17744	12821		
Formaldeyde[f]	µg/m^3	5.1	3.8	4.2	2.3	3		100[g]
								18[h]
PAH[f]:								
Naphthalene	µg/m^3	0.25	0.24	0.74	0.55	0.19		
Higher order	µg/m^3	0.005	0.039	0.056	0.027	<0.001		[i]

Substance	Units	Site						Standard
		1	2	3	4	5 (Control)	EPA reference site	
Diesel Exhaust particulate[f,j]	µg/m^3	0.8	0.44	1.82	2.06	0.27		[k]
PM2.5	µg/m^3 [l,n]	7.6					6.3	25 [m]
	µg/m^3 [f,p]	10.1 (9.0-11.0)	14.3 (11.8 – 16.3)	[q]	11.7 (8.6-20.1)	8.1 (6.6-13.1)		
	µg/m^3 [r]		12					
	µg/m^3 [s]	15.2	15.4					

Legend

a	Averaged over 4 days (25/2 to 1/3/02)
b	Occupational Exposure Standard
c	By infrared spectroscopy
d	By scanning electron microscopy
e	Particles greater than 0.5 um size
f	Averaged over 4 days (11/3 to 15/3/02)
g	WHO Goal 30 minute average
h	NEPM 24 hr average
i	Proposed NEPM is 0.3 ng/m3 for benzo(a)pyrene as an annual average
j	Elemental carbon
k	NEPM emission guidelines only
l	TEOM average of 2 days 14 and 15 March 2002
m	NEPM Goal 25 ug/m3 daily average, 8 ug/m3 annual average
p	Dust Trak average of 4 days (min - max)
q	No measurements
r	Dust Trak 14 March 2001
s	Dust Trak 15 March 2001

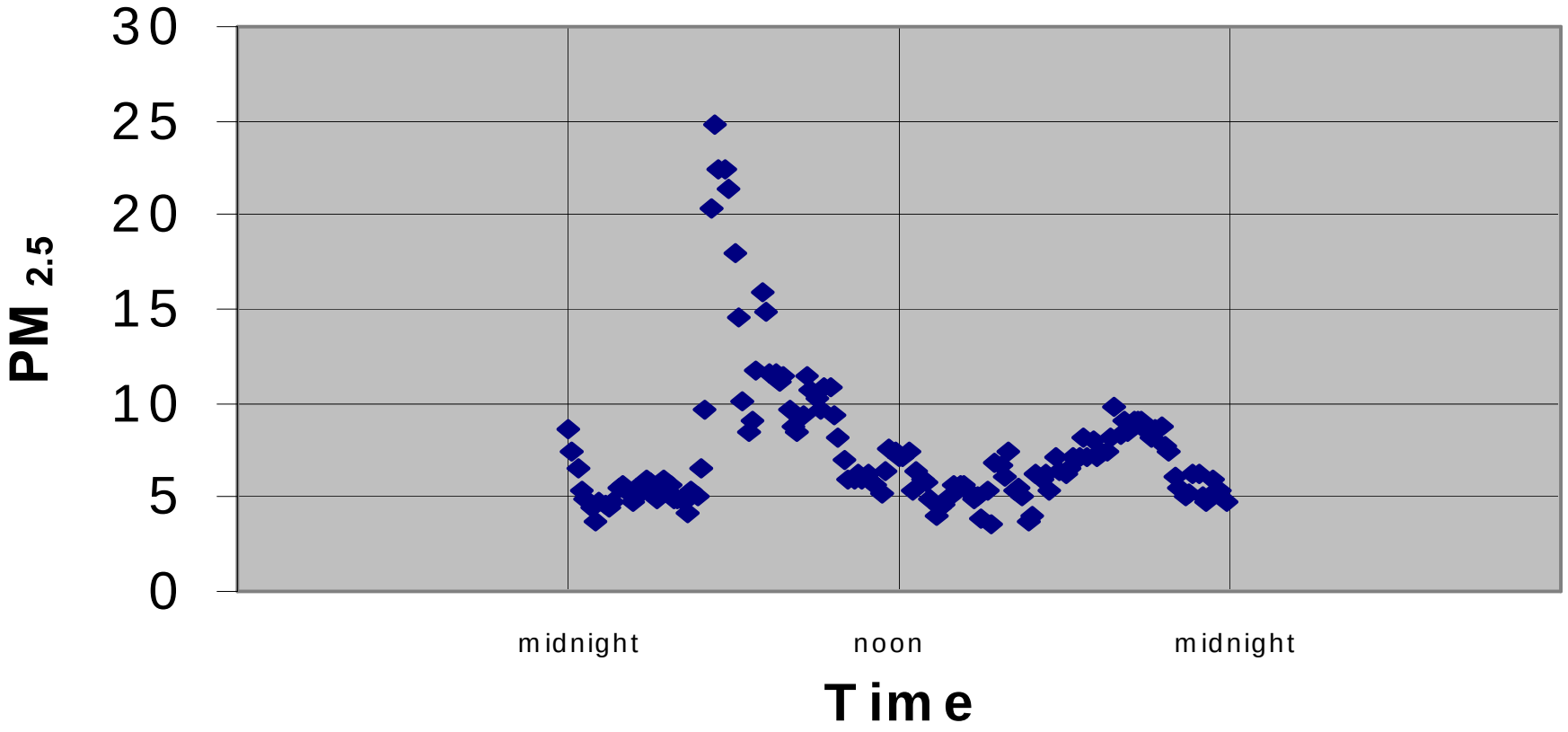
With regard to $PM_{2.5}$, the measured concentrations did not exceed the proposed 24-hour National Environmental Protection Measure[35] of 25μg/m^3. The highest 4 day average was found at site 2 (industrial). Average Dust Trak™ data for site 1 are somewhat higher than TEOM data, although there was a strong temporal correlation. Site 1 TEOM results were similar to that of an EPA reference site.

Diurnal variation of $PM_{2.5}$ was monitored and it was found that peaks often occurred early morning and late afternoon, and in some cases late evening (Figure 4-3 for a typical profile). All of the recorded peaks were less than 100μg/m^3, as a 1 minute average.

Ultrafine particulate concentrations were generally low (typically 15 000 particles per cm^3), and were highly reflective of diesel vehicle traffic. By comparison, site 3 (adjacent to a bus depot) had elevated concentrations, averaging 47 000 particles per cm^3, and ultrafine particles in the central business district of Adelaide averaged 50 000 particles per cm^3, potentially due to a combination of topography (high rise buildings) and vehicle density.

Dusts deposited on filters collected at each site were subjected to SEM. It was found that they constituted mainly aluminosilicates, calcite and gypsum (each higher at Sites 1 and 2), halite and other common soil minerals.

Figure 4-3: PM2.5 Diurnal Variation, example from Site 1



5. Chapter 5 Discussion

High lung cancer incidence and mortality in regions shared by residential homes and industry is a worldwide concern. The high standardised mortality ratio for lung cancer in the North West of metropolitan Adelaide has been well documented in the South Australian Social Health Atlas using data collected by the South Australian Cancer Registry[1]. For many years the local community in the North West of Adelaide have formed action groups to lobby against local industry operating in close proximity to residential areas, implicating the industrial airborne emissions for the high prevalence of respiratory health problems (for example asthma, bronchitis, lung cancer). It was this combination of cancer surveillance data and community concern that prompted the current case control study.

This study has demonstrated that the high lung cancer mortality in North West metropolitan Adelaide is primarily due to cigarette smoking, with an exponential dose response relationship demonstrated. This dose response was evident for each category of pack years (in 10 year increments up to greater than or equal to 40 pack years) however between 10 and 19 pack years lacked a significant association with lung cancer and did not follow the dose response pattern. The high lung cancer mortality is also partially explained by socioeconomic status (SES), as quantified by age left school (in categories of greater than, equal to or less than 14 years, with the younger age an indication of low socioeconomic status). The relationship of residential exposure with airborne carcinogens was investigated using a modified Gaussian plume equation to quantify exposure due to proximity to polluting industry. Six industries located within the study area (NW Adelaide, postcode 5007 to 5023) were selected on the basis of their likelihood for respiratory carcinogenic emissions during the time period relevant to current lung cancer

cases. An association was not found between lung cancer and residential exposure to 4 of the 6 industries investigated (2 cement manufacturers – crystalline silica emissions, 1 asbestos manufacturer – asbestos emissions, 1 soda product manufacturer – crystalline silica and particulate matter emissions). Both the 5th and 6th (power station – PAH emissions, and light industry cluster – PAH, diesel exhaust and particulate matter emissions) had a negative rather than positive association. A similar negative association has been previously reported[53], however there is a lack of biological plausibility for this result to truly be indicative of a protective effect.

The strong dose response evidence for cigarette smoking helps to confirm that this study was of strong design, thus adding credibility to the lack of association between residential exposure and lung cancer also found. In addition, a composite residential exposure score comprising the sum of exposure to each of the six industries was not significantly associated with lung cancer.

5.1. Limitations of the Case Control Study

Any retrospective study has inherent limitations, particularly the potential for response and recall bias, and exposure misclassification. The following is a description of the potential limitations of this study, and the methods employed to minimise their impact.

5.1.1. Bias

This study had a relatively low participation rate for both cases (56%) and controls (47%). This is a possibly limiting factor if participating subjects differ from non-participating (contactable however declined to take part) for the lung cancer risk factors and confounders assessed. The analysis demonstrated that of the risk factors that could be measured in non participating cases and controls (age, gender, proximity of industry from current address), the only differing factor was that at the time of recruitment non participating controls resided further from one of the selected industries than participants controls and closer to another (participants were 0.665km closer to a cement manufacturer and 1.567km further from the light industry cluster). The inverse result for these two industries is reflective of their geographic location; the cement manufacturer is closer to the Port River and other industry than the light industry cluster. The difference in participation can potentially be attributed to people residing closer to industry having greater concerns for its health implications, and hence wanting to assist with research investigating it. This differential participation means that the control sample may not have been representative of the study population, as it is biased towards members of the population living in close proximity to industry. However when the data was reanalysed to only look at the closest industry to the current address of each potential control, there was no significant difference between participants and non participants.

Post hoc, control residential exposure was adjusted for the difference in distance from industry (see Chapter 4 for detailed description of the adjustment). Whilst this is not a valid or tested method, the adjustment was likely to provide some insight into the effect of the participation bias on the residential exposure result. The adjustment did not alter the significance of residential exposure in the multivariate model; perhaps, but not conclusively, indicating response bias had a minimal role in the final study results.

Limitation of recall and recall bias are both innate problems with retrospective studies. We attempted to reduce problems of recall inaccuracy with rigorous data collection methodology. All subjects underwent a structured interview using a questionnaire derived from those previously used and tested for reliability and validity, delivered using a standardised approach regardless of case or control status. As discussed in Chapter 2, an event history calendar format was used for the interview, a method proven to improve subject recall of lifetime events[96].

The Next of Kin (NOK) of deceased lung cancer patients participated in 56% of case interviews. Deceased controls were not matched to deceased cases, hence NOK controls were not utilised in interviews. The use of surrogate historical information in retrospective studies and its potential to give rise to recall bias has been previously described (Ch 2). Therefore, five participating control subjects were sampled to determine the extent of difference in recall between subjects and their NOK using the questionnaire, finding good to excellent agreement for smoking, occupation and residence. This result indicates it is unlikely that matching deceased controls to deceased cases would have altered the case control study results.

5.1.2. Misclassification

5.1.2.1. Subject Misclassification

A strict definition of both cases and controls was enforced for this study to avoid misclassification of subjects. Cases were sourced from the South Australian Cancer Registry or the local hospital (hospital case diagnosis was later confirmed with the cancer registry). To be listed on the registry the lung cancer must be a primary cancer diagnosis, with approximately 95% of these diagnosed histologically. This registry is one of the most current, accurate and thorough in Australia due to compulsory reporting by pathology laboratories, medical records departments of hospitals, radiotherapy departments, oncologists and Births, Deaths and Marriages[76]. Cases reported from death certificate only are followed up for diagnosis confirmation. Use of randomly selected population rather than hospital or friend based controls meant the sample had the greatest chance of being representative of the population base, and also meant each control was eligible to be a case had they been diagnosed with primary lung cancer.

