A CASE-CONTROL STUDY OF MESOTHELIOMA IN SOUTH AFRICA

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DECLARATION

I hereby declare that the work forming the basis of this thesis is my own and has not been previously submitted for any degree at any university.

Signed by candidate

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14th day of November, 1995.

ABSTRACT

This thesis reports the results of a prospective multi-centred case-control study of mesothelioma carried out in South Africa. The objectives of the study were:

1) to examine asbestos exposure of cases in detail with respect to source, risk occupations, fibre type and duration;
2) to determine relative risks for level (certainty) of exposure (definite, probable, possible, unlikely), for category of exposure (occupational, environmental), and for fibre type and skin colour;
3) to determine whether cases without recall of exposure were exposed to other non-asbestos putative agents;
4) to investigate the possible protective effect of certain dietary components.

Previous studies of mesothelioma in South Africa had, with the exception of one incidence study, focused on particular occupational or case material, exposure data had been gathered in a non-systematic way, often indirectly from surrogates, and non-asbestos agents had not been investigated. In this case-control study these issues are all addressed. In addition, special efforts were made to minimise potential sources of bias (e.g. interviewer bias) and so to furnish reliable effect estimates.

The study incorporated the following methodological features:

1) a prospective approach to gather exposure and dietary

information directly from the cases and controls in life and so avoid the use of surrogates for this information;

2) the study was multicentred with study teams established in six cities, each with a major referral hospital, to maximise nation-wide coverage;

3) information was gathered with interviewers blind (at least at the beginning of the study) to study objectives and case control status at the time of the interview;

4) rigorous pathologic review was used to establish the diagnosis of mesothelioma;

5) two controls were selected for each case, a cancer and a non-cancer patient matched for hospital, sex, age and skin colour;

6) in analysis the case control datasets were treated separately (i.e cases and cancer controls, and cases and non-cancer controls were treated as two separate datasets).

One hundred and twenty three cases were accepted into the study. No case was documented with purely chrysotile exposure nor exposure to a putative non-asbestos cause of the tumour without some evidence of asbestos exposure. A minimum of 22 cases (18%) had exclusively environmental exposure, 20 were from the NW Cape (a crocidolite mining region). Fifty eight percent had occupational exposure, three of whom had mined amosite. The relative risks associated environmental exposure in the NW Cape were larger than for environmental exposure in the NE Transvaal: 21.9 versus 7.1 for the cancer

control dataset and 50.9 versus 12.0 for the medical control dataset. Increasing consumption of carotene rich fruit was found to be protective for mesothelioma when adjusted for asbestos exposure.

The results confirm the high disease burden due to occupational exposure, the importance of environmental exposure in the crocidolite mining area of the NW Cape, the relative paucity of cases linked to amosite, the rarity of chrysotile cases, and are consistent with the view that there is a fibre gradient in mesotheliomagenic potential for South African asbestos with crocidolite > amosite > chrysotile. The evidence for a protective effect of carotene rich fruit is new in the South African context.

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Cases were referred to this study by medical practitioners who were nagged for a couple of years by team coordinators and NCOH staff members. I relied on their goodwill and

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This thesis is dedicated to Susan, Kate, Jan and Nicki.

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TERMINOLOGY USED FOR REGIONS OF SOUTH AFRICA

The names of the provinces of South Africa were changed when this thesis was in its final stages. For a number of reasons the old regional terminology has been retained in the thesis. The most important is familiarity with the old names, for example the NE Transvaal asbestos fields bring to mind a particular belt of asbestos deposits which are amosite at one extreme and Transvaal crocidolite at the other. It would have been confusing to rename the locations of the fields and would have made reading the thesis difficult. Also the location of some of the asbestos deposits occurred near new provincial borders and it was not always clear into which new province they now fell. Table 2.1 lists asbestos deposits by magisterial district and region: these regions are the old regions of South Africa and are not used in the sense of provinces of South Africa.

CHAPTER ONE

Introduction

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1.1 MESOTHELIOMA: DIAGNOSIS AND AETIOLOGY.

1.1.1 Introduction

Diffuse malignant mesothelioma (subsequently termed mesothelioma) is a lethal tumour which arises from mesothelial cells of the pleura, pericardium and peritoneum. The condition is of particular importance in South Africa because of the high rates of the disease in general [Zwi et al., 1989] and in exposed communities in particular [Reid et al., 1990], and because South Africa has mined, milled, transported and used the three main commercial varieties of asbestos for decades. Despite the local importance of this tumour epidemiologic research has been limited in extent and generally confined to mine workers, the NW Cape or series of cases presenting to the National Centre for Occupational Health (NCOH) Occupational Medicine clinic.

1.1.2 Diagnosis

The diagnosis of mesothelioma is difficult histologically [McCaughey and Oldham, 1973] largely because of the morphological variability of the tumour. Malignant mesothelial cells are difficult to distinguish from benign reactive mesothelial cells (the extent of invasion into surrounding tissue is important) and may mimic other neoplasms metastatic to the sites of mesothelioma. Adenocarcinomas are especially important in this regard. Procedures in which larger amounts of tissue are collected are considered diagnostically superior, hence thoracotomy

and thoracoscopy are preferred to cytology and closed pleural biopsy (e.g. Abrams needle biopsy) [Martensson, 1990], although protocols have been developed to improve diagnostic accuracy when only pleural fluid and limited biopsy material are available [Whitaker and Shilkin, 1984]. Immunohistochemical techniques have improved the diagnosis of mesothelioma. Carcinoembrionic antigen (CEA) stains positive in under 10% of all mesotheliomas compared to more than 90% of adenocarcinomas of the lung [Brown et al., 1993; Joglekar et al., 1991; Otis et al., 1987]. Anti CEA has been found to be the best discriminating antibody for most types of mesothelioma [Brown et al., 1993; Joglekar et al., 1991; Otis et al, 1987]. Electron microscopy can be used very successfully to distinguish malignant mesothelial cells from adenocarcinomas but is of little value in separating malignant from benign reactive mesothelial cells [Whitaker and Shilkin, 1984].

The diagnostic difficulty was one factor which lead to a panel of pathologists being formed to examine the diagnosis of mesothelioma in South Africa. This Panel, called the South African Asbestos Tumour Reference Panel was formed in the mid-1960's and disbanded in early 1993, partly because of affordability and partly because of a perception that the effort in sustaining the Panel and the register was not justified by subsequent data usage. The Panel reviewed tissue submitted to it and cases considered definite or probable mesothelioma were added to a mesothelioma register maintained by the Pathology Department of the National

Centre for Occupational Health (NCOH) in Johannesburg.

1.1.3 Aetiology: asbestos fibre type

Once Wagner, Sleggs and Marchand [1960] had provided a case for the link between mesothelioma and asbestos exposure the disease was extensively investigated and many hundreds of papers have been published. Nevertheless, important questions about mesothelioma remain partially answered. Among them is the aetiology of this tumour.

The association with asbestos exposure is indisputable. The capacity for the different asbestos fibre types to cause mesothelioma in exposed individuals is less clear. A large body of evidence suggests that amphiboles are much more potent mesothelial carcinogens in humans than is chrysotile [Acheson et al., 1982; Berry, 1986; Mcdonald et al., 1982; Mossman, 1990; Wagner, 1986] and that crocidolite (blue asbestos) is more potent than amosite (brown asbestos)[Mcdonald et al., 1982; Churg and Wiggs, 1984; Gibbs et al., 1989; Sluis-Cremer et al., 1992].

The role of chrysotile (white asbestos) is controversial. The mining and milling of Canadian chrysotile is associated with a risk of mesothelioma [Churg et al., 1984a] and animal experiments have shown convincingly that all the major asbestos varieties including chrysotile can produce the cancer [Wagner et al., 1973]. Nevertheless, the causal association between chrysotile exposure and mesothelioma in humans is not established because certain chrysotile ores contain a small proportion of the amphibole tremolite and

this fibre has been found in the lungs of chrysotile miners [Pooley, 1976]. It has been shown to cause mesothelioma in rats [Wagner et al., 1982] and has been implicated as the causative agent of mesothelioma in workers exposed to vermiculite contaminated with tremolite [Mcdonald et al., 1986]. It has been suggested, therefore, that the fibrous tremolite rather than the chrysotile itself, may be responsible for the disease in the majority, if not all, of the chrysotile exposed cases [Churg and Wiggs, 1984]. Elmes [1994] has summarised the mesothelioma risk from chrysotile by writing "that it may be possible to mine chrysotile ore containing less than a certain amount of fibrous tremolite without any risk of mesothelioma. This may already be happening. Such 'clean' chrysotile should carry no risk to the user or general public provided current safety procedures are enforced".

This low risk of chrysotile, an exclusively amphibole theorey of mesothelioma causation is one end of the spectrum of opinions, is disputed by Mancuso [1988], Nicholson et al. [1990] and others, and by the findings of some studies of chrysotile exposed workers. Mancuso [1988] found that mesothelioma accounted for almost 10% of deaths in a cohort of railroad machinists exposed to chrysotile. The cohort was probably exposed to crocidolite as well as chrysotile [Churg and Green, 1990] which limits the value of the study. Nicholson and colleagues [1990] argue that the risk of mesothelioma per fibre exposure in three studies where it can be estimated directly from exposure and incidence data,

is identical for exposures to 98% chrysotile plus 2% crocidolite, 60% chrysotile plus 40% amosite, and 100% amosite, respectively. They add that in other studies where the risk cannot be estimated directly, the ratio of the number of mesotheliomas to excess lung cancers is the same for exposures to predominantly chrysotile, to 100% amosite, and to mixtures of chrysotile, amosite and crocidolite, within the uncertainties of the estimation. Supporting this view of a greater risk of mesothelioma following chrysotile exposure are reports of mesothelioma in cases whose lungs contain chrysotile but no amphiboles [Langer and McCaughey, 1982; Moringa et al., 1989; Maltoni, et al., 1990; Rogers et al., 1991]. A number of recently published studies of almost exclusively chrysotile exposed workers have shown high risks of mesothelioma. Raffn and colleagues [1992] reported on 269 men heavily exposed to asbestos and almost exclusively to chrysotile. The relative risk for mesothelioma was 22.73 for workers who had been employed at the facility for 20 or more years. Chrysotile cannot be dismissed as a cause of mesothelioma, and, given the very large number of individuals exposed to this agent, in mixtures or alone, it remains an important issue.

1.1.4 Aetiology: asbestos fibre type in South African cases

The relative contribution each variety of asbestos makes to the case load of mesothelioma in South Africa is not well established, although Cape blue (crocidolite from the NW Cape) is responsible for the great majority of cases in which fibre type is known. Webster [1973] examined the exposure history in 232 cases of pleural mesothelioma confirmed by the Panel: in 78 exposure was exclusively in mining and related activity. Seventy five of these cases (96%) had worked on crocidolite asbestos mines of the NW Cape; 2 or 3 had had amosite exposure (Penge mine) and one probably had exposure to Transvaal blue only. The author notes that the production of amosite far exceeded that of blue asbestos prior to the study and that under-ascertainment of cases from the NE Transvaal region sufficient to explain the findings was unlikely. A minor limitation of the study was that in 22 cases (9%) an exposure history was missing.

Data that amosite is less dangerous than crocidolite as far as mesothelioma is concerned have been presented by Sluis-Cremer et al. [1992]. A cohort was established in 1981 of 7317 white employees in the amosite and crocidolite mines in South Africa whose names had appeared in the personnel records of the major companies. Miners employed only on Transvaal crocidolite mines were not included in the cohort. Three sub-cohorts were defined: 3212 men whose only asbestos exposure was to amosite, 3430 exposed to crocidolite and 675

to both amphiboles. Vital status and causes of death were established from Medical Bureau for Occupational Disease files and from death certificates. Loses to follow-up numbered 167 (2%) and there had been 1225 deaths, 30 of which were attributed to mesothelioma on "best available evidence". Twenty were in crocidolite miners, 4 in amosite miners and 6 had had exposure to mixed asbestos. A group of 90 men had been exposed to Transvaal crocidolite as well as to amosite. Two of these men died of mesothelioma, thus 6.7% of mesothelioma deaths occurred in this small group comprising 1.2% of the cohort. The incidence per 100 000 subject-years was 7.8 and 44.6 for amosite and crocidolite miners respectively and the proportional mortality ratio in men followed from 20 years after first employment was 1.7% and 11.9% respectively. The authors' conclusion that there can now be no question that crocidolite is far more dangerous than amosite as far as mesothelioma is concerned appears justified since fibre concentrations were roughly similar in the two types of asbestos mines.

Mesothelioma cases from South African chrysotile mines have not been recorded [Wagner, 1986]. This statement is supported by the Panel's mesothelioma register which contains over 2000 cases, none with a history of asbestos exposure exclusively on a chrysotile mine either in South Africa or Swaziland [Personal communication: Webster I, Pathology Department NCOH, 1993]. It should be noted that an exposure history is not recorded in about 50% of these cases [NCOH Annual Report, 1990] thus reducing the significance of

these data. The lack of cases cannot be explained adequately by the small number of workers employed in chrysotile mines: from the 1930's to mid 1980 roughly 1000 to 2000 workers were employed in chrysotile mining at any one time (Personal communication, du Toit NCOH, 1991 RdT 16.27). Cullen and Baloyi [1991] described four cases of probable mesothelioma attributed to chrysotile exposure on Zimbabwean chrysotile mines but either the diagnosis (chest radiographs only in two cases) or the exposure (fitter and turner with likely asbestos exposure elsewhere in a third, and a manager for less than two years in the fourth) can be questioned in each case. There are suggestive data that Southern African chrysotile contains relatively little tremolite [Rees et al., 1992] which may be an explanation for the paucity of chrysotile cases in the region. These data are preliminary as they are based largely on a small study of lung fibre content of four ex-miners with asbestos related disease and asbestos mining exposure exclusively in chrysotile mines. Confirmatory studies are required.