5.1.2.2. Exposure Misclassification

Exposure misclassification can occur in retrospective case control studies if subjects provide incorrect information about their history of exposure, or the risk factor is incorrectly assessed or quantified. There was potential for misclassification for all risk factors investigated in this study.

The likelihood of misclassification due to poor subject recall was reduced by adopting an event history calendar to form the core structure of the questionnaire. Event history calendars have been demonstrated to increase recall accuracy by linking important and incidental lifetime events to those related to study risk factors[96]. Previous lung cancer

case control studies of this nature have not used this method, instead using a standard method with stand-alone questions regarding each risk factor or confounder in isolation.

For each risk factor investigated in this study the literature was reviewed for the most valid method of exposure assessment. This process was described in detail in the methods chapter (Ch 3). For each risk factor the method of assessment considered to be the "gold standard", or estimated to be the closest to the gold standard when one had not been identified (or in the case of residential exposure, required historical measures of air quality) was utilised.

Quantification of the risk factors cigarette smoking, environmental tobacco smoke exposure, lung carcinogen exposure due to hobby participation, family history of lung cancer, and socioeconomic status all involved mathematically transformation of data collected from subjects. Therefore exposure quantification was unlikely to be a potential source of non-differential misclassification for these risk factors (however the initial subject recall prior to quantification may still have been a source of misclassification).

An additional source of misclassification may have been introduced in the process of entering collected data into the database. This potential misclassification was reduced by using a series of Microsoft Access forms to enter data with entry criteria where appropriate, and by conducting a thorough data cleaning process at the conclusion of data entry prior to analysis.

5.1.2.3. Environmental exposure misclassification

Proximity to industry, frequency of time downwind of industry and years of residence were utilised in a modified Gaussian equation as a surrogate measure of airborne carcinogen exposure (residential exposure). Gaussian plume dispersion models are commonly used to calculate ground level pollutant concentrations for a variety of research purposes. The model is known for its relative simplicity[99]. A modified Gaussian model was used to represent the relationship between distance from industry and pollution concentration, and it was inserted into a simple model for pollution concentration (exposure = duration/distance measure) used in an epidemiological study similar to ours[48]. This method of modelling, whilst less accurate than directly measuring air quality exposure, has been deemed an acceptable proxy for long term local air quality monitoring for epidemiological studies, particularly for retrospective exposure assessment[72 97]. Three previous epidemiological studies have validated their exposure equations against ambient monitoring of copper and arsenic[72], nitrogen dioxide and benzene[97] (both using exposure = 1/distance from source), and sulphur dioxide[98] (using exposure = 1/distance*(2π/16)). In all three cases the equations were found to be good predictors of their respective ambient concentrations, hence the equation is unlikely to be a source of misclassification in this study.

It is possible that misclassification may have occurred due to differential recall of previous residence by subjects. This possibility was minimised by use of lifetime history calendars for data collection, and using government records to determine local industry rather than relying on subject recall of nearby industry.

Residential exposure within Australia but outside of the study area was classified using a government-supplied list of currently licensed industries from which those likely to emit respiratory carcinogens were identified. Due to government methods of data storage access to historical lists of industry were unavailable. Subjects were classified as exposed if they resided in the same suburb as a licensed industry. This exposure was further quantified by duration of residence, with multiple exposure periods summed. This may be a source of misclassification due to the use of a contemporary industry list. It is likely that the number of industries has reduced over time due to many industries ceasing operation or reducing emissions due to tighter government regulations[27 28](changes in the number of industries in the study area is an example of this), hence the exposure methodology would have produced exposure scores either similar or lower than true exposure. The misclassification was unlikely to be different for cases and controls. An overall decrease in exposure scores for all subjects is unlikely to alter the magnitude or significance of the resulting OR.

5.1.2.4. Occupational exposure misclassification

A 1998 review of potential sources of occupational exposure misclassification in community-based studies[106] included a table of common sources of occupational exposure misclassification. A modified version of this table follows which includes the method employed by this case control study to overcome each potential misclassification (Table 5-1). As indicated in the table, each member of the hygiene panel reassessed 30 jobs selected at random to enable investigation of the reliability of their exposure assessments. The level of agreement between each individual panel member and each member with the consensus assessment was also assessed. The agreement between each individual panel member rating and the consensus rating was good for each of the carcinogens assessed

(Kappa statistic between 0.6 and 0.8[112]). This reflects that each of the panel members made equal contributions to the overall score that was used to adjust for occupational exposure in the case control study analysis. Moderate agreement was found when panel members reassessed exposure to a subgroup of 30 jobs. The Kappa results were affected by the lack of variation between exposure scores for each subject (the majority of jobs throughout the study were rated as “unlikely” to involve exposure to each of the carcinogens) that meant expected agreement was very high for each exposure assessment.

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

Adapted from - McGuire et al [106]

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Respondent	Omit a job title	Lower	None	Prepare subject prior to interview to think about their lifetime job history	Subjects either filled in 'part a' or were asked to think about and make notes of their employment history prior to interview
				Construct a personal time-line during interview which may jog the respondent's memory	Data was collected using an event history calendar, hence a timeline of their smoking habits, employment and residence was constructed during the interview

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Respondent *(continued)*	Falsely report a job title	None	Lower	If possible, validate job titles for jobs determined to be exposed by using company records or by contacting co-workers	This was not possible in this community based case control study as there were over 3000 different employers nationally and internationally
				Additional questioning of exposed subjects	Detail questioning on occupation tasks and duties were included in the questionnaire, not merely job title

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Respondent *(continued)*	Occupational information is incomplete or vague, dates of hire and termination are not exact	Lower	Lower	If possible, obtain detail from employer or co-worker on job tasks and dates of employment	It was not possible to obtain details from other sources due to the wide variety of employers. Poor recall of dates was instead reduced by using an event history calendar
				Have an industrial hygienist review incomplete records, without knowledge of disease status, and develop follow-up questions for respondents to clarify ambiguities	0.18% of jobs assessed by the hygiene panel could not be rated due to lack of information. In all cases the job information had been provided by NOK, hence there was no source for further questioning

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Respondent *(continued)*	Difficulty recalling exposures when open ended questions rather then prompts are used.	Lower	None	Provide cue cards or probes as memory aids	Exposure cue cards were not necessary, as subjects were only required to recall details of tasks and duties undertaken, not specific exposures. However, cue cards were provided for types of respiratory protection

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Interviewer	Inadequate training to administer a lifetime occupational history questionnaire	Lower	Lower	Consult an industrial hygienist during questionnaire development and interviewer training	Occupational hygienists were consulted during selection of risk factors, and questionnaire development and piloting
				Train interviewers in a standardized way to elicit and to transcribe information on job history	Interviewers underwent similar training on questioning subjects and recording data. Regular meetings were held to ensure the interviews were standardised
				Develop standardized probes to elicit detailed information for a given job title	The questionnaire used was highly structured and interviewers were instructed not to deviate from what was written

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Data Coding	Intra- and inter-coder agreement for coding job title and/or industry is poor	Lower	Lower	Develop specific coding rules for assignment of job title and industry codes Use a data-based method for assigning codes Use an uncertainty code if there is no appropriate job title and/or industry code Conduct intra- and inter-method reliability studies Conduct validation study of assigned codes	Occupations and industry were not assigned codes for this study. Coding was deemed unnecessary as a Job or Task Exposure Matrix was not used, and the panel of hygienists were not relying purely on job title and industry to assess exposure (due to information on tasks and duties also being available).

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Data Coding *(continued)*	Information from occupational history is too vague to allow coding of job title and industry	Lower	Lower	Obtain more detail on employer, job tasks, products manufactured Identify job titles and/or industries where codes are assigned with uncertainty	As above
	Job title and/or industry codes have heterogeneous exposure	None	Lower	Assign new codes for job titles and/or industry to construct more homogeneous groups	

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Exposure Assessment	Job title falsely classified as exposed	None	Lower	Have exposure for job title assigned independently by two or more industrial hygienists	3 hygienists independently assessed exposure for each subject occupation, and then reached a consensus decision on exposure at a meeting. Agreement between each panel member and the consensus decision was good (Kappa statistic 0.6 to 0.8).

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Exposure Assessment *(continued)*	Job title falsely classified as exposed *(continued)*	None	Lower	If possible, validate exposure for jobs classified as exposed	Validation was not possible in this community based study, but false classification of exposure was reduced by collecting detailed occupational data from each subject

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Exposure Assessment *(continued)*	Job title falsely classified as unexposed	Lower	None	Have exposure for job title assigned independently by two or more industrial hygienists	3 hygienists independently assessed exposure for each subject occupation, and then reached a consensus decision on exposure at a meeting. Agreement between each panel member and the consensus decision was good (Kappa statistic 0.6 to 0.8).

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Exposure Assessment *(continued)*	Job title falsely classified as unexposed *(continued)*	Lower	None	Use bibliographic data sources and consultation with other experts to enhance hygienists' knowledge of exposures	Each hygienists reviewed the literature (including web sites, peer-reviewed journals, exposure guidelines and books) when in doubt about exposure for a particular job. This literature was then shared with the group

Source of Error	Cause of error	Effect on:		Methods suggested to reduce bias	Methods employed in this study
		Sensitivity	Specificity		
Exposure Assessment *(continued)*	Exposure assignment for job title is arbitrary	Lower	Lower	Assign level of uncertainty to exposure classification (for industrial hygienist rating) or assign probability of exposure (JEMs)	Collecting detailed job information at interview reduced the risk of arbitrary assignment. Also panel members were able to assign the exposure probability score of 'possible' when uncertain of the exact level of exposure

5.1.3. Significance of limitations on results

To induce a false negative or false positive result, bias or misclassification in the case control study needs to have a differential effect in cases and controls. In this study the only limitations to have clearly differential outcome were the response bias in control subjects (there was no difference in residential proximity to industry between participating and non participating cases) and the potential recall bias from use of NOK in case interviews but not controls.

The comparison of participating and non-participating controls indicated that the control group contained an overrepresentation of people living close to the six key industries previously identified, potentially resulting in higher median residential exposure scores in the control sample than that of the North West population (the study area). Had cases been exposed to more air pollution than controls (as hypothesised), this overrepresentation and hence potentially elevated residential exposure score in controls would have reduced the absolute difference between control and case exposure scores. This in turn would have reduced this likelihood of generating an Odds Ratio significantly greater than 1 in the analysis, and induced a false negative result. Controls in our study were significantly more likely to have been exposed to the power station than cases after adjusting for confounders, potentially as a result of the participation bias. However, as the residential exposure scores comprised the distance from industry and time downwind for each address the subject had resided in, the effect of the response bias would have been minimised for subjects with multiple addresses. Other hypothesis for this result will be discussed in Section 5.2.

The recall bias incurred due to use of NOK for cases could potentially have resulted in cases receiving lower exposure scores than they would have received had the case themselves been interviewed. This is due to NOK, in general, providing less detailed information than what the subject could provide personally (for example not knowing specific information about subject work conditions, or leaving out some occupations all together). The use of deceased cases and hence relying on information from NOK was justified in this study. Lung cancer is a disease with short life expectancy[7]; hence the exclusion of deceased cases would have greatly reduced the sample size (or increased the recruitment duration). In addition, the exclusion of deceased cases would have introduced survival selection bias in to the study. More aggressive types of lung cancer are known to be more strongly associated with tobacco smoking exposure (small cell carcinoma has a rapid growth rate and early metastasis and is highly associated with tobacco smoking[6]). Hence deceased cases are likely to have different risk factor profiles to cases surviving longer after diagnosis.

An alternative option would have been to match deceased cases with deceased controls, hence removing differential recall. The response rate for controls was below 50% for this study, no clear reason was identified for this. It was felt that had attempts been made to recruit the NOK of deceased controls, the response rate would have been further reduced due to previous studies identifying low response rates when recruiting NOK[78]. Also, use of deceased NOK for control subjects introduces new bias as deceased controls may have different risk factor profiles than live members of the population[126]. Finally, the small substudy demonstrated that controls and their NOK had good to excellent agreement when providing information for the three key exposure scores (cigarette smoking, occupation

and residence). Hence the use of live rather than deceased controls may not have influenced the final results.