The studies cited above provide convincing evidence that the risk of developing mesothelioma is determined, in part, by the nature of the asbestos fibre. These studies and other South African investigations have, however, not satisfactorily determined the relative contribution of each fibre type to the total case load. This is due to missing or incomplete exposure data [Webster, 1973; Zwi et al., 1989; NCOH Annual Report, 1990] or selection bias because referral into the case series was primarily for workers' compensation

claims and thus favoured occupationally exposed subjects and underrepresented miners and those living around mines [Solomons, 1984]. Other investigations of the tumour have been restricted to a single geographic region, namely the NW Cape [Talent et al., 1980; Botha et al., 1986; Reid et al., 1990] or to selected occupational cohorts [Sluis-Cremer et al., 1992).

A study to estimate the relative contributions of the various fibre types to the mesothelioma case load in South africa would thus provide missing information and was one question this thesis aimed to investigate.

1.1.5 Aetiology: the extent of asbestos exposure in South African cases

Despite the importance of the disease in South Africa the proportion of local cases with known asbestos exposure and the nature of this exposure are uncertain. Cochrane and Webster [1978] found exposure in 69 of 70 cases referred to the NCOH Clinic and Solomons [1984] 75 of 80 but these cases were probably unrepresentative of South African cases as individuals with exposure, and occupational exposure in particular, were probably selected for referral preferentially so that compensation claims could be submitted by the Clinic. The Panel's national mesothelioma register provides exposure information but the data are limited as about half of the cases have either no available history or no known exposure [NCOH Annual Report, 1990]. The only incidence study in South Africa relied on medical

records and other documents and there was no exposure information in 33% of cases and a further 10% had no known contact with asbestos [Zwi et al., 1989]. The proportion of cases with exclusively environmental exposure was 14% for the register cases [NCOH Annual Report, 1990]; 10% in males and 35% in females in the incidence study [Zwi et al., 1989] and 9% in the Clinic series comprising 73 men and 7 women [Solomons, 1984]. The contribution of domestic and para-occupational contact was not established. Methodological problems such as incomplete exposure information or misrepresentation of the study base reduce confidence in these data and limit the investigation of issues such as duration and likely intensity of exposure and risk occupations.

In summary, South African studies of mesothelioma have provided important information but no study has attempted to investigate the details of asbestos exposure in a standardised way in cases restricted neither geographically nor by exposure experience. Thus incomplete exposure information or under- representation of exposure categories has reduced the available data on the importance of various fibre types, the identification of risk occupations and an examination of duration and type (e.g. environmental/occupational) of asbestos exposure in cases. This thesis aimed to provide data on these issues.

1.1.6 Aetiology: putative causes and a background rate

Asbestos is not the only cause of mesothelioma. Natural fibrous zeolites, particularly erionite, are found in certain villages in Turkey and in the absence of asbestos exposure, villagers have a very high incidence of mesothelioma [Baris et al., 1987]. Erionite fibres have been shown to cause mesothelioma in rats [Wagner et al., 1985]. The evidence for non-fibrous causes of mesothelioma is less convincing. Ionising radiation is probably the strongest candidate [Antman et al., 1983; Beier et al., 1984; Anderson et al., 1985] but the putative agents include chronic inflammation [Hillerdal and Berg, 1985] and a variety of chemical agents. Pelnar [1983, 1988] reviewed the literature and listed ionising radiation, chronic irritation (e.g. following infections such as pleural tuberculosis), heavy metals (beryllium and nickel), a variety of chemicals and sugar cane as possibilities. Peterson and colleagues [1984] suggest radiation, minerals (nickel, silica dust and beryllium), man made mineral fibres (MMMF), organic chemicals, viruses and chronic inflammation. The mesothelioma risk from MMMF is unconvincing [Brown et al., 1991] and recent studies of sugar cane have not confirmed its association with the tumour [Brooks et al., 1992] despite the presence of fine biogenic silica fibres in the cane [Newman, 1986]. The case for mesothelioma arising only following exposure to fibres was summarised by Davies [1988] while Ilgren and Wagner [1991] have reviewed the evidence supporting a background incidence. Support for non-asbestos causes and a background rate for the tumour centre on the

consistent finding of an absent exposure history in a proportion of cases; usually 10%-20% [Solomons, 1984; van Gelder et al., 1989] but frequently higher. Ratzer et al. [1967] obtained a positive history in only 13% and Chiappino and colleagues [1985] 23%. Of course absent exposure may be explained by poor recall or knowledge of exposure, particularly if this occurred in childhood or to low doses of fibre. Analysis of lung fibre loads have not provided the answer as some cases without reported exposure have a lung fibre content higher than those with reported exposure and other cases have loads overlapping with controls without the disease or known exposure [Gibbs et al., 1989; Mowe et al., 1984; Mowe et al., 1985; Churg et al., 1984a]. Consequently, whether the tumour can arise in the absence of exposure to fibres is difficult to answer even with data from lung mineralogy studies, particularly since the composition, morphology, size distribution [Stanton and Wrench, 1972; Stanton et al., 1981], durability, residence time and location of fibres may all be factors related to carcinogenesis as are the biologic characteristics of exposed individuals.

The issue of a background rate may be relatively unimportant in South Africa as mining and related activity has exposed whole communities. The background rate, if it exists, may thus be overwhelmed by the vast proportion of cases with exposure. This thesis intended to explore this issue by a detailed examination of exposure to asbestos and other putative causes using an exposure questionnaire administered

to cases themselves. It would thus be the first study in South Africa which aimed to collect exposure data prospectively (i.e. in-life from the subjects) from a representative set of cases so that the role of non-asbestos agents could be examined.

1.2 CONFOUNDING OR EFFECT MODIFYING VARIABLES.

A confounder is an extraneous variable that is a risk factor for the study disease (in subjects unexposed to the study exposure) and is associated with the study exposure but must not be an intermediate step in the causal path between exposure and the disease [Rothman, 1986]. A confounder's association with the disease can be noncausal if it results from the confounder's association with causal factors other than the study exposure [Schlesselman, 1982].

The definitions above suggest that confounding may not be an important bias in measuring the association between asbestos and mesothelioma due to the extreme degree of specificity between the fibre and the tumour. If one accepts that asbestos and erionite are the only causes of mesothelioma then no risk factors satisfy the requirements for confounding the association between asbestos exposure and mesothelioma. Erionite is restricted to specific localities so asbestos is the only established cause of the disease in South Africa; increasing age is associated with increasing incidence of the tumour but only in asbestos exposed individuals. Tobacco smoking has no influence on mesothelial carcinogenesis [Rogers et al., 1991]. Nevertheless, confounding could occur in a particular dataset if a background rate exists for the tumour or if one was "created" through underascertainment of asbestos exposure in cases because of inadequate exposure assessment. In either instance a proportion of the cases would not be associated

with asbestos exposure. A variable extraneous to the association between asbestos exposure and mesothelioma which was a risk factor for mesothelioma in cases not exposed to asbestos could thus be present in a dataset.
Asbestos exposure may be a confounder in the examination of putative causes of the tumour and in the examination of factors such as diet and skin colour, if these factors are linked to asbestos exposure.

Effect modification is possible, in theory, particularly since only a relatively small proportion of asbestos exposed individuals develop the tumour. One explanation for this is that a factor modifies the effect of exposure.

1.2.1 Diet and mesothelioma

The role in carcinogenesis of dietary factors, which may be protective (e.g. beta-carotene) or promote tumorigenesis (e.g. fats for colon cancer), has been the subject of numerous investigations. There is a need for the further elucidation of the role of dietary factors in carcinogenesis [Freudenheim and Graham, 1989]. Mesothelioma has not been exempt from this interest in diet and cancer. Schiffman and co-workers [1988] reported lower consumption in mesothelioma cases than controls of homegrown produce, cruciferous vegetables, all vegetables combined and estimated usual carotene intake. A reduction in risk with increasing consumption of vegetables, especially cruciferous vegetables, was found also. They postulated a protective

effect of some vegetable related constituent.

1.2.2 Skin colour and mesothelioma

Skin colour is associated with mesothelioma rates. For example, Zwi et al. [1987] found white South Africans to have the highest incidence rates followed by those of mixed race and then black South Africans. Spirtas and colleagues [1986] found higher rates of the tumour in white than in black Americans. It is likely that differential access to health care and related factors account for these differences [Zwi et al., 1987] but a comparison of skin colour-specific risks would clarify the role of this factor.

The large number of cases of mesothelioma diagnosed in South Africa and thus available to provide a dietary history, and the diversity of South African society suggest that this country would be suitable for the investigation of diet, skin colour and mesothelioma.

1.3 CASE-CONTROL STUDIES.

1.3.1 Asbestos exposure

Mesothelioma has a number of characteristics which make the epidemiologic study of its causes and the investigation of the details of past exposure of cases problematic. It is rare (except in certain high risk groups [Reid et al., 1990]), has a long latent period between first exposure and disease and is rapidly lethal [Solomons, 1984]. The long latency reduces the availability of high quality exposure records and rarity and short survival makes it difficult to accumulate satisfactory numbers of cases for personal exposure interviews. An additional factor is that the exposure of major interest (asbestos) is present in a large variety of workplaces and dwellings and has been used in thousands of products. In mining regions it is a pollutant around mines, mills and transport routes. Exposure, therefore, can occur from birth to death and occupational or employment histories provide incomplete exposure profiles. The case-control study design is appropriate for rare diseases and consequently is not unusual in the study of mesothelioma; the earliest such investigation was conducted in the 1960's [Newhouse and Thompson, 1965] soon after the link between asbestos and mesothelioma was shown in descriptive studies. These studies were successful in establishing the strong association between asbestos and mesothelioma but for the most part, because of the factors discussed, have suffered from relatively poor exposure data.

In many studies the details of exposure were obtained not from the cases themselves but from proxy informants such as spouses, relatives, neighbours or friends [Newhouse and Thompson, 1965; McDonald et al., 1970; McEwen et al., 1970; Rubino et al., 1972; McDonald and McDonald, 1973; McDonald et al., 1980; Chiappino et al., 1985]. Others relied on, or supplemented these data with, employer, death certificate, insurance, compensation or other documentation [Ashcroft, 1973; Zielhuis et al., 1975; Teta et al, 1983; Berry, 1983; Mowe et al., 1984; Mowe et al., 1985; Schenker et al., 1986; Cicioni et al., 1991]. Lung fibre loads contributed to exposure data in some [Ashcroft, 1973; Berry, 1983; Mowe et al., 1985; McDonald et al., 1982; Rogers et al., 1991; Tuomi et al., 1991]. In a few investigations the minority of cases and controls were interviewed in life to obtain exposure data [Ashcroft, 1973; Zielhuis, 1975; Mowe et al., 1984; Schiffman et al., 1988]. In one all subjects were interviewed [Muscat and Wynder, 1991] and in another 51 of 57 cases gave a job history [Tuomi et al., 1991] but were not asked about asbestos exposure.

The effect of proxys has been to underestimate asbestos exposure in both cases and controls [Zielhuis et al., 1975], i.e. misclassification has occurred, sometimes apparently grossly, for example Rubino and colleagues [1972] obtained a history of asbestos exposure in only 18% of 50 mesothelioma cases. This is in contrast to the study which administered a questionnaire to all subjects: likely asbestos exposure was identified in 78% of 105 male cases (Muscat and Wynder,

1991). Underestimating exposure limits the examination of details such as sources of exposure, duration and likely intensity as well as the role of agents other than asbestos (since non asbestos exposed individuals are not confidently identified). Studies which rely on lung fibre load satisfactorily quantify cumulative amphibole but underestimate chrysotile exposure [Pooley, 1976; Glyseth et al., 1983] and provide limited information on the nature or source of this exposure.

This thesis aimed to address the limitations of proxy informants in case-control studies of mesothelioma by conducting personal exposure interviews with all cases and all controls participating in the study.

1.3.2 Bias: misclassification, misrepresentation and confounding

1.3.2.1 Misclassification

Comparable accuracy in measurement of exposure is required to avoid misclassification of exposure [Wacholder et al., 1992a] but a number of potential sources of bias may increase relative asbestos exposure in cases of mesothelioma compared to controls. Cases (and proxy exposure informants) with a disease known to be associated with asbestos are likely to be repeatedly questioned and to search their memories for exposure to a greater extent than controls with

diseases unrelated to known exposures. Cases may, therefore, be more likely than controls to recall exposure when questioned for a study. In contrast, the exposure recollection of healthy controls may be better than that of seriously sick cases, this would increase relative exposure in controls and thus reduce the strength of association between disease and exposure. The use of cancer controls has been suggested as a strategy to minimize this recall bias where the exposure of interest has received extensive publicity [Linet et al., 1987].

Recall bias is not the only way in which differential exposure misclassification can occur. Interviewers aware of the disease status of subjects and the possible link between the disease and exposures of interest may preferentially seek exposure information from cases. Medical and other records may exhibit the same bias particularly where medico-legal imperatives drive a search for exposure and its documentation in mesothelioma cases but not in controls. Misclassification of diagnosis can arise when a disease is closely linked to an exposure so that reported exposure becomes a criterion in diagnosis or positively influences diagnostic outcome: this has been called diagnostic suspicion bias [Sackett, 1979]. This is the case for mesothelioma [Whitaker and Silkin, 1984]. The result is preferential selection of exposed individuals as cases and is of importance in more recent studies of mesothelioma due to widespread publicity of the role of asbestos.

1.3.2.2 Misrepresentation

In general, cases and controls should be representative of the same base experience [Miettinen, 1985]. Bias will arise if the subset of the individuals studied misrepresents the study base. Since case-control studies of mesothelioma usually study a sample of individuals in a secondary base rather than a random sample from a population or primary base, misrepresentation is an important consideration . Hospitals or medical (often pathological) practices, disease registers (e.g. cancer registers) or occupational cohorts formed the base from which cases and controls were selected in all the case-control studies cited above. An important consideration in using a secondary base is to ensure that the distribution of the exposures under study in the controls is the same as that in a random sample from the same base that produced the cases (Wacholder et al., 1992b). This can be achieved in part by selecting as controls only subjects with diagnoses unrelated to asbestos exposure - for example Zielhuis and co-workers [1975] used patients with cardiovascular disease.

A particular problem with hospital controls in asbestos mining regions is non-uniform catchment of diseases by the hospital. Mesothelioma is likely to be diagnosed and treated in regional referral hospitals which thus become the source of both cases and controls. If the referral hospital is also the medical care facility for people living in the vicinity of the hospital, then the base experience of cases and controls will differ: cases are likely to be referred from

afar into the hospital while many patients and hence potential controls will be locals. Selection bias will occur in distant referral hospitals serving asbestos mining regions when cases resident near mines and mills are referred into regional hospitals while potential controls from the same area are treated at a local medical facility. These potential controls are unavailable for selection and will be replaced by locals without the exposure experience thus leading to misrepresentation of asbestos exposed controls in this subset of the study base. One method of restricting this source of bias is to limit controls to patients with the same referral potential as cases i.e. those with diseases sufficiently severe to have lead to referral into the regional hospital. Differential distribution of asbestos exposure across socio-economic strata will be important if controls and cases are of incomparable socio-economic status. Matching on hospital or likely patient profile (e.g. public or private) has been used to control this bias.

1.3.2.3 Confounding

As discussed in section 1.2 there is reason to believe that confounding may not be an important issue in case-control studies of mesothelioma, although confounding may be observed when underreporting of exposure is sufficiently large to result in a substantial proportion of cases without asbestos exposure. Confounding variables have not been reported in previous case-control studies of mesothelioma.

In summary, it can be seen that case-control studies of mesothelioma should be designed to maximise exposure information and minimize bias due to misclassification and misrepresentation.

1.4 STUDY OBJECTIVES.

The study objectives can be summarised as:

1. To examine asbestos exposure in detail in South African cases of mesothelioma studied during a prospective case-control study. Exposure detail to include sources of exposure, risk occupations, likely fibre type and duration of asbestos exposure. The contribution to the case load by Cape crocidolite, amosite and chrysotile to be determined. Incomplete exposure information was limited by restricting cases to living subjects (thus avoiding reliance on proxy informants). To reduce selection bias cases were not limited by geographic region, industry nor medical facility.

2. To determine relative risks for level (certainty) of asbestos exposure (definite, probable, possible and unlikely), for category of exposure (e.g. occupational and environmental), and for fibre type.

3. To determine whether cases of mesothelioma without recall of asbestos exposure were exposed to non-asbestos agents putatively associated with mesothelioma. Agents examined included glass-fibre, other manufactured mineral fibres, X-rays, radioactive material, beryllium, nickel and sugar-cane.

4. To investigate the possible protective effect of the consumption of vegetables, cruciferous vegetables, carotene containing fruit and vegetables, and homegrown vegetables on the development of mesothelioma.

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CHAPTER TWO

Subjects and Methods

Contents Pages

2.1 STUDY DESIGN.

A prospective multi-centred case-control study of mesothelioma using a secondary base of referral hospitals for cases and controls.

2.2 STUDY CENTRES AND RESEARCH TEAMS.

The study was conducted in six study centres. These were major industrial centres of South Africa and each centre included all hospitals within 50 kilometres of the city centre. Greater Bloemfontein, Cape Town, Johannesburg, Kimberley and Pretoria were selected as study centres because they are major industrial centres, house academic medical complexes and are geographically placed so that their tertiary hospitals serve much of South Africa including the asbestos mining regions (without being in an asbestos region itself). Port Elizabeth was selected because, except for the academic complex, it satisfied these criteria and is the largest city in the Eastern Cape and has an important harbour.

A local research team comprising a team coordinator and two interviewers was established in each study centre. The team coordinator was a doctor (community health registrars in three centres, oncologists in two and the author in Johannesburg) and interviewers were either nursing sisters or university graduates with an honours or higher degree. One interviewer was fluent in English and Afrikaans and the

other in the predominant vernacular and English. Each team was trained as follows:

1. An interactive instruction manual was sent to interviewers and the coordinator in preparation for a day long training session in the study centre (Appendix 2.1). The manual included general principles on the administration of questionnaires, information on the actual questionnaire and a detailed description of the study. The objectives of the study were not explained, however. The manual was designed to be kept as a reference and included material such as a discussion of ethics in research. It was presented in a manner designed to involve the interviewer, for example suggestions on improving the questionnaire were invited - this was not only to develop the questionnaire but also to build commitment to the project. The coordinators' information package included criteria for selection of cases and controls and technical information on the management of the project.

2. Training of the local research teams was done by the same individuals in all the study centres and consisted of intensive discussion of the role of the interviewers and the administration of questionnaires in a standard manner, and role plays of administration and, finally, practice with the questionnaire on patients selected from local hospitals.

3. To motivate local research teams regular contact was maintained and a newsletter was sent to coordinators and interviewers every few months. The newsletter served also to reinforce important points made during training and to share new information learnt in the field. Practice interviews were conducted when long periods between cases occurred.

4. To blind interviewers to case control status and thus reduce interviewer bias, interviewers were not informed of the true nature of the study. They were told that the study was to establish whether diet or exposure to a variety of dusts, fibres and other substances are associated with a variety of cancers and medical conditions.

The local research teams could not be established at exactly the same time for logistical reasons (for example sudden withdrawal of interviewer) and case collection stopped either at the pre-determined termination date of 15 March 1990 or before if the local research team was disrupted. The case collection periods were:

Bloemfontein	1 November 1988 - 28 February 1990
Cape Town	1 November 1988 - 30 November 1989
Johannesburg	1 November 1988 - 15 March 1990
Kimberley	1 November 1988 - 15 March 1990
Port Elizabeth	1 March 1989 - 15 March 1990

Pretoria 1 November 1988 - 28 February 1990

The relatively short maximum duration for case collection (about 16 months) was selected to prevent declining motivation of researchers likely to occur over an extended study period. Disrupted teams were not re-established as this would have introduced new interviewers whose training was likely to be different to the originals. The expected number of potential cases in the whole of South Africa over sixteen months would range from 225 [Zwi et al., 1987] to 159 [NCOH annual reports, 1988, 1989 and 1990]. Although the expected number of successful case interviews was difficult to estimate because of non-response by cases, inaccessible or ineligible cases (for example outside the study area) and incomplete notification to the local research teams, 100 or more cases seemed a reasonable expectation over the study period given the intensity of the search and because most of these individuals could be expected to be either treated or diagnosed in a major centre (and thus a study centre). This number exceeds that of most case-control studies of mesothelioma and was considered adequate to meet the major objectives of the study. It was difficult to estimate necessary sample size more rigorously since neither the expected number of individuals within exposure strata nor the difference in exposure experience between cases and controls could be ascertained with any confidence owing to the lack of South African data and the thesis methodology of in-life intensive interviewing of cases and controls.

2.3 CASES.

2.3.1 Case definition

All individuals with a suspect mesothelioma diagnosed or treated in one of the study centres after the start of the study were considered potential cases. Potential cases were treated as study subjects and exposure information was collected from all of them, but stringent diagnostic criteria had to be satisfied before final acceptance as a case. Potential cases were only accepted as cases if:

1. A specialist pathologist's report was available which confirmed a histologic diagnosis of mesothelioma.
2. The histologic diagnosis was supported on review of tissue by the Panel (i.e. the Panel diagnosed a definite or probable mesothelioma), or a pathologist experienced with the tumour (a Panel member) confirmed the diagnosis. The second option was introduced as the Panel ceased functioning in early 1993, before histologic review of all potential cases could take place. The Panel member (Webster I) had served on the Panel since its inception. An aim of the Panel was to standardise the histologic diagnosis of mesothelioma among its five members - one reason for disbanding the Panel was because this had been achieved in reviewing over 2 000 cases (Personal communication, Simson I (Panel Chairman), Pretoria, 1993).
3. Immunohistochemical staining supported the diagnosis with a minimum requirement of negative staining for

carcinoembrionic antigen (CEA). The relevance of this criterion is presented in Chapter One section 1.1.2 Diagnosis. In many instances staining for CEA had not been done by the diagnosing pathologist. In these instances appropriate tissue samples were obtained and stained for CEA in the NCOH Pathology laboratory. The technique used was as shown in Appendix 2.2. The stringent diagnostic criteria described above were applied partly to reduce misclassification of diagnosis (diagnostic suspicion bias): a histologic diagnosis biased toward mesothelioma because of an asbestos exposure history would be countered by immunohistochemistry which is less subjective and read independent of an exposure history.

2.3.2 Source of cases

Potential cases were all suspect mesothelioma patients diagnosed or treated in a study centre.

All pathologists, oncologists, cardiothoracic surgeons and respiratory physicians registered in the study area were contacted and invited to participate in the study by notifying their local coordinator as soon as they identified a suspect case of mesothelioma. Key practitioners most likely to encounter potential cases, for example the heads of units in large hospitals or practitioners with known interest in the condition (e.g. Panel members and selected thoracic surgeons), were visited by researchers while other practitioners were contacted by mail and telephone. All of

these medical practitioners were reminded regularly of the study and were sent brightly coloured reminder cards at intervals for display in their rooms. The receptionists of key practitioners were visited at intervals to solicit support in reminding these doctors. A standard "Thank you" note was sent to referring practitioners after each notification to encourage further interaction.

Practitioners were asked to contact the local coordinator as soon as a potential case of mesothelioma was identified. The case was then interviewed in hospital after obtaining consent from the treating doctor and the patient. This procedure (of immediate interview with the patient) was instituted to increase the likelihood of study interviewers being the first to take an exposure history from the patient: thus reducing recall bias due to multiple interrogations of cases. Diagnostic suspicion bias in pathologists would be reduced also: the pathologist's preliminary diagnosis would usually be made without knowledge of exposure and the local coordinator would be informed before confirmation of the diagnosis or examination of exposure data took place. The pathologist's final diagnosis, possibly influenced by a positive exposure history, would be of no consequence since the potential case would have entered the study at the preliminary diagnosis stage and the study diagnosis would be made independently of the referring pathologist and blind to exposure data.

2.4 CONTROLS.

2.4.1 Matching

Two controls, one with a medical condition and the other with cancer, were selected for each case. Cases and controls were matched on hospital in which the case was interviewed, skin colour, gender and approximate age (within 5 years). Matching was primarily to ensure that sufficient controls were available to estimate effects in gender and ethnic subgroups and to balance cases and controls with respect to possible unknown confounders associated with socio-economic status. The probable differences in diet across regions and communities were important in this regard.

2.4.2 Inclusion and exclusion criteria

General exclusion criteria for both medical and cancer controls were that they should not have asbestosis or asbestos related pleural disease or an undiagnosed condition or one which further investigation might identify as a mesothelioma or asbestos related lung or pleural pathology (e.g. pleural effusion or ascites of unknown origin). Controls with cancers generally accepted to have an association with asbestos were not accepted nor were patients with any malignancy of the pleura or peritoneum. Only lung and pleural or peritoneal malignancies were accepted as asbestos related. A number of studies have found an association with other tumours and asbestos, for example, a recent meta-analysis of colorectal cancer and asbestos

exposure provided suggestive evidence that exposure to amphibole asbestos may be associated this cancer as the summary SMR was elevated (1.49; 95% confidence interval 1.09-2) for asbestos workers relative to reference populations. No association was found with chrysotile asbestos [Homa et al., 1994]. Nevertheless, because the causal association with other cancers is not well established [Doll and Peto, 1985; WHO, 1986; Garabrant et al., 1992] and the proportion of cases caused by asbestos is likely to be small, subjects with tumours of these sites were not excluded. Patients disorientated for time, place or person were excluded as were those with conditions of the central nervous system (to avoid selection of controls with disease-related memory deficits). To increase the likelihood that cases and controls were of the same population base with the same referral dynamics and pressures into the source hospital controls were limited to patients with a condition likely to warrant the same referral pressures as patients with the signs and symptoms of mesothelioma. Referral hospitals often serve the primary medical care and secondary level needs of the local community as well as providing tertiary level services. To avoid misrepresentation through selection of these patients with relatively minor conditions (unlike mesothelioma cases), skin cancer patients were excluded as were all medical patients with fewer than five in-patient days (for the current admission). This procedure would ensure also that cases and controls were of comparable severity of illness.