Other potential limitations identified are unlikely to influence final results as it is unlikely they were differential in their effects on cases and controls. It has been previously reported that cases in a case control study are more likely to recall exposure to relevant agents than the control subjects, hence leading to a false positive result[127]. Standard methods were used to reduce the impact of this recall bias; recruiting and interviewing incident lung cancer cases as soon as possible after diagnosis, and asking subjects for recollection of lifetime events (i.e. jobs they have had), rather than of specific exposures (i.e. asbestos exposure level at work). In addition, the use of an event history calendar is thought to increase the reliability and validity of retrospectively collected data[96].

5.2. The Present Results in Context with the Literature

The result of this study implicating cigarette smoking for the high incidence of lung cancer is consistent with international lung cancer research. Cigarette smoking was formally identified as carcinogenic to lungs in 1985 by the Surgeon General[10] and since then there has been a large volume of research reporting an association between tobacco smoking duration, dose (represented by pack years[61], age commenced[62] and ceased[11]) and passive exposure with increased risk of lung cancer[12]. A large European multi-centre case control study (7 609 cases, 10 431 controls) investigating the lung cancer relationship with tobacco smoking found a considerably larger dose response relationship compared to our study[80] (Table 5-2). It is likely that the larger dose response found in their study was because it did not include any other risk factors or confounders for lung cancer as our study did. Also it should be noted that their study did not include non-smokers in the analysis

Table 5-2: Results for Smoking and Lung Cancer Relationship from European Case Control Study - OR(95%CI)[80]

Smoking status (Pack yrs)	Males (n=6035 cases, 7967 controls)	Females (n=1574 cases, 2464 controls)
Non smoker	1.00	1.00
<20	11.04 (8.87-13.74)	3.45 (2.73-4.36)
20-29	18.17 (14.54-22.70)	8.81 (6.42-12.08)
30-39	27.91 (22.30-34.94)	18.09 (11.82-27.68)
40+	37.08 (29.99-45.85)	19.61 (13.22-29.08)

The positive association between low socioeconomic status (SES) and lung cancer has been previously reported[82]. Education (age left school) was used as an indicator of SES, consistent with methods of the Australian National Health Survey[128]. Previous research has attributed the association between SES and lung cancer to the increased prevalence of tobacco smoking amongst less educated people[82], hence SES and tobacco smoking are covariates and are alternative measures of the same risk factor (cigarette carcinogen exposure). In this study it is also possible that SES is providing a flag for factors not otherwise measured such as detailed aspects of cigarette smoking (i.e. inhalation depth), or for lung carcinogens (or sources of) not yet identified in epidemiological or molecular research and hence not assessed in this study. Additionally, leaving school early may be a surrogate of working in "dirtier" blue collar jobs and hence exposures to carcinogenic agents in the workplace that perhaps were not measured by our occupational exposure assessment methods.

Exposure to Environmental Tobacco Smoke (ETS) was not a significant risk factor for lung cancer in our multivariate analysis despite being significant in the bivariate analysis. A meta-analysis in 2001[12] analysed 43 case control and cohort studies, finding a significant pooled RR of 1.29 (95%CI 1.17-1.43) for never smoking women exposed to passive smoking from their spouse, and the 9th report on carcinogens produced by the US Dept of Health and Human Services concluded exposure to ETS increased risk of lung cancer development by 20%[39]. A recent large (35 561 subjects) prospective study in the US found opposing results, citing ETS exposure from a spouse who smoked was not significantly associated with increased lung cancer mortality in non smokers (RR 0.75 95%CI 0.42-1.35)[129], however this study did not take into account ETS from other sources (such as work) and their sample may not have been representative of the population. Each

of these previous studies assessed the relationship between ETS and lung cancer in non-smoking subjects only. In the our study, just 6% of cases and 35% of controls were non-smokers. Previous studies have identified an association between ETS and direct cigarette smoking, potentially meaning it would be expected that ETS dropped out of this multivariate model when included with smoking due to the high percentage of smokers in the sample.

This study did not find an association between occupational exposures to lung carcinogens and lung cancer status, a relationship that has been well documented for a number of different occupational process' and substances by epidemiological studies and reviews[38]. The exposure scores for subjects in this study were very low, with most medians scores for both cases and controls at zero (exceptions were cases exposed to PAH, and controls exposed to asbestos and PAH). This result is comparable to a previous case control study conducted in metropolitan Adelaide to investigate the association between occupational exposure and mortality from various cancer types. This previous study used the same occupational hygiene panel method to assess exposure in deceased subjects from lifetime occupation as reported on death certificates[94]. The study found that, of numerous carcinogenic agents investigated, a significant elevation of lung cancer was only associated with prolonged (greater than 30 mins per day) exposure to coal tar (PAH) (OR 5.2, 95% CI 1.2 to 22.3). However, as in the present study, the analysis was based on low numbers of exposed subjects.

This case control study demonstrated residential exposure (measured by proximity) to 4 of 6 potentially lung carcinogen emitting industries to have no association with lung cancer in the multivariate analysis. The 5th and 6th industry, a local power station and a light

industry area, were found to be negatively associated with lung cancer, however there was no dose response relationship evident. One previous study by Pawlega et al[53] has demonstrated a similar significantly negative effect (OR 0.28 95%CI 0.15-0.51). That study used a direct method (as opposed to our indirect method) to quantify air pollution exposure, sampling and calculating mean yearly levels of total suspended particles and sulphur dioxide. As discussed in Chapter 2, their protective result may have been due to poor confounder adjustment and lack of air pollution gradient across the study area. In the present study it is plausible that this negative association is due to the participation bias in control subjects.

In Chapter 2 five studies were identified that used a relatively superior study design to investigate the relationship between lung cancer and air pollution (see Ch 2 for justification of their selection, briefly, all studies were case control or cohort design and adjusted for the confounding effects of smoking and occupation)[36]. The following table (Table 5-3) indicates the relative strengths of these studies in comparison to the present research. Aspects of these studies were selected for inclusion in this table based on the Bradford Hill criteria for causality used in Chapter 2, and standard aspects of epidemiological study design identified from text books[127].

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

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Design	Case control	Case control	Case control	Cohort	Cohort	Case control
Sample						
Sample size	755 cases, 755 controls	194 cases, 194 hospital & 194 population controls	1042 cases, 1274 alive & 1090 deceased controls	552 138 enrolled	319 000 utilised for $PM_{2.5}$ analysis	143 cases, 415 controls
Response rate (or loss to follow up for cohort)	81% cases, 83% controls	Not reported for cases or hospital controls, 41% population controls	87% cases, 88% population & 82% deceased controls	2% loss	7% loss	59% cases, 47% controls

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Source:						
Cases	Death registry	Hospital	Cancer registry	American Cancer Society Cancer Prevention Study (friends/neighbours/ acquaintances of volunteers)	American Cancer Society Cancer Prevention Study (friends/neighbours/ acquaintances of volunteers)	Cancer registry
Controls	Death registry	Hospital & Residential registry	Population & death registries			Electoral roll
Use of NOK	Yes, all cases & controls	No	Yes, 93% cases, and 21% of population controls & separate group of deceased controls	No	No	Yes, cases

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Location	Trieste, Italy	5 German cities	Stockholm, Sweden	USA	USA	North West Adelaide, Australia
Exposure Assessment						
Lifetime history	No for residence, Yes for tobacco and occupation	Yes for all	Yes for all	Yes, smoking only, others for duration of cohort (7yrs)	Yes, smoking only, others for duration of cohort (7yrs)	Yes for all

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Residential exposure	Direct – total suspended particulate concentration at nearest sampling station. Sampling undertaken between 2 and 14 years prior to case death from lung cancer.	Direct – SO_2 emission index for county & 8 pollutant categories based on available air pollution, energy & coal consumption, SO_2 emission, industrialisation. Sampling previously conducted was extra and interpolated.	Direct – NO2 & SO2 emission index based on monitoring & traffic and industry activity. Exposure calculated for 1950 & at time of diagnosis.	Direct – SO_2 or fine particulate concentration at nearest sampling site. Data collected in the 3 years prior to subject enrolment in the cohort.	Direct – $PM_{2.5}$ concentration at nearest sampling site. Data collected in the 3 years prior to subject enrolment in the cohort.	Indirect – modified Gaussian equation using proximity, wind direction frequency and duration as a surrogate for exposure.

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Confounders						
Tobacco smoke	Lifetime average cigarettes per day	Lifetime pack years	Lifetime average cigarettes per day	Lifetime smoking duration (yrs) & average cigarettes per day (prior to study enrolment only)	Lifetime smoking duration (yrs) & average cigarettes per day (prior to study enrolment only)	Lifetime pack years

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Occupation	Hygiene panel assessed exposure; no, possible or likely exposure at some stage during career	Lifetime exposure assessed by job title/task according to literature, weighted lifetime exposure	Lifetime carcinogen exposure assessed by job exposure matrix & hygiene panel; none or low exposure vs. high	Self reported regular exposure to list of substances (yes or no)	Self reported regular exposure to list of substances (yes or no)	Hygiene panel assessed, weighted lifetime exposure

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Results						
Association (95%CI)	Positive assoc. OR 1.4 (1.1-1.8)	No assoc.	No assoc.	Positive assoc. for SO_2; RR 1.36 (1.11-1.66). No assoc for fine particulate	Positive assoc. RR 1.14 (1.04-1.23)	No assoc. with composite score and 4/6 industry, negative assoc. with: Finsbury OR for exposure score 1-1.4 is 0.47 (0.24-0.94), Power Station OR for exposure score >3 is 0.37 (0.16-0.83)

Study Aspect	Barbone et al, 1995[47]	Jockel et al, 1992[50]	Nyberg et al, 2000[52]	Pope et al, 1995[46]	Pope et al, 2002[44]	Present study
Dose response demonstrated	Yes – p=0.022	No	No	No	No	No
Potential source of bias/ misclassification	Recall misclassification due to use of NOK Missing residential data No indication of smoking duration	Survival bias Residential exposure misclassification	Recall misclassification due to use of NOK No indication of smoking duration	Confounder misclassification Residential exposure misclassification due to no record lifetime history	Confounder misclassification Residential exposure misclassification due to no record lifetime history	Response bias Recall bias or misclassification due to use of NOK

Three of the six studies listed in Table 5-3 found a significantly positive relationship between lung cancer and their measure of residential exposure. One of four case control studies found a significant positive result, as opposed to 2 of 2 cohort studies (these 2 studies were a separate analysis, carried out at different stages and with different sample subgroups of the same cohort study). The studies showing a positive effect tended to have a larger sample size than those showing no significant effect. All except this study used the direct method of exposure assessment; sampling air quality at set locations and assigning each subject the air quality of their closest monitoring station. As described in Chapter 3 (Methods) the direct method of environmental exposure quantification is preferred where relevant air quality monitoring data is available. The three studies with significant results had the poorest quantification of smoking when adjusting for its confounding effects.

After consideration of this study in context with the stronger previous studies, there is not sufficient evidence to conclude a positive association between lung cancer and air pollution. There are inconsistent results both between and within studies, little dose response evidence and it is possible that significant positive results were influenced by poor confounder adjustment. It is likely that if an association does exist between lung cancer and air pollution then it is difficult to demonstrate because the effect is small in comparison to the well documented effect of tobacco smoking (indicated by the small OR in significant studies and the apparent association trend between sample size and study significance).

5.3. Future Epidemiological Research

Future research investigating high lung cancer incidence and mortality in shared industrial and residential zones need to address the issues of response bias and misclassification.

A large cohort study running over a minimum of 15 years (due to the latency period[69]) would be a superior study design to investigate the association between air pollution and lung cancer. A prospective study would enable continual monitoring of pollution exposure for each individual cohort member, account for subjects moving residence outside of the geographical area of the study, enable continual collection and validation of confounder data (smoking and occupation), and eliminate problems of recall, particularly reliance on information from Next of Kin of deceased subjects. However, funding and implementation time is not readily available for such large prospective studies, particularly in Australia. The cohort studies undertaken in North America (Beeson et al[43] and Pope et al[46])[44] have produced inconsistent results, proving that even prospective studies have difficultly defining the association between lung cancer and air pollution exposure, and may be susceptible to attrition bias.

Potential future improvements to the design of a case control study include recruiting lung cancer patients at the specific time of diagnosis to reduce the need to rely on information collected from NOK, although using a source of lung cancer cases other than from a cancer registry increases the likelihood that not all eligible lung cancer patients will be approached to participate (for example patients diagnosed at death, or by their general practitioner without referral to a specialist). Excluding deceased cases is not feasible as the sample will then not be representative of all lung cancer

patients, and those who die soon after diagnosis may have a different type of cancer with different aetiology (for example small cell carcinoma which is strongly associated with cigarette smoking).