2.4.3 Selection

Controls were selected in a standardised manner in all study regions by the team coordinators. Controls were identified from the appropriate ward nearest to the ward in which the case was interviewed. Following interview of a case a list of patients who satisfied the age and diagnostic criteria and, for medical controls, date of admission, was compiled by the team coordinator from the ward admission book of the nearest medical or oncology ward - In smaller hospitals without oncology wards the nearest surgical ward was used. A patient was randomly selected from the list (name drawn from a bag) and asked to participate in the study. In the majority of instances only one or two patients satisfied selection criteria thus simplifying the procedure in practice.

2.5 EXPOSURE INFORMATION.

Exposure information was obtained directly from cases and controls by the administration of a structured questionnaire, the examination of sputum samples for coated fibres and the data contained in letters mailed to the researchers by the study subjects.

2.5.1 The questionnaire

A detailed questionnaire [Appendix 2.3] on residential and occupational history, and domestic exposures was administered in the preferred language of the subject in a standard manner by the interviewers. To reduce interviewer bias questions were largely closed-ended or tightly structured, thus allowing little interpretation by the interviewer even if case control status was inadvertently known. Some open-ended questions were asked toward the end of the interview to promote completeness of information. Two methods of piloting were adopted: twenty patients of the Occupational Medicine Clinic of the NCOH with known asbestos exposure were tested (the questionnaire successfully described exposure in all 20); and during training of interviewers the primary researchers observed the administration of 14 questionnaires and identified problematic and misunderstood phrases. Questionnaires were translated from English into Afrikaans, Sotho, Tswana, Xhosa and Zulu by a process of translation, back translation and consensus seeking on words identified as problematic through

back translation.

The questionnaire included a residential history, time spent near dockyards, mines, mills, asbestos using factories, stores of asbestos, parents' occupation, domestic and leisure time exposure to dust, a complete occupational history with detailed questioning on asbestos exposure, questions on diet (see 2.7 Diet for details) and tobacco smoking. Two components of the questionnaire were developed as "memory joggers" to aid recall of particularly important potential sources of asbestos exposure. Section 3.3 of the questionnaire covered time spent in the asbestos mining regions of South Africa while 5.2 and 5.3 listed important industries, occupations and activities with a known risk of asbestos exposure. Interviewers were trained to return to the occupational history if a positive response to section 5.2 or 5.3 revealed jobs not reported during the occupational history. The industry and occupation lists were compiled by collating information from three sources, namely literature, consultation with experienced occupational health practitioners and the patient database of the Occupational Medicine Clinic of the NCOH. General references [Health and Safety Commission, 1979; Michaels and Chissick, 1979; ILO, 1983; Nicholson et al., 1982] were consulted to compile an initial list. To this was added the important exposure settings reported by patients who had attended the Clinic (patients were cross-filed by exposure category and these were used). The list was then refined by two experienced occupational medicine practitioners and two

experienced industrial hygienists who together produced the final 31 primary memory joggers or occupational risk settings (Note: mining and milling of asbestos was covered in a prior section of the questionnaire).

2.5.2 Non-asbestos agents

Exposure to agents other than asbestos was covered by the comprehensive design of the questionnaire, for example a full occupational history (section 5.1); the non-specific nature of the first half which asked about "dust and fibres" rather than asbestos, for example section 4.3; and by specific questions on MMMF, ionising radiation, beryllium, nickel (section 5.4 and 5.5) and sugar-cane (section 5.2).

2.5.3 Coated fibres in sputum

The validity of exposure data derived from questionnaires is affected by failure to recall or recognise past exposure. The extent of failure will be influenced by many factors including the agents of interest [Joffe, 1992]. In an attempt to identify some of the "failures" in this study spontaneous sputum samples (i.e. sputum samples not induced by inhalation of aerosol) were collected from subjects by the interviewer after completion of the questionnaire - interviewers were instructed to ensure that subjects understood that sputum, rather than saliva, was required. Samples were then examined for coated fibres at the NCOH. (The term coated fibres as used here is synonymous with ferruginous bodies). Coated fibres are found in spontaneous

sputum samples of some individuals with significant asbestos exposure, the proportion exhibiting them determined in part by extent of past exposure [Farley et al., 1977; Bignon et al., 1973] so that positive sputum samples of occupational cohorts vary from 33% [Greenberg et al., 1976] to 80% in long service workers [Farley et al., 1977]. These coated fibres do not occur in the general population [Modin, et al. 1982; Bignon, et al. 1973] and a recent study found no evidence that occupational exposure to MMMF led to ferruginous body formation [McDonald et al., 1992]. Their presence is therefore good evidence of significant asbestos exposure.

An attempt was made to collect two sputum samples from each study subject, the first after completion of the questionnaire and, in an attempt to collect a 24 hour sample, a container was left with the subject for post-collection postage in a pre-paid envelope. Sputum examination was done at the NCOH by experienced technicians blind to case control status using a standard technique [Smith and Naylor, 1972].

2.5.4 The letter

To allow reporting of post interview recall of exposure a reporting form addressed to the researchers was left with the subjects with an invitation to report anything of importance forgotten during the interview. An addressed postage paid envelope was provided. The information yield from these letters was scant. Information on whether a

letter was returned to us was missing for 12 subjects, of the remaining 333 only 34 subjects (10.3%) returned letters. Four (three cases and one control) provided asbestos exposure information not obtained from the original questionnaire. In two the information concerned calender years employed at particular workplaces and in two additional asbestos exposure was reported: in one case this led to a revision of exposure class from probable to definite.

2.6 ASBESTOS EXPOSURE CATEGORIES.

Subjects were grouped by probability of exposure to asbestos, the likely fibre type and the nature of this exposure (e.g. occupational or environmental).

2.6.1 Exposure classes

Magisterial districts with deposits of asbestos were located by transposing a large scale map of the districts onto a 1:1 000 000 mineral map of the region [Department of Mineral and Energy Affairs, 1981]. The districts in which deposits had been mined or milled were identified by collating information from four major reference books [Hall, 1918; Hall, 1929; Coetzee, 1976; Stander and La Grange, 1964], published articles [Gossling, 1985; Hart, 1988], the Quarterly Reports of Industrial Minerals produced by the Department of Mines, Union of South Africa for 1949, 1954 and 1957 and the Minerals Bureau's directories of Operating mines in the Republic of South Africa [1971, 1979, 1991]. The result is shown in Table 2.1. The mining districts outside the NW Cape, E Transvaal and NE Transvaal are named OTHER districts when referred to collectively in this thesis. (Notes: provincial names have changed recently but the old names have been retained for concordance with previous literature; Table 4.2 shows approximate tonnage of asbestos mined in the NW Cape, E and NE Transvaal). The period (months) spent in any of these districts was recorded for each subject using questionnaire data.

Table 2.1: Asbestos deposits and mining by district, fibre type and region

District	Fibre type: Deposit	Fibre type: Significant mining	Region
Barkly West	CC	CC	NW CAPE
Hay	CC	CC	"
Kuruman	CC	CC	"
Postmasburg	CC	CC	"
Prieska	CC	CC	"
Tlhaping-Tlharo	CC	CC	BOPHUTHATSWANA
Vryburg (1)	CC	CC	NW CAPE
Barberton	Cr	Cr	E TRANSVAAL
Carolina	Cr	Cr	"
Eerstehoek	Cr	Cr	"
Nelspruit	Cr	Cr	"
Pilgrims Rest	Cr	Cr	
Lydenberg	TC A	A	NE TRANSVAAL
Pietersburg	TC A Cr An	TC A	"
Sekhukuneland	TC A Cr	TC A	LEBOWA
Thabamoopa	TC A	TC A	LEBOWA
Letaba[a]	TC A	TC A	NE TRANSVAAL
		OTHER[b] districts	
Thabazimbi	TC	-	N TRANSVAAL
Warmbad	TC	-	"
Marico	A	-	"
Messina	A Cr	-	"
Cullinan	Cr	-	"
Soutpansberg	An	An	N TRANSVAAL
Potgietersrust	Cr	-	N TRANSVAAL
Eshowe	Cr	Cr	ZULULAND
Kranskop	Cr	Cr	ZULULAND
Groblersdal	Cr	-	NE TRANSVAAL
Krugersdorp	Cr	Cr	S TRANSVAAL
Dundee	T	T	NATAL
Nqutu	T	-	NATAL

A = amosite, An = anthophyllite, CC = Cape crocidolite, Cr = chrysotile, T = tremolite, TC = Transvaal crocidolite.

[a] District boundries have changed over time; asbestos fields no longer in Letaba.

[b] This set of districts (Thabazimbi to Nqutu) referred to as OTHER districts in the text and tables.

Subjects were asked to provide a residential history by town and district; where only town names could be provided the town was placed in a district by referring to a list of towns by districts supplied by the South African Department of Justice. The sources used to identify mining districts were also used to compile a list of the names of past and current asbestos mines of South Africa. An additional source of mine names was the 96 identified by the Epidemiology Unit of the Medical Bureau for Occupational Disease (MBOD), Johannesburg [Personal communication: du Toit R, Johannesburg 1993]. The final list was used to validate reported asbestos exposure related to mining and to ascertain fibre type.

Table 2.2 shows criteria used to allocate subjects to either definite, probable, possible or unlikely asbestos exposure classes.

Living "near" an asbestos mine or mill was not restricted to a specified distance since it is well known that extensive areas around mines and mills were contaminated particularly in the NW Cape [Marchand, 1991] and NE Transvaal [Felix et al., 1994]. "High risk" occupations or activities are those listed in sections 5.2 and 5.3 of the questionnaire [Appendix 2.3] in which asbestos exposure was thought to be probable even if the subject did not actually recall exposure: 5.2 A, C, F, L, M, P, R, S, U, and V were labelled "High risk" while the rest of 5.2 (excluding sugar-cane) and 5.3 were labelled "Risk" occupations or activities.

Table 2.2: Criteria for asbestos exposure classes

Definite

1. Direct or indirect occupational exposure reported.

2. Contact with asbestos while spending time in an asbestos mining district (contact included playing on tailings dumps; living near a mine or mill; parent working on a mine or mill; asbestos fibre contaminating work or domestic environment).

3. Domestic exposure reported.

Probable

1. Worked in High Risk occupation or activity without recall of occupational exposure.

2. Spent 12 months or longer in an asbestos mining district of NW Cape, NE Transvaal or E Transvaal without reported contact with asbestos.

3. Co-resident worked with asbestos products in the residence.

Possible

1. Worked in a Risk occupation without recall of occupational exposure.

2. Spent less than 12 months in NW Cape, NE Transvaal or E Transvaal district without recall of contact.

3. Domestic use of asbestos cement products or heating panels.

4. Lived or worked in an asbestos cement structure.

5. Lived or worked within 1 km of a dockyard or asbestos product manufacturing factory.

6. Uncertain direct or indirect occupational exposure reported.

Unlikely

No recall of exposure.
No Risk or High Risk occupation or activities
Lived in OTHER district without reported contact.

OTHER districts mined asbestos in limited quantities in a small section of the district often for only a relatively short period. Consequently asbestos exposure was considered unlikely merely as a result of residence in OTHER districts - reported contact with asbestos, however, led to a classification of definitely exposed.

The latent period between first asbestos exposure and diagnosis of mesothelioma almost always exceeds 10 years [Selikoff et al., 1980; Peto et al., 1982], thus more recent exposure usually makes scant contribution to disease risk. For this reason cases and controls were allocated to a second set of exposure classes which included only subjects with remote exposure (first exposure 10 years or more). These classes were designated definite-remote, probable-remote and possible-remote.

2.6.2 Fibre type

Likely fibre type was determined by reference to Tables 2.1 and 2.3. Table 2.3 is a composite of information from the scientific literature [Coetzee, 1976; Stander and La Grange, 1963; Health and Safety Commission, 1979; WHO, 1986] and communication with knowledgeable individuals [du Toit R, NCOH, Johannesburg; Hart P, Griqualand Exploration and Finance Company, Johannesburg; Gibson B, Johannesburg; Prince R, ex Capil, Benoni South].

Table 2.3: Uses of amphibole asbestos

Use	Amphibole
AC pipes	C, A
AC building products (e.g. flat and corrugated sheets and moulded products)	C, A
Insulation products	
e.g. fabrics (blankets for steam locos)	C
power station turbine insulation	C
pipe lagging	C, A
thermal and acoustic spray	C
mattresses	C
felted insulation	A
coverings for jet engines, marine turbines, ship bulkheads etc	A
Fire resistant insulation boards, particularly wallboard	A
Moulded plastics and battery boxes	C
Jointings, packings and gaskets	C
Fillers, reinforcers and filters (particularly acid resistant)	C
Gas masks	C
Chemical filters	T
Textiles	C
Heating panels	C, A
Welding electrodes	C, T

AC = Asbestos cement
C = Crocidolite, A = Amosite, T = Tremolite

Asbestos in floor tiles and sheets and in friction materials such as brake linings and clutch plates has been exclusively chrysotile for decades, although prior to 1945 crocidolite was used in friction materials in the United Kingdom [Berry and Newhouse, 1983]. Although asbestos cement products are made predominantly from chrysotile they are listed in Table 2.3 as they generally contained a small proportion of amphibole; large diameter asbestos cement pipes are particularly important in this regard.