This study utilised optimal methods of data collection[13 96], smoking[11] and occupational exposure[106] classification available. The method used to assess and quantify residential exposure may have been improved by the availability of historical air quality monitoring however this would only have assisted if it were thorough monitoring of relevant airborne carcinogenic agents in the specific geographical area of the study. The use of proximity to industry to quantify exposure could be enhanced if historical emission data from point sources were available in conjunction with more detailed information on the stack emitting pollutants and weather patterns surrounding the stack (air temperature and velocity). However, the literature does suggest that the addition of this information does not greatly alter results from that when the current method is used.

5.4. Discussion of Ambient Air Quality

The contemporary air quality monitoring undertaken has demonstrated that air quality with respect to specific respiratory carcinogenic substances in the North Western suburbs of metropolitan Adelaide (the case control study area) is satisfactory according to national and international health based guidelines.

With one exception, airborne asbestos was not detected. This is consistent with other studies of environmental asbestos, non-occupational exposure to mineral fibres [130], and is to be expected given the lack of operational contemporary sources. The significance of the observed low levels of quartz is thus unclear at this stage as, unlike occupational situations, there is a lack of data on airborne crystalline silica in the general environment. Consistent with EPA data, airborne formaldehyde was present at very low levels[34]. Across the sites PAH's and diesel exhaust particulate data were closely related, possibly suggesting a principle contribution from local traffic particularly as concentrations were highest at high density traffic sites.

$PM_{2.5}$ data from TEOM and Dust Trak™ instruments indicate relatively low average concentrations, with some variability during the day that appears to be due to a combination of local and mesoscale meteorology[131], motor vehicle traffic and, in the case of Sites 1 and 2, some industrial contribution. The instantaneous absolute concentrations may exceed 25μg/m^3 which if sustained, could be associated with respiratory health effects in susceptible individuals, particularly illnesses with short latency such as asthma and colds. For example, a previous Australian clustered randomized control study demonstrated respiratory health effects (sore throat, colds) in children from short term exposure to high concentrations of indoor nitrogen

dioxide[132]. The interpretation of our data should be tempered by the limited amount of real time monitoring at the sites, however based on the current guidelines the data do not suggest an appreciable health risk. The diurnal variations were seen across the various sites in Adelaide and historical real time nephelometry data appears to parallel current $PM_{2.5}$ measurements[27]. The natural tendency is for air pollution to rise in the early morning (anabatic airflow), subside, and then reappear in late morning or afternoon due to the emergence of katabatic (air current blowing downhill due to air in the upper slope being cooled and becoming denser) onshore airflow. Thus a distinguishing feature in the case of NW Adelaide may be industrial contributions superimposed on normal meteorological and traffic related trends.

From Table 4.40 it can be seen that the Dust Trak™ $PM_{2.5}$ values for Site 1 are approximately 30% higher than the corresponding TEOM values (10.1 vs 7.6 $\mu g/m^3$). It appears from the literature that the Dust Trak™ oversamples by a factor of about 2[125 133]. However, use of the environmental enclosure may result in some losses to the inlet of the Dust Trak™ impactor due to the presence of tubing, thus probably reducing the typical Dust Trak™ oversampling issue. Our reported values are essentially consistent with the other studies, which have found the Dust Trak™ device to be reasonably precise compared with referenced methods[125 133 134] and having the benefits of being relatively cheap and easy to set up. It is important though, that side-by-side sampling be conducted to accurately determine the extent of over sampling.

The monitoring of ultrafine particles was for very short periods of time (5 to 15mins) due to the limitations of the monitoring equipment. Guidelines for airborne concentrations of ultrafine particles have not been developed, however we were able

to see short term fluctuations (<10sec) in recordings when buses were present in close proximity (<100m), and higher averages in areas with greater traffic density and in built up areas (CBD).

The location of air sampling equipment in private residences has allowed for a more thorough investigation of localized air pollution. In addition we have investigated a range of ambient lung carcinogens, some of which are not routinely monitored (ie. asbestos, crystalline silica). However the generalisability of our investigations could be limited by short and long term weather patterns and the short duration of monitoring. This sampling campaign was conducted during a dry period (6 weeks of no rain) but strong winds were not observed, and there were no bushfires or dust storms. As such, resuspension of settled dust may not be as relevant as otherwise might be expected. However, if industrial production was a dominant contributor to ambient concentrations of lung carcinogens this would have been evident in our data. Somewhat higher values of $PM_{2.5}$ were observed at the industrial sites (compared to control Site 5) but these were still well below NEPM guidelines. In general, these data are consistent with other measurements conducted by the SA EPA during the entire year (across multiple weather patterns)[34].

In the context of current lung cancer cases in the NW Adelaide region, it is likely that the extent of industrial air pollution in the 1960's to 80's was greater than current values. There is evidence of this from the documented changes in the industry arising from clean air regulations introduced in 1972 and Australian design rules in the 1970's[27 28]. Examples of industry change in this period include closure of an insulation factory, an oil fired power station, and the changeover from coal and oil to

natural gas for firing of industrial kilns and furnaces. Improvements in emission control during this 30-year period include taller chimneys and particle filtration. Thus these monitoring results are inconclusive as to airborne carcinogen concentrations in previous decades.

The health significance, including non-cancer endpoints, of the observed short-term outdoor peaks remains unclear in this study and in the literature. Further research should explicitly investigate this phenomenon.

5.5. Summary

Residents in the North West of metropolitan Adelaide have formed a number of community action groups to protest against air pollution from local industry. Such groups have blamed industry emissions for the high incidence of a range of respiratory health problems including lung cancer and have lobbied local government for stricter emission guidelines and, in extreme cases, to close down local industry. This has proved a quandary for government, as the industry provides many jobs for the local community and income for the government through taxes and exports.

The review of previous epidemiological studies investigating the relationship between lung cancer and air pollution indicated inconsistency amongst methods of exposure assessment (both confounders and air pollution) and study results. There had not been a case control or cohort study carried out in Australia to investigate this relationship. In addition, although government bodies carry out regular air quality monitoring in the North West of Adelaide and through out Australia, this monitoring has not been of known or potential lung carcinogens.

This case control study has been carried out using optimal methods of exposure assessment in an attempt to identify the risk factors associated with the elevated incidence of lung cancer in the North West of Adelaide. This study has shown that residential proximity to industry with potential to emit airborne lung carcinogens is not positively associated with lung cancer incidence after controlling for the confounding influence of occupational exposure and tobacco smoking. Instead, lung cancer was primarily attributed to tobacco smoking duration and intensity (as measured by pack years), socioeconomic status (as measured by age left school) and

negatively associated with residential exposure to 2 of the 6 industries investigated. Complementary to the case control study, contemporary monitoring of air quality carried out found that the concentrations of airborne lung carcinogens in the study area were not elevated above that allowed by Australian guidelines.

Therefore, this study has indicated that a reduction or cessation of industry emissions in the North Western suburbs of metropolitan Adelaide is unlikely to significantly reduce lung cancer incidence and mortality in the region and hence would be an unnecessary public health initiative. Instead it is important that future public health initiatives and policies to reduce lung cancer in the area specifically focus on smoking prevention and reduction strategies, incorporating community education on the health effects of cigarette smoking in both young people and adults.

6. Chapter 6 Appendices

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

NORTH WESTERN ADELAIDE HEALTH EFFECTS STUDY

Dear Mr/Mrs [patient name],

I am writing to ask for your help in a study of the area that you live in which is being conducted by The Queen Elizabeth Hospital. You may have already heard about this study on television or read about it in the Advertiser or your local Messenger (see enclosed). I am passing on this letter to you on behalf of a research group at the hospital, as I believe you would be a suitable participant in their research*.

What is the study about?

This study wants to examine why there are more health problems of certain types in the Lefevre Peninsula area than in some other parts of metropolitan Adelaide. They want to find out whether there is a connection between health and the work that people have done during their lifetime. Another possibility they want to investigate is whether the distance of houses from possible sources of industrial pollution (air pollution) has anything to do with the development of certain health problems.

Why have you been chosen?

You have been selected because you have cancer of the lung. I am aware of the importance of privacy to you and want to assure you that should you participate in this study, only the investigator and the researcher of this project will have access to your name and address, which will be treated with utmost confidentiality.

What happens if you take part in the study?

If you are prepared to assist please fill in the attached slip that accompanies this letter and return it in the envelope provided, or call 8222 6898 to register you interest. This action will result in someone from the research program # contacting you to arrange an interview time. In this interview you will be asked questions relevant to your occupational, residential and smoking history, which should take less than one hour. They will have no need to contact you again following this interview.

What happens with the personal information from the study?

Your personal details and answers will be kept in a locked cabinet at The Queen Elizabeth Hospital. Your personal details will be destroyed at the end of the study. Your name and address will not appear in any way in relation to the results of this study.

NORTH WESTERN ADELAIDE HEALTH EFFECTS STUDY

What happens if I do not participate in the study or if I drop out of the study?

Thank you, if you choose to be part of this study, however, you need to be aware that you are free to withdraw, if you wish, at any time. This will in no way affect your future treatment at The Queen Elizabeth Hospital, but your participation would be greatly appreciated.

Results and benefits?

The aim of this study is to gather scientific evidence about the occupational and environmental exposures to substances in the air being breathed at home and work that may cause health problems. If results show any link between air quality and health problems then an improvement in air quality could eventually lead to the prevention of some ill health.

What if I have questions?

If you have questions about the research, you can call Dr. Brian Smith (Investigator) or Melissa Whitrow (PhD candidate) on 8222 6898. If you wish to talk to someone at the hospital who is not involved in the study, please ring Paul Miller, from the Research and Ethics Committee at the Queen Elizabeth Hospital on 8222 6841.

If you choose to take part in this study please complete the attached slip and return it in the postage paid envelope provided as soon as you can.

Thank you for your help.

Yours sincerely,

[Diagnosing Dr]

[Diagnosing Hospital and address]

Please complete this form and return it to the Queen Elizabeth Hospital as soon as possible, or alternatively, phone Melissa Whitrow on 8222 6898 to register your interest

Surname:_____

First names:_____

Contact phone number:

Home ( )_____ Work ( ) _____

Address:

_____

_____

Please tick appropriate box and return in envelope provided.

☐ **Yes**, I would like to help with the research by participating in the study, and I give permission for a researcher at the Queen Elizabeth Hospital to contact me and send me a brief questionnaire/calendar.

☐ **No**, I will be unable to participate.
Reason (optional)_____

Signed:_____

** In information letters sent out to follow up patients who have not replied, the preceding sentence is replaced with "I was concerned that you may not have received the first letter I sent therefore I am passing another copy of the original letter to you on behalf of a research group at the hospital, as I believe you would be a suitable participant in their research".*

 # The information letter sent to potential cases whilst 'part a' of the questionnaire was utilised included the following phrase "sending you a brief preliminary questionnaire and then"

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

NORTH WESTERN ADELAIDE HEALTH EFFECTS STUDY

Dear [Next of Kin name],

Thank you for agreeing to participate in the North West Adelaide Health Effects Study when you spoke to [Diagnosing Doctor name]. I am writing to tell you more about this study, which is being conducted by The Queen Elizabeth Hospital. We want to find out whether there is a connection between health and the work that people have done during their lifetime. We would like you to participate in the study on behalf of your late [case relationship to NOK], [name of case]. This may assist us to find out about causes of health problems. This letter explains in more detail what participation in this study involves, and why this research is being carried out.

What is the study about?

This study wants to examine why there are more health problems of certain types in the North Western Adelaide area than in some other parts of metropolitan Adelaide. They want to find out whether there is a connection between health and the work that people have done during there lifetime. Another possibility they want to investigate is whether the distance of houses from possible sources of industrial pollution (air pollution) has anything to do with the development of certain health problems.

Why have you been contacted?

Your [cases relationship to NOK]'s name was identified because [he or she] had cancer of the lung. Your name has been obtained from your [cases relationship to NOK]'s Doctor. I am aware of the importance of privacy to you and want to assure you that should you participate in this study, only the investigator and the researcher of this project will have access to your and your [cases relationship to NOK]'s name and details, which will be treated with utmost confidentiality.