2.6.3 Nature

Nature of exposure was categorised as occupational, environmental, domestic, or incidental. Direct occupational was use at work by the subject while Indirect was exposure due to the use of asbestos by coworkers. Environmental-mining was due to contamination of the general environment by asbestos mining, milling and related activities while Environmental-other exposure arose from living within a kilometre of an asbestos using factory, store of asbestos or dockyard. Domestic exposure occurred at home either due to contaminated workclothes (Domestic-clothes) or work with asbestos products (Domestic-use) which included hobbies and the servicing of motor vehicles' brakes. Incidental exposure was use of asbestos cement garden furniture, spending time in asbestos cement structures and use of asbestos heating panels.

2.7 DIET.

The exposure component of the questionnaire was comprehensive and consequently long. Since it was intended for sick in-patients of hospitals, administration time could not be excessive. The dietary component, therefore, was designed to collect information only on the consumption of dietary constituents significantly associated with mesothelioma in the Shiffman study [1988] and included only fruits and vegetables important locally (in South Africa).

The Schiffman study found the consumption of homegrown produce, cruciferous vegetables, all vegetables combined and estimated carotene intake lower in cases than in controls. The Research Institute for Nutritional Diseases (RIND) of the South African Medical Research Council, provided a list of the important dietary sources of carotene in South Africa and the usual cruciferous vegetables. The RIND listed nine cruciferous vegetables and 12 vegetables and 7 fruits rich in beta carotene. Only two of these items were not included in the questionnaire (Appendix 2.3, pp 21-22); persimmon, as piloting revealed that subjects were unfamiliar with the fruit, and beetroot leaves as these are not eaten to any extent in South Africa. Wild greens (imifino and marog) were included. The last question in the diet section of the questionnaire was open-ended to allow for reporting of consumption of sources of beta carotene not specifically mentioned such as peas, green beans and parsley.

The format for measuring frequency of consumption of fruits and vegetables allowed the subject seven grades of frequency of consumption ranging from never to a few times a day (Appendix 2.3 pp 21-22). Seasonal items (such as apricots) are problematic to categorise into usual consumption over a year as it can vary from never for much of the year (the off season) to a few times per day in season. The average consumption over a year is thus very similar for all subjects despite peaks of consumption in season for some. To differentiate between subjects the in-season frequency was accepted as the frequency of consumption rather than the average over the whole year.

Average frequency over the past five years was measured to reduce reporting of dietary changes brought about by recent illnesses. Interviewers were taught to stress the "past five years" phrase during questioning and the introduction to the patient was "I am now going to ask you some questions about the food you usually ate **before** you were admitted to hospital".

The dietary components of interest contained a fairly long list of items (e.g. eight cruciferous vegetables). To ensure that subjects considered each item the words were printed onto cards which were handed to the subject during questioning on that particular component. Interviewers were instructed to proceed slowly with illiterate subjects and to repeat the names of the vegetables and fruits slowly.

No attempt was made to include fruits and vegetables peculiar to particular communities (e.g. those of Chinese or

Indian background) as only a few cases of mesothelioma were expected in these groups and excluding these few cases from analysis of diet would, therefore, be more efficient than attempts to design an all-inclusive questionnaire.

2.8 DATA MANAGEMENT AND ANALYSIS.

All data were coded blind of the case control status of the subject by the principal researcher and subsequent allocation to exposure classes, fibre types and nature of exposure was done without knowledge of status.
Questionnaires were double-punched, the datasets were compared and corrected by referring to the original questionnaire.
Univariate and bivariate statistical analysis was done with the assistance of the Epiinfo Version5 software programme [Dean et al.,1990]. In general, for bivariate analysis of continuous variables across different categories of other variables, analysis of variance (ANOVA) was used or the Mann-Whitney or Wilcoxon Two-Sample test where variances differed significantly. For categorical variables Chi^2 tests in four fold tables were done.
Variables derived to describe asbestos exposure and to examine the association between asbestos exposure and mesothelioma are described in Appendix 2.4. The basic measure of asbestos exposure was asbestos exposure class in which the base level of exposure was unlikely; possible,

probable and definite classes were ascending levels of exposure. These classes were refined by excluding subjects in whom asbestos exposure occurred within 10 years of diagnosis (cases) or interview (controls).

2.8.1 Case-control analysis

For certain bivariate and for all multivariate analyses either conditional or unconditional logistic regression was used to calculate odds ratios (OR), 95% confidence intervals and p values. The EGRET Software Package was used for these analyses [EGRET, 1991]. Only two independent variables were used in the multivariate analyses (asbestos exposure and one other) and an a priori modelling strategy was adopted. The cases and cancer controls and cases and medical controls were treated as two separate datasets and, unless otherwise stated, matching was retained in analysis and conditional logistic regression used to calculate adjusted odds ratios. Additionally, medical and cancer controls were pooled with a view to examining the effect of greater power on the effect estimates and their confidence intervals, on the assumption that the two sets of controls are not representing different populations. Where controls were pooled matching was retained to produce triplets of one case and two controls and conditional logistic regression was used to calculate ORs. Where matching was disrupted (for example, when all the cases and all the controls were incorporated into a single dataset) logistic regression was applied. Odds ratios and 95% confidence intervals were calculated for class and

nature of asbestos exposure and occupation-specific ratios were calculated for asbestos miners, workers who had had contact with asbestos insulation material and for workers using asbestos cement.

Whether asbestos exposure had occurred exclusively to a single fibre type could not be determined confidently in many subjects, for example asbestos cement product users (chrysotile plus amphibole or only chrysotile in more recent times), and those with possible exposure in a risk occupation or residence in a number of NE Transvaal mining districts (amosite and/or Transvaal crocidolite). For this reason fibre specific odds ratio calculations were limited to three situations:

1. District specific risks - subjects with asbestos exposure exclusively in the NW Cape (Cape crocidolite); NE Transvaal (amosite and/or Transvaal crocidolite) or E Transvaal (chrysotile) were used for these analyses.

2. Those in whom crocidolite exposure had occurred even if this was not necessarily limited to crocidolite (Variable name crocidolite-any). Subjects in this category were those who had spent time in the NW Cape (residence, mining crocidolite, transporting crocidolite etc), who reported exposure in the manufacture of battery casings or large diameter water pipes and those who reported crocidolite exposure (for example blue asbestos mining or milling).

3. Workers with exposure exclusively in asbestos mining or mining related work.

The odds ratios were calculated by conditional logistic regression from the case-control pairs for cancer and medical controls separately and then by conditional logistic regression with matched triplets with both sets of controls in a single dataset.

2.8.2 Latency, duration and smoking

A number of factors were examined to determine whether they were associated with mesothelioma. These were latency (the period from first exposure to diagnosis of mesothelioma in cases and to administration of the questionnaire in controls); duration of exposure and tobacco smoking. Latency was unknown in some subjects (e.g. poor recall of dates or work in a Risk or High risk occupation). For residents of mining districts date of first exposure was assumed to be the start of period of residence, this probably artificially prolonged latency in some of these subjects since actual exposure would have occurred later. Latency was therefore examined separately for subjects with occupational and with environmental exposure, and those with an uncertain first date of work contact were excluded from the analyses. Duration of exposure was examined in a number of ways: as years of exposure, half-years (6 month long periods) either in a job or in a mining district, and as categorical variables with duration as absent, medium (up to

120 months) and long (>120 months) periods of exposure. Smoking was considered as a categorical variable (current,ex and non-smoker) and as packyears of smoking (average number smoked per day/20 x years smoked). Pipe smokers were excluded from analysis of packyears as most of the pipe smokers provided poor data on amount of tobacco used (e.g. a packet per week without specifying the size of the packet). The effects of the smoking variables were examined by calculating ORs using conditional logistic regression analyses. In addition, multivariate analyses were done with the smoking variables and asbestos exposure class to calculate ORs adjusted for asbestos exposure.

2.8.3 Skin colour

Matching on skin colour while selecting controls meant that this variable could not be examined as an independent risk factor for mesothelioma. To examine the possible influence of skin colour odds ratios were, therefore, calculated for white and for black subjects separately (In other words, skin colour specific datasets were created and skin colour specific odds ratios calculated). Only 16 cases (13%) were of "mixed race", they were therefore excluded.

2.8.4 Diet

Subjects reported frequency of consumption of vegetables and fruit by seven levels of consumption from never to a few times per day. A number of summary and categorical variables were derived from these data (Appendix 2.5). Dietary

constituents examined were the frequency of consumption of all vegetables (as reported by the subject), homegrown vegetables, cruciferous vegetables, carotene rich fruit, carotene rich vegetables, salads and green vegetables. These variables were categorised in two ways: as dichotomous variables (low and high consumption) with never to once per week the base level and a few times per week to a few times per day the high level. The second categorical variable had three levels of consumption with the base level never to about monthly, the medium level once per week and the high level a few times per week or more.

Two summary consumption scores were derived. The first (CAROTSUM) was a measure of carotene rich fruit and vegetables together and was calculated as the sum of the consumption scores for carotene rich fruit and vegetables. The second (ALLSUM) was a measure of consumption of all fruit and vegetables; this was calculated as the sum of the individual consumption scores excluding "all vegetables". These two variables were categorised by dividing them into low, medium and high exposure levels with each level having approximately equal numbers of subjects.

The various measures of consumption of vegetables and fruits were compared by region and by skin colour using ANOVA where the variances were homogeneous and the Mann-Whitney test where variances differed.

The possible protective effect of the dietary constituents on developing mesothelioma was examined by calculating odds ratios [EGRET, 1991]. Matched analyses were done for cancer

and medical controls separately using conditional logistic regression. Regional specific odds ratios were calculated for Johannesburg, Pretoria and Kimberley (the three regions with the most subjects) by creating separate datasets for each region. Skin colour specific odds ratios were calculated for the white and black subjects separately again by creating separate datasets. Bivariate analyses with the dietary variable as the independent variable and mesothelioma present or absent as the outcome measure were performed. These analyses were then done with the odds ratios adjusted for asbestos exposure class (i.e. definite, probable, possible and unlikely). In some cases convergence could not be attained using asbestos exposure class: in these cases exposure class was replaced with a dummy dichotomous asbestos exposure variable where exposed = definite or probable, and unexposed = unlikely or possible.

Interaction between class of asbestos exposure and dietary variables associated with mesothelioma was examined by constructing indicator (dummy) variables. Indicator variables took the value of 0 or 1 to designate the presence or absence of an attribute and thus did not have an artifactual scale of measurement (as would have been the case if interaction terms were simple products of exposure class (designated 0, 1, 2 or 3) and consumption level (e. g. designated 1, 2 or 3 for carotene-fruit2). The indicator terms were entered into the regression analyses with exposure class and the dietary variable.

2.9 ETHICS.

Ethical issues common to many studies such as confidentiality, informed consent and access to patients through the treating medical practitioner were considered. Written informed consent was obtained from all subjects and interviewers were trained in the use of the consent form [Appendix 2.6] which was available in six languages. Interviewers were trained in presenting the consent form to subjects [Appendix 2.3: front cover]. Subjects were advised that treatment would not be affected by refusal to participate and that the interview could be terminated at any time. (This was particularly important as some subjects were in pain or emotionally unsettled - interviewers were trained to offer postponement of the interview should this become necessary).

Confidentiality was guaranteed in that study numbers (rather than names) were used in analysis and anonymity of cases and controls would be protected during presentation of data.

Patients were only approached with the prior consent of the treating medical practitioner and consent to conduct the study was obtained from the superintendents of all the hospitals in which interviews were conducted.

Other ethical issues arose out of the particular nature of the study. Cases of mesothelioma eligible for compensation

would be identified in the course of the study. Research team coordinators who were experienced in submitting claims undertook to complete the submission procedures in cases where the treating medical practitioner had not accepted the responsibility. The central study team submitted cases for the inexperienced team coordinators.

Questionnaires were administered as soon as a potential case of mesothelioma was identified. Many of these patients were unaware of their diagnosis and because of negative perceptions of asbestos, questions concerning exposure to the agent may have led the person to conclude that s/he had cancer. The same ethical concern was present for controls as well, in that sick people unaware of their diagnosis and faced by persistent exposure questioning may "realise" that they have a serious condition. To prevent this, study objectives were expressed in general terms without deceiving the subject [Appendix 2.3: front page]. The interviewer was unaware of the subjects diagnosis (blind to case control status) and informed the patient of this and that the subject had been selected without any knowledge of his or her particular exposure history. The questionnaire was general in nature for the most part and only specifically mentioned asbestos in the second half of the interview and after many other questions had been asked. Interviewers were trained to respond to the question, "Why did you select me?" by "Because you are within the age group that is important for the study".

Ethical approval was obtained from the provincial administrations of the Transvaal and the Cape and from the ethics committees of the Universities of the Witwatersrand and Cape Town.

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CHAPTER THREE

Results

Contents Pages

3.1 THE CASES OF MESOTHELIOMA.

3.1.1 Case ascertainment

One hundred and forty six potential cases were interviewed during the study. Twenty three were subsequently not accepted as cases: six had a cytological diagnosis only, tissue could not be obtained for confirmation of diagnosis in another six and 11 were rejected (either CEA negative or classed unlikely or possible mesothelioma on histologic review). Table 3.1 presents the potential cases by region and acceptance as cases (according to criteria described in Methods).