What happens if you take part in the study?

Someone from the research program will contact you to arrange an interview time. In this interview you will be asked questions relevant to your [cases relationship to NOK]'s occupational, residential and smoking history, which should take about 30 minutes. We will have no need to contact you again following this interview.

What happens with the personal information from the study?

All personal details and answers will be kept in a locked cabinet at The Queen Elizabeth Hospital. These personal details will be destroyed at the end of the study. Names and addresses will not appear in any way in relation to the results of this study.



NORTH WESTERN ADELAIDE HEALTH EFFECTS STUDY

What happens if I do not participate in the study or if I drop out of the study?

Thank you, if you choose to be part of this study, however, you need to be aware that you are free to withdraw, if you wish, at any time. This will in no way affect your future treatment at The Queen Elizabeth Hospital, but your participation would be greatly appreciated.

Results and benefits?

The aim of this study is to gather scientific evidence about the occupational and environmental exposures to substances in the air being breathed at home and work that may cause health problems. If results show any link between air quality and health problems then an improvement in air quality could eventually lead to the prevention of some ill health.

What if I have questions?

*If you have questions about the research, you can call Dr. Brian Smith (Investigator) or Melissa Whitrow (PhD candidate) on **8222 6898**.* If you wish to talk to someone at the hospital who is not involved in the study, please ring Paul Miller from the Research and Ethics Committee at the Queen Elizabeth Hospital on 8222 6841.

If you choose to take part in this study please complete the questionnaire to the best of your ability and return it in the postage paid envelope provided as soon as you can.

Thank you for your help.

Yours sincerely,

Melissa Whitrow

Clinical Epidemiology and Health Outcomes Unit

The Queen Elizabeth Hospital
28 Woodville Rd
WOODVILLE SOUTH SA 5011

** The information letter sent to the Next of Kin of potential cases whilst 'part a' of the questionnaire was utilised included the following phrase "If you are prepared to assist, please fill in questionnaire that accompanies this letter and return it in the envelope provided"*

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

NORTH WESTERN ADELAIDE HEALTH EFFECTS STUDY

Dear Mr/Mrs [Next of Kin name],

I'm writing to ask for your help in a study being conducted by The Queen Elizabeth Hospital. They want to find out whether there is a connection between health and the work that people have done during their lifetime. We would like to know if you wish to participate in the study on behalf of your late [cases relationship to NOK], [name of NOK]. This may assist us to find out about causes of health problems. I am therefore passing this letter to you on behalf of a research group at this hospital. It explains in more detail what participation in this study involves, and why this research is being carried out.

What is the study about?

This study wants to examine why there are more health problems of certain types in the Lefevre Peninsula area than in some other parts of metropolitan Adelaide. They want to find out whether there is a connection between health and the work that people have done during there lifetime. Another possibility they want to investigate is whether the distance of houses from possible sources of industrial pollution (air pollution) has anything to do with the development of certain health problems.

Why have you been contacted?

Your [cases relationship to NOK]'s name was identified because he had cancer of the lung. Your name has been obtained from your [cases relationship to NOK]'s Doctor. I am aware of the importance of privacy to you and want to assure you that should you participate in this study, only the investigator and the researcher of this project will have access to your and your [cases relationship to NOK]'s name and details, which will be treated with utmost confidentiality.

What happens if you take part in the study?

If you are prepared to assist, please fill in the tear off slip that accompanies this letter and return it in the envelope provided, or call 8222 6898 to register your interest. This action will result in someone from the research program * contacting you to arrange an interview time. In this interview you will be asked questions relevant to your [cases relationship to NOK]'s occupational, residential and smoking history, which should take between 30 minutes and one hour. They will have no need to contact you again following this interview.



NORTH WESTERN ADELAIDE HEALTH EFFECTS STUDY

What happens with the personal information from the study?

All personal details and answers will be kept in a locked cabinet at The Queen Elizabeth Hospital. These personal details will be destroyed at the end of the study. Names and addresses will not appear in any way in relation to the results of this study.

What happens if I do not participate in the study or if I drop out of the study?

Thank you, if you choose to be part of this study, however, you need to be aware that you are free to withdraw, if you wish, at any time. This will in no way affect your future treatment at The Queen Elizabeth Hospital, but your participation would be greatly appreciated.

Results and benefits?

The aim of this study is to gather scientific evidence about the occupational and environmental exposures to substances in the air being breathed at home and work that may cause health problems. If results show any link between air quality and health problems then an improvement in air quality could eventually lead to the prevention of some ill health.

What if I have questions?

If you have questions about the research, you can call Dr. Brian Smith (Investigator) or Melissa Whitrow on 8222 6198. If you wish to talk to someone at the hospital who is not involved in the study, please ring Paul Miller from the Research and Ethics Committee at the Queen Elizabeth Hospital on 8222 6841.

If you choose to take part in this study please complete the attached slip and return it in the postage paid envelope provided as soon as you can.

Thank you for your help.

Yours sincerely,

[Diagnosing Doctor]
[Diagnosing Hospital and Address]

Please complete this form and return it to the Queen Elizabeth Hospital as soon as possible, or alternatively, phone Melissa Whitrow on 8222 6198 to register your interest

Surname:_____

First names:_____

Contact phone number:

Home ( )_____ Work ( ) _____

Address:

_____

_____

Please tick appropriate box and return in envelope provided.

☐ **Yes**, I would like to help with the research by participating in the study, and I give permission for a researcher at the Queen Elizabeth Hospital to contact me and send me a brief questionnaire/calendar.

☐ **No**, I will be unable to participate.
Signed:_____

** The information letter sent to the Next of Kin of potential cases whilst 'part a' of the questionnaire was utilised included the following phrase "If you are prepared to assist, please fill in questionnaire that accompanies this letter and return it in the envelope provided"*

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

Dr Date _____

Thank you for agreeing to call your patient for the **Lung Cancer in the North West of Adelaide case control study**.

Patient Name _____

DOB _____

Patient Phone Number _____

Below are some suggestions of things you may wish to say to the patient when you contact them.

- I am calling to invite you to participate in a study that is trying to find out why so many people in the North Western suburbs are being diagnosed with lung cancer. You might have heard about this study on the channel 10 news or on the radio, or read about it in the Advertiser, Sunday Mail or your local Messenger.
- Participation only involves filling out a brief form and then taking part in a one off 30 minute interview where you will be asked questions about your previous occupations, places you've lived and smoking history
- The interview can take place at the hospital, in your home or at your work at any time that is convenient to you
- It's ok if you don't remember everything, the researchers just need you to do the best you can. Any information you can provide is useful to them.
- The study does not involve you taking any medications or having to repeatedly have appointments with the researchers

The goal of the conversation is to get them to **agree to take part** or to **agree to the researcher (Melissa) calling them** to give them more information about the study and answer their questions. The patients may not be persuaded further if they say no at any stage of the conversation.
Once you have contacted the patient please phone **Melissa Whitrow (x26898 or 0412 828 780)** to inform her of the outcome. If I do not hear from you I will be in contact in approximately a week to hear how you have gone.

Yours sincerely

Melissa Whitrow
Clinical Epidemiology and Health Outcomes Unit

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

Dr Date _____

Thank you for agreeing to contact the Next of Kin (NOK) of your patient for the **Lung Cancer in the North West of Adelaide case control study**.

Patient Name _____

DOB _____ DOD _____

NOK Name _____

NOK contact Ph _____

Below are some suggestions of things you may wish to say to the patient's NOK when you contact them.

- A research group at the Queen Elizabeth Hospital are trying to find out why so many people in the North Western suburbs of Adelaide are getting Lung Cancer, you might have heard about their research on the Channel 10 news or the radio, or read about it in the Advertiser, Sunday Mail or your local Messenger.
- In their study they are gathering information about people who have had lung cancer and from people who are well to try to see what is different about them
- They would like you to participate on behalf of your late (Husband, wife etc)
- Participation only involves filling out a brief form and then taking part in a one off 30 minute interview where you will be asked questions about their previous occupations, places they lived and their smoking history
- The interview can take place at the hospital or in your home or work at any time that is convenient to you
- It's ok if you don't remember everything, the researchers just need you to do the best you can. Any information you can provide is useful to them.
- The study does not involve you taking any medications or having to repeatedly have appointments with the researchers

The goal of the conversation is to get them to **agree to take part** or to **agree to the researcher (Melissa) calling them** to give them more information about the study and answer their questions. The patients NOK may not be persuaded further if they say no at any stage of the conversation.

Once you have contacted the patient please phone **Melissa Whitrow (x26898 or 0412 828 780)** to inform her of the outcome. If I do not hear from you I will be in contact in approximately a week to hear how you have gone.

Yours sincerely

Melissa Whitrow
Clinical Epidemiology and Health Outcomes Unit

Appendix 6: Original information letter to controls

Dear [control name]

The Queen Elizabeth Hospital and University of Adelaide are conducting an important study looking at the causes of respiratory disease in the North West of Adelaide, including your suburb, [name of controls suburb]. * You might have heard about our research on Channel 7 and 10, or on ABC radio, 5AA or 5UV, or even read about it in the Sunday Mail, Advertiser or your local Messenger (see enclosed).

This study wants to investigate why there is more respiratory disease in the North West of Adelaide than in some other parts of metropolitan Adelaide. We want to find out whether there is a connection between health and the work that people have done during their lifetime. Another possibility we want to investigate is whether the distance of houses from possible sources of industrial pollution has anything to do with the development of certain health problems. If our results show a link between respiratory disease and air quality at home or work, then improvements in air quality in your community may be the solution to reducing ill health

For this research we need people who do not have lung cancer from [name of controls suburb], to compare to the people who do. You have been specially selected from the South Australian Electoral Roll because your age and gender match that of someone we have already chosen who has lung cancer and lives near your area.

Helping us involves # being interviewed at a time and place convenient to you for 20 minutes by a research person from the hospital. In this interview we will ask questions relevant to the jobs you've had, the places you've lived and any cigarette exposure you may have had. The success of this study relies heavily on support from people like you. Without it we may not be able to interview enough people to show any potential causes of these diseases (see enclosed Sunday Mail article).

⇨

---------- Tear here ----------

Please fill out and return in the reply paid envelope

Name _____

Home phone _____ Work phone _____

Address _____

Please tick appropriate box

☐ **Yes**, I would like to help with the research by participating in the study, and I give permission for a researcher at the Queen Elizabeth Hospital to contact me

☐ **No,** I will be unable to participate,

Reason (optional) _____

Signed:_____

Your Privacy:
We are aware of the importance of privacy to you. Should you participate in this study, only the investigator and the researcher for this project will have access to your name and address, which will be treated with utmost confidentiality, kept in a locked cabinet at the hospital, and destroyed at the end of the study. Your name and address will not appear in any way in relation to the results of this study.

What happens if I do not participate in the study or if I drop out of the study?
If you choose to be part of this study you are free to withdraw, if you wish, at any time. This will in no way affect any future treatment you may have at The Queen Elizabeth Hospital. But your participation would be greatly appreciated.

What if I have questions?
If you have questions about the research, or would like to speak with someone about the study, you can call Dr. Brian Smith, Melissa Whitrow (PhD candidate) on 8222 6897 at the hospital. If you wish to talk to someone at the hospital who is not involved in the study, please ring Paul Miller who is the Chairman of the Ethics of Research Committee at The Queen Elizabeth Hospital on 82226841.

If you choose to take part in this important research we ask that you complete the tear off slip below and return it to us in the postage paid envelope provided as soon as you can.

Thank you for your help.