Table 3.1: Potential cases and cases by region

Region	Interviewed potential cases	Accepted cases	Failed interviews
Johannesburg	61	48	11
Pretoria	24	21	5
Kimberley	22	22	4
Bloemfontein	20	19	2
Cape Town	15	10	4
Port Elizabeth	4	3	1
TOTAL	146	123	27

In addition to the 23 potential cases who were interviewed but rejected, a further 27 were referred to the research teams but questionnaires were not obtained (Failed interviews in Table 3.2). Research teams were not meticulous in compiling records of failed interviews (Personal communication, Team coordinators), consequently the 27 documented individuals should be considered the minimum

number of eligible potential cases who failed to enter the study. Only one of these 27 individuals refused an interview; six were inaccessible (one in prison and five had inadequate tracing information), five were too sick or died before interview, four had a cytological diagnosis with no further diagnostic procedures planned, two were interviewed but the questionnaires were lost, four cases left the study area before interview and the reason for failure to interview was not established in the remaining five. These uninterviewed potential cases did not include patients diagnosed clinically and radiologically only (i.e. without histological or cytological evidence), a not unusual practice in the Kimberley region due to the high incidence of mesothelioma and relative lack of specialist medical services. Five potential cases in Johannesburg and one in Pretoria were diagnosed on cytology and interviewed in anticipation of confirmatory procedures which were not performed. These potential cases failed the entry criteria for cases and were not considered as cases in this thesis. Nevertheless, selected features of five of these subjects are presented below as they may have been true cases of mesothelioma because all five were considered mesothelioma on review by two experienced cytologists and EM examination was performed on two and confirmed the diagnosis in both.

Completeness of case ascertainment cannot be calculated confidently as the number of cases who entered the study areas during the period of investigation is not known. The

Panel's register and the Zwi incidence study [Zwi et al., 1987] provide data to estimate ascertainment although neither database used as stringent diagnostic criteria as this study and both collected cases from the whole country rather than from selected geographic areas as in this study. One hundred and sixty nine cases were reported per year to the Zwi study [1987] over the period 1980-84 while on average, 119 were registered by the Panel per year for 1988-90. In this case-control study case collection took place over about 16 months, thus the expected number of potential cases in the whole of South Africa would have ranged from about 225 (Zwi) to 159 (the register).

3.1.2 Case characteristics

Table 3.2 presents site of mesothelioma and gender, race and mean age of cases for each region - these subjects are the cases used in subsequent analyses. The relatively young age is notable: the generally very long latent period between first exposure and this disease suggests that mesothelioma might be considered a condition of people no longer of working age. In this series 79.7% of cases were 65 years or younger, while 51.2% were under 56 years of age. The age range for the whole series was 33 to 86 years. Figure 3.1 shows that black cases were significantly younger than the other two groups (mean years black, coloured and white cases respectively = 49.9, 57.4 and 58.1; $p = 0.0026$). There was little difference in the mean age of women and men, and of cases with and without environmental exposure.

Table 3.2: Case characteristics

Region	Site*		Gender		Race			Age	
	Pleura	Peritoneum	Male	Female	White	Black	Coloured	Mean	(SD)
Johannesburg n = 48	44	3	43	5	26	21	1	55.8	(13)
Pretoria n = 21	20	1	15	6	18	3	0	58.2	(11)
Kimberley n = 22	20	2	16	6	1	13	8	52.6	(12)
Bloemfontein n = 19	18	1	16	3	16	1	2	52.3	(10)
Cape Town n = 10	10	0	9	1	6	0	4	58.9	(15)
Port Elizabeth n = 3	3	0	3	0	1	1	1	57.3	(7)
TOTAL (%)	115 (94)	7 (6)	102 (83)	21 (17)	68 (55)	39 (32)	16 (13)	55.4	(12)

*Excludes pericardium: Johannesburg = 1 case

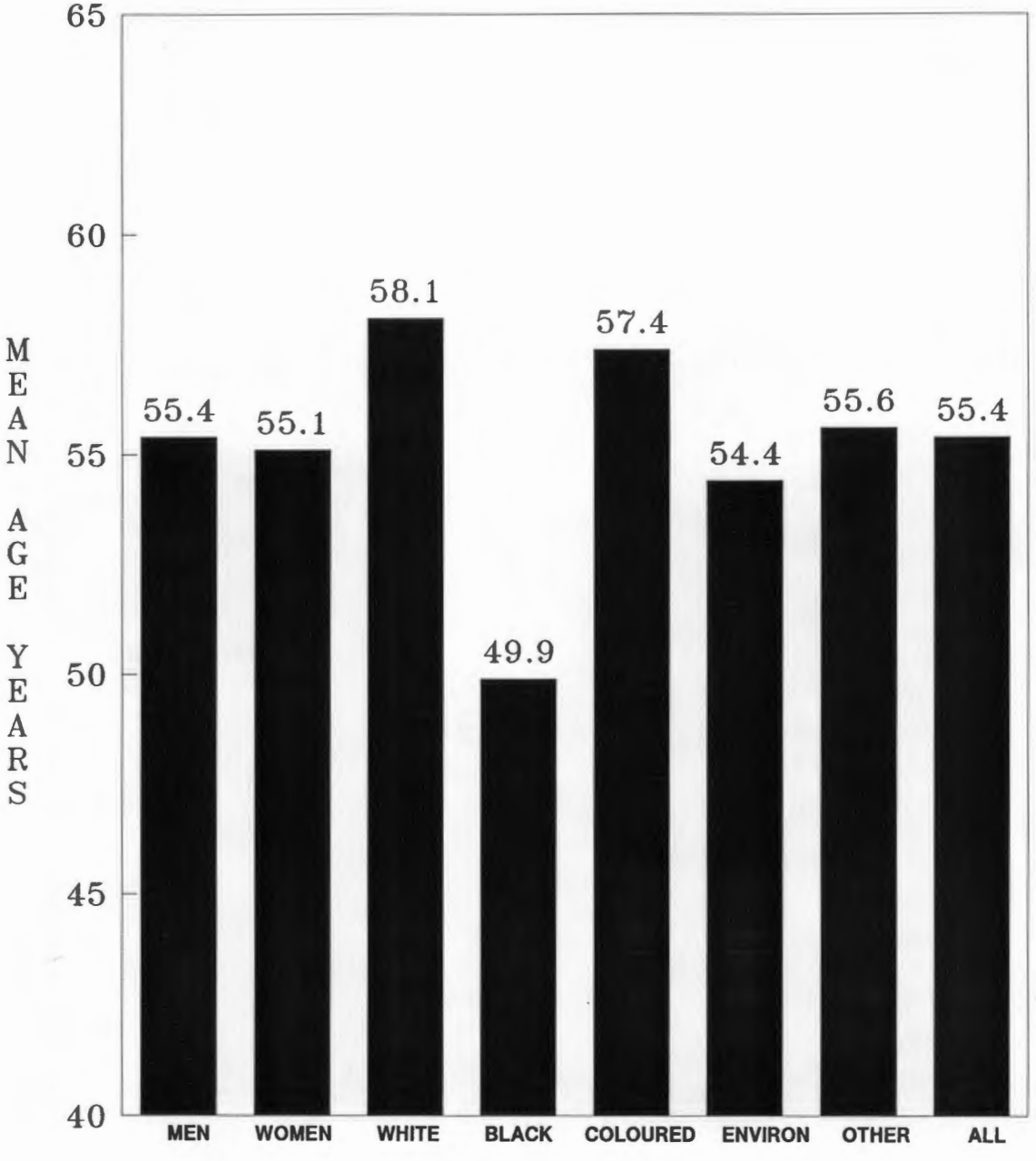

Figure 3.1: Mean age of mesothelioma cases by gender, skin colour and type of exposure. Environ = cases with exclusively environmental exposure and other = cases other than those with environmental exposure.

Surprisingly cases born in a magisterial district which mined asbestos were not significantly younger at diagnosis (54.4 years) than were the other cases (55.6 years). Four of the five cytology cases were of the pleura and one of the peritoneum. Three were men, two were white and three black. They had a median age of 53 years (range of 46 to 56 years); all were thus of working age.

3.2 THE CONTROLS: NUMBERS AND DISEASE PROFILES.

One hundred and nineteen cancer controls and 103 medical controls were available for analysis. Since there were 123 cases, the datasets were four cancer and 20 medical controls short. This arose in the cancer control dataset because of inappropriate controls being selected (e.g. not matched on age, hospital or skin colour, or disease not a cancer) and in 19 medical controls primarily because medical controls were not interviewed in the Bloemfontein region and this could not be rectified before the study team was disrupted. The remaining medical control had a pleural effusion and was therefore excluded as mesothelioma had not been excluded. Table 3.3 shows cancer controls by site of tumour and medical controls by organ or system affected, or by disease. It can be seen that the pathologies of the controls spanned a wide spectrum of disorders. The major cancer category (alimentary tract) included cancers from the oesophagus to the rectum and the major medical category (heart) included atrial fibrillation and pericarditis.

Table 3.3: Pathologic condition in cancer and medical controls

Cancer		Medical		
Site or nature of malignancy	n (%)	Organ, system or disease	n (%)	Most common disease
Alimentary Tract	22 (18)	Heart	27 (26)	Cardiac failure, angina
Lymphoma	16 (13)	Respiratory	15 (14)	Asthma, airflow limitation
Leukaemia	15 (13)	Diabetes	10 (10)	
Haematopoietic (Other)	5 (4)	Infection	9 (9)	
Prostate	15 (13)	Vascular	8 (8)	Hypertension
Ear, nose, sinuses or larynx	11 (9)	Haematopoietic	6 (6)	Anaemia
Breast	8 (7)	Alimentary	6 (6)	Peptic ulcer
Liver	8 (7)	Nervous	6 (6)	
Bone	5 (4)	Hepatobiliary	5 (5)	
Cervix	4 (3)	Renal Failure	3 (3)	
Sarcoma	3 (3)	Skin	2 (2)	
Testis	3 (3)	Arthritis	2 (2)	
Bladder	2 (2)	Pancreas	2 (2)	
Pancreas	2 (2)	Thyroid	1 (1)	
		Splenomegaly	1 (1)	
TOTAL	**119**		**103**	

3.3 ASBESTOS EXPOSURE IN CASES AND IN CONTROLS.

3.3.1 Classes

Subjects were classed as definite, probable, possible and unlikely asbestos exposure according to Table 2.2. These classes were refined to take account of the usual minimum latent period between first exposure and disease diagnosis: subjects known to have been first exposed at least 10 years prior to diagnosis are presented in the tables.

In Table 3.4 it can be seen that 86% of the cases had either definite or probable asbestos exposure (75% definite + 11% probable). The distribution of exposure classes was very similar for the cancer and medical controls with about one third having either definite or probable exposure. There was no significant difference in exposure class between the two sets of controls.

Missing data were a feature of classes by remote exposure mainly because exposure was inferred (not reported directly by the subject) for a proportion of subjects, particularly in the possible class and hence date of first exposure was unknown. Only three cases had their first reported exposure less than 10 years prior to diagnosis.

The 17 cases classed as possible or unlikely are presented in Table 3.5. A fairly convincing case for asbestos exposure can be made in many of them. Subjects 6 and 7 visited NW Cape mining districts, albeit for short periods; subject 3 had coated fibres in his sputum; subjects 4, 8, 9, 10 and 11 worked in jobs known to be associated with asbestos.

Table 3.4: Mesothelioma cases and controls by exposure class

Class	Cases		Cancer controls		Medical controls	
	n	(%)	n	(%)	n	(%)
Definite	94	(75)	24	(20)	20	(19)
Probable	14	(11)	16	(13)	15	(15)
Possible	12	(10)	39	(33)	33	(32)
Unlikely	5	(4)	40	(34)	35	(34)
Total	**123**		**119**		**103**	
Definite - remote[a]	88	(72)	20	(17)	19	(18)
Probable - remote	14	(11)	12	(10)	11	(11)
Possible - remote	3	(2)	9	(7)	11	(11)
Unlikely - remote	8	(7)	46	(39)	36	(35)
Missing data	10	(8)	32	(27)	26	(25)

[a] = Only accepted into class if exposure occurred ≥10 years prior to diagnosis. Reclassified "unlikely" if xposure occurred <10 years prior to diagnosis.

Table 3.5: Exposure history in cases of mesothelioma categorised possible or unlikely asbestos exposure class

Nature of possible exposure	Duration (months)	Occupational		Exposure to non-asbestos agents	Comments
		Major	Other		
Possible					
1. Winch driver: gold mine 1975/77	36	Gold miner	Nil	Nil	Well 5 years post diagnosis
2. a Office worker: factory manufactured bodyfiller (chrysotile)	36	Typist	Clerk	Nil	History confirmed. Chrysotile confirmed. First exposed 1986.
b Used asbestos heaters	?				
3. Grinder (metal finishing in workshop including railway company)	456	Grinder	Storeman	Nil	Coated fibres in sputum
4. Electrician in dockyard (Hamburg) and ships electrician at sea	84	Electrician	Construction electrician	Nil	History confirmed
5. Pay clerk: sited on construction sites on pay days.	54	Accounts clerk	Salesman	Glass fibre	History confirmed
6. Visited family in NWCape (Prieska) 7 times for 1 week per visit	2	Nurse		Nil	Visits 1932 - 1939
7. a Visited NW Cape (Koegas) 9 times for 10 days per visit	3	Animal feed production & research		Yttrium	Visits 1979 - 1987
b Used asbestos heating plates on stove	?				
8. a Lived in Kimberley area 1916-1983 next to an open cast diamond mine	804				Reported frequent inhalation of "diamond mine dust".
b Plumber and construction site worker (bricklayer)	336	Builder	House refurbishing	Nil	1916-1983
9. a Alcohol production: production foreman: blending & bottling	168	Foreman			
b Rubber tyre manufacture	168	Factory	Musician	Nil	-
10. a Sailor: ship maintenance	120	Sailor, whaler crane driver		Nil	Subject reported "uncertain" occupational asbestos exposure
b Installed window frames (on construction site)	132	Busdriver, handyman window frame installer			
c Cleaned asbestos roof once					
11. Moulder in a foundry 1924-1929:	516	Moulder	Clerk	Nil	1924-1967 in foundry near furnaces. Wore heat protective clothing and reported "uncertain" asbestos exposure.
12. a Shoe manufacture	36	Storeman	Shoe maker	Nil	Reported "uncertain" asbestos exposure
b Worked in asbestos-cement structure	120				
c Construction site worker	6				
Unlikely					
1. Aluvial diamond diggings Alexander Bay and Kleinsee	99	Fettler: Foundry	Diamond miner	Nil	History confirmed
2. Father labourer at Koegas asbestos mine	?	Animal skin tanner	-	Nil	No recall of contamination of home with asbestos. No recall of residence in a mining district.
3. Underground gold miner (driller)	144	Gold miner	-	Nil	Driller 1947-1963
Surface gold miner	360				Surface 1959-89
4. Resided Kagiso (Krugersdorp)	216	Domestic worker	-	Nil	-
5. Trench digger: Thabazimbi	18	Platinum mine: Security	-	Nil	-

Alcohol filters were made of asbestos and widely used in South African industry until recently (Personal communication, Smit JS, Distillers Corporation: 1994); subject 1 may have been exposed to fibres from the brake shoes of the winches (Cases exposed in this way have been documented in South Africa - Personal communication, Davies JCA, NCOH: 1993); subjects 5 and 12 spent time on construction sites. Subject 2 had a complete exposure history taken after the study and was then questioned about exposure during two subsequent consultations. The only potential sources of exposure were chrysotile at work (X-ray diffraction done at the NCOH confirmed that the fibres in workplace material were chrysotile) three years prior to diagnosis and use of asbestos panel heaters. Tissue collected during the pleural biopsy was obtained, digested and the residue examined for asbestos fibres as described by Rendall [1988]: two fibres with the spectral characteristics of tremolite were found on scanning electron microscopy. In summary, a case for asbestos exposure could be made for all 12 of these individuals. Subject 1 is of interest in that he was well five years after diagnosis, still working underground in a physically demanding occupation and had no evidence of a tumour on chest radiograph: despite fulfilling stringent diagnostic criteria he may not have had mesothelioma.

Two of the five subjects classed unlikely provided information weakly suggestive of some asbestos contact.

Subject 1 worked on the north western Cape diamond fields: it has been suggested that crocidolite fibres may have been carried to these alluvial fields by the Orange River which passes through the NW Cape crocidolite fields on its way to the Atlantic Ocean (Personal communication, Davies JCA, NCOH: 1993). He worked in a foundry also but had no recall of asbestos exposure, did not work near the furnaces and had never worn heat protective clothing. A thorough exposure history was obtained from the patient by an experienced occupational medicine physician (for compensation purposes): no additional evidence to support exposure could be obtained and no coated fibres were present in his sputum. Subject 2 reported that her father worked at the Koegas asbestos mine - she had no recall of having lived in a mining district herself and could recall no contamination of the home by workclothes; nor did she know whether she had been born before or after this employment.
Four of these five "unlikely" subjects provided sputum: in none was coated fibres detected.

History confirmed in the comments column of Table 3.5 means that a full exposure history was repeated by the author: in all three cases the repeat history did not provide exposure information not obtained from the questionnaire.
In summary, from Table 3.5 it can be seen that the proportion of cases with evidence of asbestos exposure ranged from 86.1% (stringent criteria) to 97.6% (lenient criteria).

Table 3.6 compares class of exposure by sex and skin colour.

Table 3.6: Exposure class by sex and skin colour (cases only)

Class	Cases				Cancer controls				Medical controls				Skin colour of cases					
	Men		Women		Men		Women		Men		Women		White		Black		Coloured	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Definite	82	(81)	10	(48)	23	(24)	1	(5)	19	(22)	1	(6)	53	(78)	30	(77)	9	(56)
Probable	7	(7)	7	(33)	13	(13)	3	(14)	12	(14)	3	(17)	8	(12)	3	(8)	3	(19)
Possible	10	(10)	2	(10)	34	(35)	5	(24)	29	(34)	4	(22)	7	(10)	2	(5)	3	(19)
Unlikely	3	(3)	2	(10)	28	(29)	12	(57)	25	(30)	10	(55)	0		4	(10)	1	(6)
TOTAL	**102**		**21**		**98**		**21**		**85**		**18**		**68**		**39**		**16**	

Men and women cases had significantly different classes of exposure (Chi^2 = 15.08; p = 0.002) but the proportion with either definite or probable exposure was similar (88% versus 81%). The distribution of exposure classes was very similar for men cancer and medical controls and for women controls. As with all the cases, a larger proportion of women were classed unlikely than were men and the distribution of controls over the classes was different for men and women, although significantly so only for the cancer controls (Medical: Chi^2 = 5.9; p = 0.19. Cancer: Chi^2 =7.8; p = 0.049). Exposure class was not significantly associated with skin colour in cases, although four of the five cases with unlikely exposure were black.

3.3.2 Nature of asbestos exposure

Subjects were categorised by nature of exposure as described in Methods and are shown in Table 3.7. Only three cases were categorised "none" - these three plus the two cases categorised OTHER district only make up the "unlikely" class of Table 3.4. Fifty eight percent of the cases had had occupational exposure to asbestos compared to 17.5% and 17% of the cancer and medical controls respectively. The two control groups were very similar in their distribution of nature of exposure. No case had exposure exclusively as a consequence of contaminated workclothes (Domestic-clothes) but this was nevertheless an important source of exposure as 13 cases (11%) reported contact with asbestos in this way. All of them had either worked with asbestos or lived in a

Table 3.7: Nature of asbestos exposure in cases and controls

Nature	Cases n	Cases (%)	Women cases n	Women cases (%)	Cancer controls n	Cancer controls (%)	Medical controls n	Medical controls (%)
Occupational								
Direct	63	(51)	1	(5)	18	(15)	14	(14)
Indirect	9	(7)	1	(5)	3	(2.5)	3	(3)
High risk	0		0		1	(1)	4	(4)
Risk	8	(7)	0		23	(19)	19	(18)
Uncertain	2	(2)	0		1	(1)	3	(3)
Environmental								
Mining	22	(18)	15	(71)	15	(13)	12	(12)
Other	0		0		3	(2.5)	2	(2)
+ Uncertain occupational	4	(3)	1	(5)	0		2	(2)
+ Risk	8	(6)	0		12	(10)	8	(8)
OTHER district only	2	(2)	1	(5)	2	(2)	1	(1)
Domestic								
Clothes	0				0		0	
Use	2	(2)	1	(5)	1	(1)	0	
Incidental	0				2	(2)	2	(2)
None	3	(2)	1	(5)	38	(32)	33	(32)
TOTAL	**123**		**21**		**119**		**103**	

mining district and were thus not allocated to Domestic-clothes. Two cases had Domestic-use as the major source of exposure: one built his own house and cut asbestos ceilings and the other was exposed while her husband insulated their house. An inspection of the house revealed asbestos lagging on water pipes between the roof and ceiling. An evaluation of asbestos-in-air levels was done: no fibres were present in the rooms but the concentration was 0.003 fibres/ml between ceiling and roof. The lagging material was examined by X-ray diffractometry and found to be 0.5 - 1% chrysotile and 0.5 - 2% either amosite or crocidolite (Personal communication, du Toit RSJ, NCOH: 1989). This woman had another possible source of exposure as she had worked as a pay clerk and visited construction sites for about 30 minutes per week for many years.

3.3.3 Occupational asbestos exposure

Table 3.8 lists all subjects who reported occupational asbestos exposure by the industry for which they had worked, and the occupation of the exposed subject. Asbestos mining was the most important industry. A number of unexpected occupations are represented. For example, the policeman was a detective responsible for criminal investigations on the asbestos mines in the district in which he worked. The farmer worked with asbestos cement products in building and maintenance on the farm. Table 3.9 shows cases and controls grouped into four major occupational exposure categories. Twenty eight subjects had worked on Cape crocidolite mines.

Table 3.8: Occupational asbestos exposure in cases and control by industry and occupation

Industry

Mining or milling asbestos	35	Engineering		Gold mining	1
		Heavy	6	Dry cleaning	1
		Light	3	Agriculture	1
Construction		Power	8	Rubber	1
Transport	14	Battery manufacture	2	Commerical	1
Asbestos product manufacture		Foundry	2	Public service	1
		Chemical	3	Missing data	1
		Law enforcement	1		
Asbestos cement	7	Fire control	1		
Friction materials	3	Navy	1		
Floor tiles	1				

Occupation (number of subjects)

Asbetos mining

Underground	14	General maintenace	2	Motor vehicle mechanic	1
Surface	12	Office, administrative	2	Farmer	1
Mill	6	Boiler operator	2	Upholsterer	1
Transport	3	Factory foreman	2	Toolmaker	1
Fitter and turner	11	Welder	2	Crane driver	1
Machine operator	6	Laboratory superivisor	2	Cleaner	1
Construction		Sailor	1	Foreman	1
Carpenter	5	Steam loco maintenance	1	Building inspector	1
General Labour	4	Furnace Mason	1	Policeman	1
Other	4	Factory manager	1	Salesman	1
Railway line	1	Turbine maintenance	1	Painter	1
Driver	4	Engineer		Storeman	1
Boilermaker	4	Marine	1	Missing data	1
Electrician	4	Unspecified	1		

Table 3.9: Major categories of occupational asebestos exposure in mesothelioma cases[a]

	Mining and related[b]					Asbestos cement		Insulation	Other
	CC	TC	A	TC+A	Cr	Building Products	Pipes		
Cases (N = 123)	23	1	3	3	-	10	2	22	8
Cancer controls (N = 119)	2	-	-	-	-	9	0	4	6
Medical controls (N = 103)	3	-	-	-	-	5	0	6	3
TOTAL	28	1	3	3	0	24	2	32	17

CC = Cape crocidolite, TC = Transvaal crocidolite, A = Amosite, Cr = Chrysotile.

[a]This table excludes 6 cases, 1 cancer and 5 medical controls who reported "uncertain" occupational exposure.

[b] TC mine = Transvaal Blue Asbestos; A mine = Penge; TC+A mines = Matshikane (Mafefe), Coco and Makapeng (Mafefe), Lucerne (Mafefe).

CC mines = Bretby, Cape Blue Asbestos, CBM, KCB, Koegas, Kuruman, Pomfret, Riries, Whitebank, Beeshoek, Roddies.

Two of the mines (Beeshoek and Roddies) were not on the list of mines compiled as described in the Methods: both werenamed by controls. Three cases reported employment at Penge, an amosite mine in the NE Transvaal. It is notable that no subject had worked on a chrysotile mine.

3.3.4 District specific exposure

A proportion of the cases and the controls had had no asbestos exposure other than that which may have occurred due to living in or visiting an asbestos mining district or from occupational or other contact with asbestos mined in the particular district. In these individuals asbestos fibre type could be confidently identified as the exposure had been exclusively in a mining district - these individuals were thus exposed to NW Cape crocidolite only, NE Transvaal amosite with or without Transvaal crocidolite, E Transvaal chrysotile or the slight possibility of exposure to unspecified asbestos in an OTHER district. These individuals are presented in Table 3.10 by case control status and whether workplace exposure occurred or not. In addition, subjects with "significant" exposure (i.e. > one month and at least 10 years prior to administration of questionnaire) are shown. No case reported E Transvaal exclusive exposure but one case spent 369 months in chrysotile mining districts and only three months in NE Transvaal mining districts. This subject was a policeman who conducted criminal investigations on chrysotile mines in the E Transvaal and on an asbestos mine in the NE Transvaal (in 1958).

Table 3.10: Subjects with asbestos exposure exclusively in asbestos mining districts

Region	Cases				Cancer controls				Medical controls			
	n	(%)[a]	Significant exposure[b]	(%)	n	(%)[a]	Significant exposure[b]	(%)	n	(%)[a]	Significant exposure[b]	(%)
NW Cape	44	(36)	40	(33)	11	(9)	9	(8)	7	(7)	5	(5)
Occupational[c]			22	(18)			4	(8)			2	(2)
NE Transvaal	7	(6)	7	(6)	4	(3)	3	(3)	4	(4)	4	(4)
Occupational[c]			6	(5)			1	(1)			0	
E Transvaal	0		0		6	(5)	0		2	(2)	1	(1)
Occupational[c]			0				0				0	
OTHER	2	(2)	0		3	(3)	0		2	(2)	0	
Occupational [c]			0				0				0	

Number of cases = 123, cancer control = 119, medical controls = 103.