Yours sincerely,

Dr Brian Smith
Director of Respiratory Medicine
The Queen Elizabeth Hospital and Lyell McEwin Health Service

Please fill out the form on the reverse side
and send it to us in the reply paid envelope provided,
or call 8222 6897 to register your interest
with Melissa Whitrow

** In information letters sent out to follow up potential controls who have not replied, the following sentence is inserted "I was concerned that you may not have received the first letter I sent therefore I am passing another copy of the original letter to you".*

 # The information letter sent to potential controls whilst 'part a' of the questionnaire was utilised included the following "filling out a brief question sheet and"

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

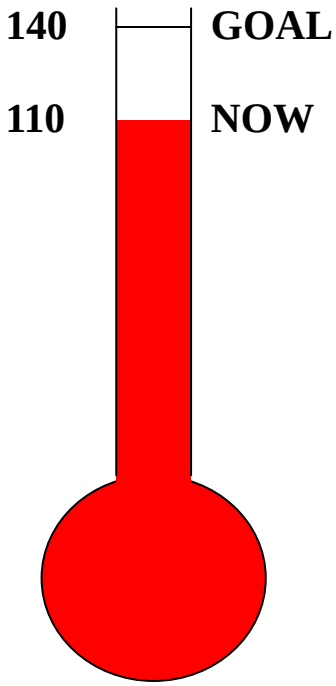
Hello, my name is ….., I'm a health researcher with respiratory medicine at the Queen Elizabeth Hospital.
(pause)

We're looking at the causes of respiratory disease in the North West of Adelaide, including *(insert their suburb)*.

Your might have heard about our lung disease research on Channel 10 or on ABC or 5AA radio, or even read about it in the Advertiser, Sunday Mail or the Messenger.
Some suburbs in the North West have lung cancer rates 4 times that of others, therefore we are interested in talking briefly to (*age)* year old *(gender)* who don't have lung cancer in your area, so we can unravel the mystery as to what is different between the people with and without the cancer. You have been specially selected to represent your suburb in this age and gender group.
(pause)

We meant to send you an information letter about this, sorry if you didn't receive it, would you be interested in taking part in a short 20 min interview about jobs that you've done and places you've lived to help with our important research into lung cancer?

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



NORTH WEST ADELAIDE

We're nearly there!

As of the 16th of April **110** cases have been recruited and interviewed for the Lung Cancer in North West Adelaide Case Control Study thanks to doctors like you contacting lung cancer patients.

A big thank you for your perseverance with patient recruitment, there's not long to go now so let's make a big effort to recruit these last few patients!

From Melissa Whitrow (x26898) and the Clinical Epidemiology and Health Outcomes Unit

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

This publication is included on p. 286 in the print copy of the thesis in the University of Adelaide Library.

Hailstone, Barry
Smokers in the high cancer risk suburbs.
The Advertiser (Adelaide, S. Aust.), 4 August, 2003, p. 3.

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

Adelaide Community Healthcare Alliance Inc

55 Anzac Highway
Ashford SA 5035
Phone: (08) 8375 5000
Fax (08) 8471 1272
Email: info@acha.org.au
Web: www.acha.org.au

26th March 2002

Ms Melissa Whitrow
Clinical Epidemiology and Health Outcomes Unit
8th floor CDRC Building
The Queen Elizabeth Hospital Campus
28 Woodville Road
Woodville SA 5011

Dear Ms Whitrow

Re: Research Project – "Lung Cancer in Port Adelaide"

Thank you for your correspondence dated 5th March together with enclosures.

I now have pleasure in advising that your request to recruit patients from the Memorial, Western and Flinders Private hospital sites was approved by the ACHA Research & Ethics Committee at the meeting held on 21st March 2002.

In addition, I confirm that the patient information documents were noted and approved.

Yours sincerely

DR JOY GILBERTSON
GROUP DIRECTOR RESEARCH & DEVELOPMENT

Research and Ethics
Committee

REPATRIATION GENERAL HOSPITAL
DAW PARK

Telephone: 08 8275 1876
Fax: 08 8374 0225
Email: Sarah.Moulds
@health.sa.gov.au

29/99

Contact
Reference

A Teaching Hospital of Flinders University

27 September 1999

Ms Melissa Whitrow
Clinical Epidemiology and Health Outcomes Unit
The Queen Elizabeth Hospital
North Western Adelaide Health Service
28 Woodville Rd
Woodville SA 5011

Dear Melissa

Re: Occupational and environmental hazards associated with lung cancer in Port Adelaide. Protocol No 29/99

Thank you for your letter of 31 August 1999 in which you responded to queries raised by the Research and Ethics Committee at its meeting on 14 July 1999.

Your reply has been found satisfactory by the reviewer and Chairman, and ethical approval to proceed has been given. I have enclosed the approved version of the information sheet and consent form

Ethical approval is given initially for a period of one year, and an annual report will be requested. As a condition of ethical approval you should report immediately anything which might affect ethical acceptance of the protocol, including adverse events, protocol changes, and unforeseen events which may affect continued ethical acceptability. The Committee is to be notified when the study is completed or discontinued.

Yours sincerely

David Cosh
Chairman
Research and Ethics Committee

encl

Daws Road, Daw Park, South Australia 5041
Telephone: (08) 8276 9666, Facsimile (08) 8277 9401

Medical research at RGH is supported by Foundation Daw Park Incorporated
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Flinders Medical Centre
Bedford Park South Australia 5042
Flinders Clinical Research Ethics Committee

Telephone (08) 8204 5511
International 618 8204 5511
Telephone (08) 8204 4507
Facsimile (08) 8204 4006
email: Carol.Hakof@fmc.se.gov.au

22 November 1999

MEMORANDUM

TO: Ms. M. Whitrow, Clinical Epidemiology & Health Outcomes Unit, TQEH

FROM: A/Prof. A. Vedig, Chairman, Flinders Clinical Research Ethics Committee

TOPIC: **Research Application 77/99**

Your attention is drawn to the following extract from the Minutes of the Committee's meeting held 8 November 1999.

4653.14 Research Application 77/99 – Dr. B. Smith/Ms. M. Whitrow
Occupational and environmental hazards associated with lung cancer in Port Adelaide.
Reviewer: Mr. K. Schmitz

Facsimile dated 5 November 1999 responding to this Committee's queries was received and noted. Contact letter and participant form were approved.

A. Vedig
Department of Critical Care Medicine
Extension 65206

MODBURY PUBLIC HOSPITAL

All correspondence to:
Smart Road
Modbury, SA 5092

HEALTHSCOPE

Healthscope Limited
A.C.N. 008 405 157

10 August 1999

Dr Brian Smith
Director
Clinical Epidemiology & Health Outcomes Unit
Senior Lecturer, Department of Medicine
The Queen Elizabeth Hospital
28 Woodville Road
WOODVILLE SA 5011

Dear Dr Smith

Re Collaborative project with North Western Adelaide Health Service & The Cancer Registry of South Australia - **"Study of high death rate from lung cancer in Le Fevre Peninsula."**

I am writing to let you know that your project has been given full Research and Ethics Committee approval and can now proceed.

Please note adequate record-keeping is important and you should retain **at least** the completed consent form which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Should you wish to alter the structure or process of this project you will need to contact me before doing so, as the changes may have ethical implications.

Do not hesitate to contact me if you have any queries or concerns.

Yours sincerely

per **Associate Professor Julian McNeil**
Chairperson
Research and Ethics Commmittee

smith 11/08/99

NORTH WESTERN ADELAIDE HEALTH SERVICE

Ethics of Human Research Committee

10 April 1997

Ms M Nitschke
Clinical Epidemiology Unit
The Queen Elizabeth Hospital

Dear Ms Nitschke Application Number 23/97

The Ethics of Human Research Committee at the last meeting considered your protocol entitled:

Occupational and environmental hazards associated with lung cancer in Port Adelaide

Approval Status Final

Protocols are approved for up to twelve months only and a report is required at the end of the study or 12 month period. Extensions will not be granted without a report to the Committee.

The Ethics of Human Research Committee must be notified should there be significant changes to a protocol.

Yours sincerely

Dr. M. Hoby
Chairman
Ethics of Human Research Committee

NORTH WESTERN ADELAIDE HEALTH SERVICE

Ethics of Human Research Committee

29 February 2000

Ms M Whitrow
Clinical Epidemiology & Health Outcomes Unit
The Queen Elizabeth Hospital

Dear Ms Whitrow Application Number 23/97

The Ethics of Human Research Committee Chairman has considered modification and extension to your protocol entitled:

Occupational and environmental hazards associated with lung cancer in Port Adelaide

Your modification has been reviewed and approved.
Extension has been granted with further reports due in Feb 2001

Approval Status Final

Protocols are approved for up to twelve months only and a report is required at the end of the study or 12 month period. Extensions will not be granted without a report to the Committee.

The Ethics of Human Research Committee must be notified should there be significant changes to a protocol.

Yours sincerely

Dr. M. Hoby
Chairman
Ethics of Human Research Committee

Royal Adelaide Hospital

Medical Administration
Level 3, Margaret Graham Building,
Royal Adelaide Hospital
North Terrace, Adelaide 5000
South Australia
Telephone (08) 8222 5345
Facsimile (08) 8222 5936
Web http://www.rah.sa.gov.au

8222 4139

7 October 1999

Ms M Whitrow
Clinical Epidemiology & Health Outcomes Unit
THE QUEEN ELIZABETH HOSPITAL

Dear Ms Whitrow,

Re: "Study of Lung Cancer in Port Adelaide."
RAH Protocol No: 991002

****Please note: Approval is conditional on the following:**
"The Information Sheet must be sent to potential participants by the diagnosing doctor."

I am writing to advise that ethical approval has been given to the above project. Please note that the approval is ethical only, and does not imply an approval for funding of the project.

Human Ethics Committee deliberations are guided by the Declaration of Helsinki and N.H. and M.R.C. Guidelines on Human Experimentation. Copies of these can be forwarded at your request.

Adequate record-keeping is important and you should retain at least the completed consent forms which relate to this project and a list of all those participating in the project, to enable contact with them if necessary, in the future. The Committee will seek a progress report on this project at regular intervals and would like a brief report upon its conclusion.

If the results of your project are to be published, an appropriate acknowledgment of the Hospital should be contained in the article.

Yours sincerely,

Michael James

DR M JAMES

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

North Western Adelaide Health Service

Standard Consent Form

1. I, the undersigned

.....

hereby consent to my involvement in the research project titled:

Occupational and environmental hazards associated with lung cancer in North West Adelaide.

2. I have read the information sheet, and I understand the reasons for this study. The research worker has explained the ways in which it will affect me. My questions have been answered to my satisfaction. My consent is given voluntarily.

3. The details of the research project have been explained to me, including:

- the expected time it will take
- any discomfort which I may experience

4. I understand that the purpose of this research project is to improve knowledge of the causes of lung cancer, but my involvement may not be of benefit to me.

5. I have been given the opportunity to have a member of family or a friend present while the project was explained to me.

6. No information about my medical history will be taken from the hospital without the researcher being present. My identity will be kept confidential, and nothing will be published which could possibly reveal my identity.

7. My involvement in the project will not affect my relationship with my medical advisers. I understand I am free to withdraw from the project at any stage without having to give any reasons, and that if I do withdraw from the project it will not affect my treatment at this, or any, hospital in the future.

SIGNED .....

ADDRESS .....

(please print) .....

WITNESS .....

RESEARCH WORKER .....

DATE .....

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

CONFIDENTIAL - PERSONAL RESIDENCE AND WORK CALENDAR

Surname:_____ First names:_____

Contact phone number: Home ( )_____ Work( )_____

Please complete the calendar and return it in enclosed reply-paid envelope as soon as possible.

Instructions:

❶ **Age:** The column for age is already filled in.

❷ **Year:** Write down the year of your birth opposite "Born", then write in each year up to your present age. Add extra lines if you are over 85.

❸ **Where lived:** Opposite the age and year you started to live at a place, write down the street, town or suburb and State. If overseas, write down the town and country. If you lived in more than one place in any year, write down the place where you lived longest in that year.

❹ **School or job:** Write down the name of each school you went to, and job you have had opposite the year you started there. If you went to more than one school or had more than one job in any year, write down the one that you had the longest in that year.

❶ Age	❷ Year	❸ Where lived	❹ School or job
Born	19__		
1	19__		
2	19__		
3	19__		
4	19__		
5	19__		
6	19__		
7	19__		
8	19__		
9	19__		
10	19__		
11	19__		
12	19__		
13	19__		
14	19__		
15	19__		
16	19__		
17	19__		

❶ Age	❷ Year	❸ Where lived	❹ School or job
18	19__		
19	19__		
20	19__		
21	19__		
22	19__		
23	19__		
24	19__		
25	19__		
26	19__		
27	19__		
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44	19__		
45	19__		
46	19__		
47	19__		
48	19__		
49	19__		
50	19__		
51	19__		
52	19__		

❶ Age	❷ Year	❸ Where lived	❹ School or job
53	19__		
54	19__		
55	19__		
56	19__		
57	19__		
58	19__		
59	19__		
60	19__		
61	19__		
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73	19__		
74	19__		
75	19__		
76	19__		
77	19__		
78	19__		
79	19__		
80	19__		
81	19__		
82	19__		
83	19__		
84	19__		
85	19__		

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

QUESTIONNAIRE

Hello, my name is _____ and I am from The Queen Elizabeth Hospital. I am here for the appointment I made with you to go through a questionnaire. The information from this questionnaire is going to be used for a study on the effect work conditions and the environment can have on health. Any information you give me will remain confidential; any data published from this study will be group data, so you will not be identified in any way. Before we start I need you to read through and sign this consent form (Interviewer to go through points on consent form with subject).

Are you ready to begin?

(enter following details on information booklet cover sheet)

Date - _____

Type of interview - Direct-1 / Proxy-2 / Assisted-3

If proxy or assisted, relationship to subject - _____

How many years have they known subject - _____ yrs

And lived with subject - _____ yrs

Give subject their own calendar for reference (get it back at end of interview)

We need to start by checking over your residential and occupational calendar to make sure everything is included and correct:

(age and year sequences, address and job history completeness checked prior to interview, blanks in next section also completed, all calendar information entered onto database)

- You were born in 19___, is that correct? *(amend if required)*
- And you retired in 19___ / You have not retired? *(cancel one pre-interview)*

Now we can begin the questionnaire

1. **Smoking**

Firstly we need to know about your/his/her smoking history. We'll begin with cigarette smoking.

(USE **SMOKING** CALENDAR)

1.1 Have you/he/she ever smoked cigarettes for a period of 6 months or more?

Yes - go to Q1.2

No - go to Q1.11

Enter 0=No, 1=Yes, 97=DK, 98=NR in Born row under cigs column

1.2 In what year did you/he/she first/next start smoking cigarettes?

Calendar - enter S next to year started smoking in cigs column

1.3 After (year) did you/he/she ever stop smoking for 6 months or more?

Yes - go to Q1.4

No - go to Q1.5

1.4 In what year did you/he/she stop?

Calendar - enter Q next to year stopped smoking in cigs column

1.5 How many cigarettes on average did you/he/she smoke in a day during that period?

Calendar - enter cigarette number next to year started in cigs/day column

1.6 Were these cigarettes filter or non-filter?

Calendar - F=filt, N=N-filt. DK= don't know, 98=NR in filter column next to year started

1.7 What tar level cigarettes were smoked during this period (or what brand if tar unknown), or did you/he/she roll your/their own?

Calendar - level number/brand in tar/brand column next to year started, RYO if rolled their own, or 97=DK, 98=NR

1.8 During that period did you/he/she usually inhale the smoke into your chest or just into your/his/her mouth (ie. just puffed)?

Calendar - C=chest, M=mouth, DK=Don't' know, 98=NR in inhale column next to yr started

1.9 I need to know how far down you/he/she smoked your/their cigarettes:

For filter cigarettes what was the butt length in centimetres?

Show filter cigarette with ½ cms marked on

Calendar – enter F and length in butt cm's column next to year started

For non-filter cigarettes what was the butt length in centimetres?

Show non-filter cigarette with ½ cms marked on

Calendar - enter NF and length in butt cm's column next to year started

1.10 *(ONLY IF STOPPED)* Did you/he/she ever start smoking cigarettes for a period of 6 months or more again?

Yes - go to Q1.2

No - go to Q1.11

Now about cigars:

(USE **SMOKING** CALENDAR)

1.11 Have you/he/she ever smoked cigars for a period of 6 months or more?

Yes - go to Q1.12

No - go to Q1.18

Enter 0=No, 1=Yes, 97=DK, 98=NR in Born row under cigar column

1.12 In what year did you/he/she first/next start smoking cigars?

Calendar - enter S next to year started smoking in cigar column

1.13 After (year) did you/he/she ever stop smoking for 6 months or more?

Yes - go to Q1.14

No - go to Q1.15

1.14 In what year did you/he/she stop?

Calendar - enter Q next to year stopped smoking in cigar column

1.15 How many cigars on average did you/he/she smoke in a day during that period?

Calendar - enter cigar number next to year started in cigar/day column

1.16 During that period did you/he/she usually inhale the smoke into your chest or just into your/his/her mouth?

Calendar - C=chest, M=mouth, 97=DK, 98=NR in inhale column next to year started

1.17 *(ONLY IF STOPPED)* Did you/he/she ever start smoking cigars for a period of 6 months or more again?

Yes - go to Q1.12

No - go to Q1.18

Now about tobacco pipes:

(USE **SMOKING** CALENDAR)

1.18 Have you/he/she ever smoked a pipe for a period of 6 months or more?

Yes - go to Q1.19

No - go to section 2

Enter 0=No, 1=Yes, 97=DK, 98=NR in Born row under pipe column

1.19 In what year did you/he/she first/next start smoking a pipe?

Calendar - enter S next to year started smoking in pipe column

1.20 After (year) did you/he/she ever stop smoking for 6 months or more?

Yes - go to Q1.21

No - go to Q1.22

1.21 In what year did you/he/she stop?

Calendar - enter Q next to year stopped smoking in pipe column

1.22 How many grams of tobacco, on average did you/he/she smoke in a day during that period?

Calendar - enter number of grams next to year started in gms/day column

1.23 During that period did you/he/she usually inhale the smoke into your chest or just into your/his/her mouth?

Calendar - 1=chest, 0=mouth, 97=DK, 98=NR in inhale column next to year started

1.24 *(ONLY IF STOPPED)* Did you/he/she ever start smoking a pipe for a period of 6 months or more again?

Yes - go to Q1.19

No - go to section 2

(USE **WORK** CALENDAR)

2. OCCUPATION

Now I would like to discuss the jobs that you have listed in your/his her occupation calendar to find out more about your/his/her tasks there.

(USE WORK CALENDAR)

NB: Options of 97=DK and 98=NR for all questions

2.1 In 19___ you/he/she started worked as _____.

Do you remember the name of the company or your/his/her employer?

Calendar – enter name in employer column next to year started working there.

2.2 What was the address where you/he/she worked (if within Australia)?

Calendar – enter address in address column next to year started working there (or country if not in Australia).

2.3 What kind of business was it, that is, what did the company do?

Probe – What sort of service was offered, what was produced, stored or transported there?

Calendar – enter in employer kind column next to year started.

2.4 How many days per week did you/he/she work there?

Calendar - enter in dy/wk column next to year started.

2.5 How many hours per week did you/he/she work there?

Calendar – enter in hrs/wk column next to year started

2.6 What percentage of time would you estimate you/he/she spent inside while working there?

Calendar - enter in inside % column next to year started.

2.7 Was your/his/her role supervisory or were you/he/she a more general worker?

Calendar – enter 0=supervisory, 1=general, 97=DK, 98=NR in role column next to year started.

2.8 What were your/his/her main/new duties and responsibilities there, the things you did on most days?

If house duties – Did these tasks include contact with your husbands workclothes that were covered in dust or asbestos, by shaking or washing them?

Calendar – enter in duties column next to year started/changed.

For each task: (use separate task table page)

2.9 Tell me a bit more about what you actually did, what equipment and substances did you work with whilst doing this task?

2.10 How often did you do this task? (ie once/week or day)

2.11 How much time did you spend on this task? (ie 30mins per session)

2.12 For how long, whilst working as a _____ did you do this task? (which years, ie first 5)

2.13 Did you wear any of these for protection while doing this task?

Show card with respiratory protection photos (Card A)

No - go to Q3.10

Yes - Calendar – enter picture code in protection column next to year started for any equipment used.

2.14 How often did you wear this equipment whilst doing this task?

3 – more than half of the time

2 – approximately half of the time

1 – less than half of the time

0 - never

Calendar –enter 0, 1, 2 or 3 in when column next to task

2.15 Was the area that you/he/she worked in dusty so that visibility was restricted to less than 20 metres?

Enter Y=Yes or N=No in D column next task.

2.16 Was the area that you/he/she worked in smoky so that visibility was restricted to less than 20 metres?

Enter Y=Yes or N=No in S column next to task

2.17 Did this environment irritate you? ie did it make your eyes itchy or watery or make you cough?

Enter Y=Yes or N=No in I column next to task.

2.18 Do you believe that the environment in which you were working was adequately ventilated?

Enter Y=Yes or N=No in V column next to task

Ask 2.9 – 2.18 per task

2.19 Were there any additional occasional tasks that weren't part of your usual duties that resulted in dust generation or were done in a dusty environment?

Ask 2.9 to 2.18 per additional task

2.20 Were you/he/she ever regularly exposed to the tobacco smoke of others for a period of 6 months or more at this place of work?

Yes - go to Q2.9

No - go to section 3

Enter 0=No, 1=Yes, 97=DK, 98=NR in Born row under passive column

2.21 When did you/he/she first start working with these people?

Calendar - enter S next to year started working with them in passive column.

2.22 Did you/he/she ever stop working with them for 6 months or more?

Yes - go to Q2.11

No - go to Q2.12

2.23 When did you/he/she stop working with these people?

Calendar - enter Q next to year stopped working with them in passive column.

2.24 During this time did these people smoke in your presence all day or just during work breaks?

Calendar - enter answer next to year started in hr/month column.

2.25 (ONLY IF STOPPED) Did you/he/she ever work for 6 months or more with someone else who smoked? *Yes - go to Q2.9* *No - go to section 3*

3. **HOBBIES**

Now I need to find out about any hobbies (not occupations) that you/he/she have been involved with.

(USE **HOBBY** TABLE)

3.1 Did you/he/she ever do any of the following **as a hobby** for 6 months or longer?

Show list of hobbies (card B)

Yes - enter hobby in the hobby column of the hobby table, or 97=DK, 98=NR

No – go to section 5

For each hobby ask Q4.2 to 4.5

3.2 In what year did you/he/she start this hobby?

Table - enter year started next to specific hobby

3.3 In what year did you/he/she stop this hobby?

Table - enter year stopped next to specific hobby

Table – calculate number of years and enter in # column next to specific hobby.

3.4 During this period, how many hours do you estimate you/he/she spent on this hobby per week?

Table - enter hours/week next to specific hobby

3.5 Was protective equipment worn whilst doing this hobby?

No - go to Q4.2 for next hobby, or section 5 if no other hobbies

If yes – What sort of protective equipment?

If respiratory - show respiratory photos (card A)

Table - enter no (if nothing worn), or equipment code in protection column next to specific hobby, or 97=DK or 98=NR.

4. **RESIDENTIAL**

I need to know how long you/he/she spent at home for each of the addresses you/he/she has indicated living at, and whether there was any industry nearby.

Begin with first address and continue through all listed addresses until current address.

(USE **RESIDENTIAL** CALENDER)

4.1 In your/his/her first/next address, would you say you spent;

2. A lot of time at home (more than 16hrs per day)
1. A medium amount of time at home (between 8 and 16hrs per day)
0. A small amount of time at home (less than 8hrs per day)

Residential Calendar - enter 0, 1 or 2 next to year started living there in time column (or 97=DK, 98=NR).

4.2 Was there a factory within 2 kilometres of your home?

Yes – go to Q5.3

No – go to Q6

Calendar - enter 0=No, 1=Yes, 97=DK in factory column next to year started living there

4.3 What was the name of this factory?

Calendar – enter name in factory name column next to year started living there

4.4 What was the address of this factory?

Calendar – enter address in factory address column next to year started living there

4.5 What sort of work did they do there?

Prompts – Steelworks, Smelter, Foundry, Mineral processing plant, Quarry, Fibreglass manufacturing, Chemical plant, Petrochemical plant, Fertilizer

Calendar – enter work in factory work column next to year started living there

Next I need to know about any exposure you/he/she may have had to passive tobacco smoke at this home.

4.6 Were you/he/she ever regularly exposed to the tobacco smoke of others for a period of 6 months or more in your home?

Yes - go to Q2.2

No - go to Q2.8

Enter 0=No, 1=Yes, 97=DK, 98=NR in Born row under passive column

4.7 When did you/he/she first start living with this person?

Calendar - enter S next to year started living with them in passive column.

4.8 After (year) did you/he/she ever stop living with this person for 6 months or more?

Yes - go to Q2.4

No - go to Q2.5

4.9 When did you/he/she stop living with this person?

Calendar - enter Q next to year stopped living with them in passive column.

4.10 How many people did you/he/she live with during this time that smoked?

Calendar - enter number next to year started living with them in # column.

4.11 During this time for how many cumulative hours per **month** did these people smoke in your presence (ie. If 2 people smoked for 1hr/week each that equals 8hrs/month)?

Calendar - enter hour number next to year started in hr/month column

4.11 (ONLY IF STOPPED) Did you/he/she ever live with anyone else for a period of 6 months or more who smoked?

Yes - go to Q2.2

No - go to Q2.8

Continue 4.1 until questions have been asked for all addresses.

6. **EDUCATION**

Now I need to know a little about what education you have received.

(ENTER ANSWERS ON CALENDER **SUPPLEMENT**)

NB: Can use 97=DK or 98=NR

6.1 At what age did you leave school?

Show age card C

6.2 Did you complete the highest level of secondary school available to you?

Yes – go to Q7.3

No – go to Section 8

6.3 Which of these best describes the highest qualification you have completed?

Show card D

7. **ELECTORAL ROLE**

(ENTER ANSWERS ON CALENDER **SUPPLEMENT**)

7.1 I also would like to know if you voted in the last election. This is because we are getting our control subjects, that is people without lung cancer, from the electoral role so we need to know if everyone involved in the study is registered to vote.

1=Yes, 0=No, 97=DK, 98=NR

8. **FAMILY HISTORY**

Finally I need to find out whether you/he/she have/had a family history of lung cancer.

(ENTER ANSWERS ON CALENDER **SUPPLEMENT**)

1=Yes, 0=No, 97=DK, 98=NR

8.1 Were any of the following people in your/his/her family ever diagnosed with lung cancer?

Mother, Father, Sister, Brother

8.2 If yes, did this person ever smoke?

This concludes the interview, thank you very much for giving some of your time to participate in this study.

Guidelines for Implementing the Port Adelaide Lung Cancer Questionnaire

Prior to the interview

- **v** Compete as much of the general information sheet as possible.
- **v** Check the job calender (part A) for consistency between age and date data.
- **v** Enter subject ID number onto ALL pages of the calendar
- **v** Fill out address column of residential calender, and school or job column of work calender

During the interview

- **v** Normal font indicates spoken, italics indicates an action, underline indicates the appropriate column to use for that question
- **v** Do not deviate from what is written down in the structured questionnaire
- **v** Probing must be kept to a minimum unless specified on the questionnaire. It is vital to not probe differently for cases and controls
- **v** Always double check you are using the correct calendar/table for the questionnaire section when entering data
- **v** If you run out of room for an answer in a particular column when writing next to the year started or stopped something then continue the answer in the next line of the same column

Post interview

- **v** Immediately check all questions have been answered and correctly filled in
- **v** Enter data into Access database

Alternative answers

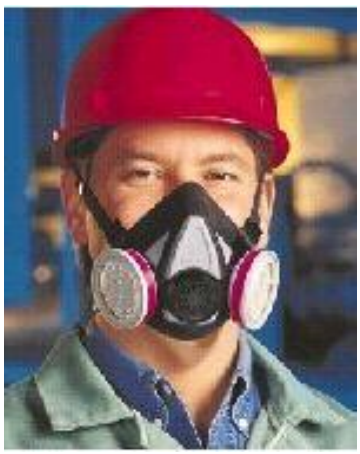
- **v** **DK**=97 – don't know – the subject can not recall the answer to the question
- **v** **NR**=98 – no response – the subject refused to answer the question
- **v** **NA**=99 – not applicable – the question is irrelevant to this subject.

Card A (Types of Respiratory Protection):



1. HALF FACE DISPOSABLE

2. HALF FACE AIR PURIFYING, NON DISPOSABLE





3. FULL FACE AIR PURIFYING, NON DISPOSABLE



4. COMPRESSED AIR SYSTEM, HALF FACE

5. COMPRESSED AIR SYSTEM, FULL FACE





6. SELF CONTAINED BREATHING APARATUS

Card B – List of Hobbies

Card B – HOBBIES

- Mechanical repairs (i.e. spray painting, working with brakes, diesel engine work, drag racing)
- House renovations (i.e. knocking down walls, redoing floors, electrical work)
- Pottery work and/or sculpting

Card C – Levels of Schooling

CARD C – EDUCATION

1. Never went to school
2. Under 14 years
3. 14 years
4. 15 years
5. 16 years
6. 17 years
7. 18 years
8. 19 years
9. 20 years
10. 21 years and over

Card D – List of Qualifications

CARD D – QUALIFICATIONS

1. Secondary School Qualification
2. Nursing Qualification
3. Teaching Qualification
4. Trade Certificate/Apprenticeship
5. Technician's Certificate/Advanced Certificate
6. Certificate other than above
7. Associate Diploma
8. Undergraduate Diploma
9. Bachelor Degree
10. Post-graduate Diploma
11. Master Degree/Doctorate
12. Other (Specify)

Appendix 14: Booklet Used to Record Data Collected at Interview

GENERAL INFORMATION:

ID # - _____

Surname - _____

First names - _____

Contact details:

Home phone - _____ Work - _____

Address - _____

_____

Interview details:

Date - _____

Type of interview - 1-Direct / 2-Proxy / 3-Assisted (circle)

If proxy or assisted, relationship to subject - _____ (specify)

1=Parent, 2=Partner, 3=Sibling, 4=Son/Daughter, 5=Friend, 6=Other

How many years have they known subject - _____ yrs

And lived with subject - _____ yrs

Appendix 15: Example of Occupational Information Provided to Occupational Hygiene Panel for Exposure Assessment

Job ID 536 **Subject ID** 353 **Gender** 1 (1=M, 0=F)

426 Employer (Name of company)

Outer Harbour SA

AUST

Maritime Industry

Occupation Jetty Builder

01/01/1948 **TO** 01/01/1951

6 **Days per week** 100 **% of time spent inside**

45 **Hours per week** 1 **0= Manager, 1=General staff**

TASKS

364 Jetty Builder Woodwork - repairing and building jetties.

Undertaken **X Per** **and**

TO

Resp. protect. not worn (1=y, 0=n) 1 Type- How often worn- **Dusty?** 0 **Smoky?** 0 **Irritating?** 0 **Poorly ventilated?** 0 **(1=Yes, 0=No)**

365 Machinist Rolling machine, drilling machine, pressing machine.

Undertaken **X Per** **and**

TO

Resp. protect. not worn (1=y, 0=n) 1 Type- How often worn- **Dusty?** 0 **Smoky?** 0 **Irritating?** 0 **Poorly ventilated?** 0 **(1=Yes, 0=No)**

Panel Member: Name Job ID: _____ Subject ID: _____

Likelihood and level of exposure (please tick one)

Carcinogens	**Probable**				**Possible**	**Unlikely**	**Indicate the yrs exposed if NOT for job entirety**	**Notes (if required)**
	High	**Med**	**Low**	**Very low**				
Asbestos (0.1 fibre/mL air)								
Formaldehyde (1ppm) PAH								
Diesel exhaust Crystalline silica ($0.2\ mg/m^3$)								
Fine Particulate ($5\ mg/m^3$) Arsenic ($0.05\ mg/m^3$)								
Beryllium ($0.002\ mg/m^3$)								
Nickel ($1\ mg/m^3$)								
Cadmium ($0.01\ mg/m^3$)								
Chromium 6 ($0.05\ mg/m^3$)								
Radon (20mSv/annum)								

Exposure standards - NOHSC – 8hr exposure limits (other than Radon – annual exposure limit)

High = ≥ 100% exposure standard : Medium = ≥ 42% and < 100% : Low = ≥ 5% and < 42% : Very Low = < 5%

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

Members of the Australian Institute of Occupational Hygienists were surveyed via email to determine their interpretation of the quantification of categories of “low” and “medium” workplace exposure. The email sent was as follows:

Hi Folks,

We are undertaking a research project involving retrospective exposure assessment. I am seeking opinions from practicing hygienists as to what they interpret as "medium" exposure to chemicals which have exposure standards based on long-term effects. The poll question is as follows, with only one option allowed and no discussion on any aspect of the question.

In your judgement "medium" exposure is:

(i) between 0.1x and 1x the current exposure standard

(ii) between 0.2x and 1x the current exposure standard

(iii) between 0.33x and 1x the current exposure standard

(iv) between 0.5x and 1x the current exposure standard

I'd be grateful if you could just email me back with your "answer".

I can feedback the "results" to you, as an overall frequency distribution.

Nineteen responses were received. All respondents were Australian occupational hygienists.

Occupational Hygienist Responses to the Question "What is your judgement of medium exposure?"

Answer	Number of responders
(i) between .1x and 1x the current exposure standard	0
(ii) between 0.2x and 1x the current exposure standard	1
(iii) between 0.33x and 1x the current exposure standard	8
(iv) between 0.5x and 1x the current exposure standard	10

When the views of the hygiene panel were combined with the results of the survey we found an equal number of responses for Option (iii) and (iv), resulting in the decision to average these two results so that medium became ≥ 42% and < 100% of the current health based exposure standard.

CONFIDENTIAL - PERSONAL RESIDENCE AND WORK CALENDAR

Your details:

Surname:_____ First names:_____

Contact phone number: Home ( )_____ Work( )_____

Details of your Next of Kin (the person taking part in the full study):

Surname:_____ First names:_____

Instructions:

Remember, you are answering these questions on behalf of _____, please do not ask this person for help, we need to see how much you are able to remember by yourself.

If you run out of room in any columns, just go onto the next line down.

1. **Year and Age**: These columns are already filled in.
3. **Where lived:** Opposite the age and year they started to live at a place, write down the number, street, town or suburb and State. If overseas, write down the town and country. If they lived in more than one place in any year, write down the place where they lived longest in that year.
4. **Job:** a) Write down the title of the job they had opposite the year they started there. If they had more than one job in any year, write down the one that they had the longest in that year. b) Write down the main tasks they did next to each job. Main tasks are the things they did on most days, be as detailed as you can. c) From the list on page 3, select and write down the name of the industry they were working in for each job next to the year they started there.
5. **Smoking:** a) If they smoked, write down when they smoked cigarettes for a period of six months or more next to the year they started. Also indicate when they stopped smoking (if relevant). b) Indicate the average number of cigarettes they smoked per day during the years they were smoking.

It's alright if you have trouble remembering some things, please just do the very best you can.

1. Year	2. Age	3. Where lived (number, street, suburb, state)	4.a) Job Title	4.b) Tasks (things done on most days – as much detail as possible)	4.c) Industry (select from attached list)	5.a) Smoked (yes/no)	5.b) Amount smoked (cig/day)
1970							
1971							
1972							
1973							
1974							
1975							
1976							
1977							
1978							
1979							
1980							
1981							
1982							
1983							
1984							
1985							

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

Clinical Epidemiology & Health Outcomes Unit
8th floor, Basil Hetzel Institute, 28 Woodville Road
WOODVILLE SOUTH SA 5011
Phone: 8222 7542 Fax: 8222 6896

To: [Name of Participant]

5 January 2004

Dear [First name of Participant]

During 2001 and 2002 you took part in research done by the Clinical Epidemiology Unit and University of Adelaide. The research looked at reasons for lung cancer deaths in the NW suburbs of Adelaide. We would now like to share the results with you.

Lung Cancer death rates in some parts of North West metropolitan Adelaide are up to two times that expected from state averages. Melissa Whitrow (PhD candidate) did a study in NW Adelaide to find out why this is happening. Due to the number of factories in this area, the study looked at how close a person's house was to a factory and whether or not someone had worked at a factory. We also looked at cigarette smoking as that has already been shown to be associated with lung cancer in other studies.

This study found no link between living near or working in industry and lung cancer. The study results found that cigarette smoking was the main reason for higher lung cancer rates in NW Adelaide. We did not find any links between lung cancer and any other risk factors that were looked at (hobbies that people had done, whether a family member had also had lung cancer).

Thank you for making the time to speak with us. Without your help this study would not have been possible. If you would like further information about the study results, please ring the number above and ask to speak to [Name of research assistant].

Thank you again
Yours sincerely

Associate Professor Brian Smith
Director – Clinical Epidemiology & Health Outcomes Unit
Director – Respiratory Medicine
On behalf of the lung cancer study research team

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