[a] = % of all cases or cancer or medical controls.

[b] Significant exposure = cases or controls who spent longer than a month in the district more than 10 years prior to completing the questionnaire.

[c] Number of the district exclusive subjects with occupational and environmental exposure.

The biopsy material obtained from the case was digested according to Rendall [1988] and examined at the NCOH for fibres under phase contrast microscopy. Three asbestos fibres were identified; 160, 170 and 220 um in length. They were straight and, according to an experienced fibre counter, amphiboles. Fibres were not identified during scanning electron microscopy.

3.3.5 Exclusively environmental exposure

Table 3.11 shows the exposure details of 22 cases with exclusively environmental asbestos exposure. Two cases (NW Cape 5 and NE Transvaal 1) spent years in asbestos cement structures; the relevance of this contact is unclear, thus these two cases are presented as exclusively environmental. In 15 of the 21 cases with information (71.4%) exposure beyond mere residence in a district was documented - it is notable that this was directly related to mining and related activity. Latency between first exposure to asbestos and diagnosis of mesothelioma was compared in cases with exclusively environmental exposure and those with other exposure. In this analysis first exposure for the environmental cases was calculated as date first entered district - date diagnosed: it is likely that this lengthened the latent period of the environmental cases as exposure may not have commenced on first entering the district. In one hundred and six cases date of first exposure was available: the mean latent period was 40.6 years with a standard deviation (SD) of 15.8 years.

Table 3.11: Twenty two cases with exclusively environmental exposure

Region		Months spent in district	Nature of asbestos contact or potential contact	Year of first entering district
NW Cape	1	1.5	Stayed <5 kms from Danielskuil mine	1948
	2	2	None recalled. 3 visits x 3 weeks each	1932
	3	12	None recalled	1953
	4	30	Stayed <5 km from Riries mine. Father miner	1958
	5	84	Lived in asbestos cement building 1964-1969	1929
	6	192	Father miner - clothes contaminated home	1927
	7	192	1944-1957 lived <500 m from store of asbestos at Prieska station	1941
	8	228	Farmer: Asbetos mill on farm boundry	1927
	9	228	Missing information	1920
	10	312	Spouse miner: clothes contaminated home	1942
	11	360	Brother miner: clothes contaminated home	1944
	12	384	Lived within 1 km of an asbestos mine	1956
	13	384	Lived within 5 km of Bretby mine	1950
	14	396	Lived within 0,5 km of Riries mine	1953
	15	480	Lived near Prieska railway station	1958
	16	528	None recalled	1935
	17	588	Father was a miner. Lived within 5km of an asbestos mill	1939
	18	708	Asbestos transported past his home - broken bags contaminated area	1930
	19	720	Mother worked at Pomfret mine	1929
	20	780	None recalled	1924
NE Transvaal	1	228	Taught in asbestos cement classrooms 1934-1975	1923
E Transvaal + NE Transvaal	1	372	Policeman - regular trips to asbetos mines	1958

The median latent period was of 39.5 years (38.0 for those with occupational exposure). The 22 environmental cases had a significantly longer latent period than the 84 other cases: mean 49.2 versus 38.3 and SD12.8 versus 15.8 ($F = 6.97$; $p = 0.009$).

3.3.6 Duration and crocidolite exposure.

Table 3.12 presents data on the duration of asbestos exposure. Three cases had less than five months exposure: one manufactured asbestos cement products (4.5 months) and two visited the NW Cape mining districts: one for three months and the other for a month - the latter stayed close to Danielskuil asbestos mine. Not included with these three is subject 7 Table 3.5 because she reported use of asbestos heating plates for an unspecified duration. Not shown in the table is that two other cases had short exposure: both worked on Cape crocidolite mines, one for seven and the other for eight months.

Subjects with "non-trivial" exposure are shown in Table 3.12. Unfortunately missing data were common as many subjects classed as possible exposure did not report contact (e.g. worked in a Risk occupation) and thus had no information on date of first exposure nor on duration.

The table shows also cases and controls by crocidolite exposure. Positive evidence of exposure to this fibre was limited to subjects exposed in the NW Cape mining districts, those with occupational mining exposure (NW Cape except for one NE Transvaal case), occupational contact with large

Table 3.12: Duration of asbestos exposure in mesothelioma cases and in controls, and crocidolite exposure in mesothelioma cases and in controls

	Cases N = 123		Cancer controls N = 119		Medical controls N = 103	
Months of exposure Mean (SD)	252	(194)	78	(167)	70	(137)
Subjects with recent[a] exposure	2		7		2	
Subjects with duration <5 months	3		5		3	
Asbestos exposure: non trivial						
Definite + remote + >1 month	85	(69)	19	(16)	18	(18)
Probable + remote + >1 month	13	(11)	11	(9)	10	(10)
Possible + remote + >1 month	1	(1)	4	(3)	3	(3)
Unlikely + remote + >1 month	9	(7)	48	(40)	37	(37)
Missing data or no exposure	15	(12)	37	(31)	35	(34)
Crocidolite exposure						
Remote[b] + >1month	65	(53)	14	(12)	14	(14)
≤ one month	2	(2)	7	(6)	2	(2)
Recent[a]	1	(1)	2	(2)	0	
Unspecified or none[c]	54	(44)	94	(79)	87	(85)
Missing data	1	(1)	2	(2)	0	

[a] Recent = first exposure occurred <10 years before diagnosis (cases) or interview (controls).

[b] Remote = first exposure occurred ≥10 years before diagnosis (cases) or interview (controls).

[c] Unspecified = crocidolite exposure could not be excluded nor established with certaintly.

diameter asbestos-cement pipes (two cases), battery casings (two cases) or reported by the subject (one case). Some cases not included in Table 3.12 as crocidolite exposed may well have had substantial contact with this agent - for example, three cases mined asbestos in the Pietersburg asbestos fields and were thus probably exposed to both Transvaal crocidolite and amosite. These cases were not included in the crocidolite group to limit this group to cases with almost incontestable crocidolite exposure. Of note is that the distribution of crocidolite exposure was similar for the two sets of controls.

3.4 EXPOSURE TO NON-ASBESTOS AGENTS.

Reported exposure to glass fibre, other manufactured mineral fibres (MMMF), X-rays, radioactive material, beryllium, nickel, radiotherapy and sugar-cane is shown in Table 3.13 for both cases and controls. Reported exposure to glass fibre was not unusual but of similar proportions in cases and controls. Twenty of the 21 cases with exposure to glass fibre were classed as definite or probable asbestos exposure. The remaining case is subject 5 Table 3.5 and was classed as possible exposure. Nine cases reported exposure to an agent other than glass fibre: eight of them had definite or probable asbestos exposure, the remaining case is subject 7 Table 3.5. She was classed possible asbestos due to visits to the NW Cape. No case had exposure to one of the agents listed and unlikely asbestos exposure.

Table 3.13: Exposure to non-asbestos agents in cases and controls

Agent	Cases n	(%)	Cancer controls n	(%)	Medical controls n	(%)
Glass fibre	21	(17)	18	(15)	12	(12)
MMMF[a]	3	(3)	6	(5)	7	(7)
X-rays	0		2	(2)	1	(1)
Radio-active material	2	(2)	0		2	(2)
Berylluim	0		0		0	
Nickel	3	(3)	0		2	(2)
Radiotherapy[b]	0		5	(4)	0	
Sugar-cane	1	(1)	0		0	

Cases = 123, cancer controls = 119, medical controls = 103.

[a] MMMF = Manufactured mineral fibres.

[b] Excludes therapy for current illness.

3.5 LOGISTIC REGRESSION ANALYSES: ASBESTOS EXPOSURE AND MESOTHELIOMA.

Table 3.14 presents odds ratios (ORs) and 95% confidence intervals for cases matched with a cancer and a medical control (i.e. 1:2 matching) and for cancer and medical controls separately (1:1 matching). In the 1:2 matching only 103 triplets were available for analyses since complete triplets could not be formed unless both a medical control (n = 103) and a cancer control (n = 119) were available. The numbers of cases and controls in the analyses using either medical or cancer controls (1:1 matching) were as presented previously in the descriptive tables. For example, Table 3.4 shows the number of cases and controls used in the calculation of odds ratios for exposure classes.
The odds ratios increased as class of asbestos exposure increased from possible to definite exposure. The lower 95% confidence interval for mesothelioma associated with the possible exposure class was less than one for all three datasets irrespective of remoteness of first exposure. Odds ratios for only three categories of nature of asbestos exposure are presented in the table, namely occupational, environmental and Risk occupation. Odds ratios could not be calculated for the other categories due to the small number of cases in these categories (Table 3.7). Working in a Risk occupation without recall of exposure was significantly associated with mesothelioma only in the dataset with both medical and cancer controls - the other analyses produced a lower 95% confidence interval of less than one.

Table 3.14: Odds ratios (OR) for mesothelioma according to class and nature of asbestos exposure - base level of exposure = unlikely

Asbestos exposure	Cancer and medical[c] OR	95%CI	Cancer controls OR	95%CI	Medical controls OR	95%CI
Possible	4.4	0.96 - 20.5	1.7	0.4 - 8.2	10.0	0.9 - 108.7
Probable	5.5	1.4 - 22.5	7.5	1.7 - 37	10.5	1.2 - 89
Definite	58.7	14.0 - 246	40.8	9.2 - 109	104.5	10.6 - 1026
Possible - remote	1.4	0.2 - 10.7	0.9	0.06 - 11.9	1.7	0.1 - 27.3
Probable - remote	4.4	1.2 - 15.9	5.0	1.0 - 24.8	6.2	1.1 - 33.5
Definite - remote	42.1	10.5 - 168	74.1	8.6 - 641.9	43.7	6.9 - 277
Nature[a]						
Occupational	80.6	15.7 - 414	45.9	8.0 - 262	38.9	9.7 - 182.8
Environmental	19.6	3.7 - 105	12.2	2.2 - 67.0	15.1	3.3 - 79.9
Risk occupation	15.9	2.9 - 84.3	3.3	0.5 - 20.2	2.3	0.4 - 13.9
Occupational						
Mining CC	85.5	14.5 - 505	160.5	11 - 2339	145.4	11.2 - 1885
Insulation	76.4	14.4 - 406	163.3	11.2 - 2374	87.3	8.3 - 918
Asbestos cement	27.7	4.9 - 154	13.8	2.3 - 83	43.6	3.9 - 486
Environmental[b]						
NW Cape - remote	32.7	8.1 - 131	21.9	4.7 - 102.4	50.9	7.2 - 360
NE Transvaal - remote	12.7	1.9 - 84.7	7.1	0.2 - 171	12.0	1.2 - 117
Crocidolite						
- <2 months	20.7	2.8 - 151	5.6	0.8 - 37.9	31.9	2.1 - 492
- any	72.7	14.5 - 365	57.9	10.9 - 309	68.1	8.0 - 578
- remote + >2 months	42.4	11.2 - 162	77.7	13.4 - 452	59.5	7.2 - 489

CC = Cape crocidolite.
[a]Occupational = direct or indirect exposure reported by subject.
Environmental = time spent in a mining district the only source of exposure.
Risk occupation = worked in an occupation associated with exposure but no recall.
[b]Remote = first exposure occured ≥10 years before diagnosis (cases) or interview (controls).
[c] 1:2 matching with case and a medical plus a cancer control.

The number of subjects in the occupational categories of mining CC, insulation and asbestos cement are as presented in Table 3.9. It is notable that working with asbestos cement (relative to no asbestos exposure) was strongly associated with mesothelioma in all three datasets. Environmental categories are as shown in Table 3.10. There were no E Transvaal exclusive cases, odds ratios could, therefore, not be calculated. Even short contact with crocidolite (< 2 months) was associated with a fairly substantial relative risk of mesothelioma in the cancer + medical control dataset (OR = 20.7) and in the medical control dataset (OR = 31.9).

Not shown in Table 3.14 are the sex specific ORs for class of asbestos exposure: these are of interest given the differing nature of exposure in the two groups. For the cancer control dataset the ORs for women and men respectively were definite = 28.6 and 38.5; probable = 10.3 and 5.5, and possible = 2.3 and 1.5. Convergence was not obtained using the medical controls and class of exposure so ORs were calculated with the dichotomous exposure variable exposed (definite + probable) and a base level of unexposed (possible + unlikely). The ORs for women and men respectively were 11 (95% CI 1.4-85.2) and 15.3 (95% CI 4.8-49.3).

The effect of duration of exposure was considered in a number of ways: as years of exposure, half years (i.e. 6 month long intervals) either in a magisterial district or in a job, and as categorical variables with duration as absent,

medium (up to 120 months) and long (>120 months) periods of exposure. Missing duration data were frequent, for example all the subjects in the possible exposure class (since they did not recall exposure they could not provide a period of exposure). For this reason the examination of the effect of duration of asbestos exposure was limited to subjects in either the definite or probable exposure classes. The medical control dataset showed that duration of exposure was unimportant as the duration variables had an OR with a lower 95% confidence interval less than one, ORs near unity and p values > 0.05. The cancer control dataset showed some significant associations between total years of exposure and duration spent in mining districts: these are presented in Table 14a. It should be remembered that all the time spent in a mining district was counted but that this is not a measure of continuous exposure for many subjects: some probably had an initial exposure free period (e.g. in infancy for some subjects born in the district) and then exposure interspersed with unexposed periods. It is possible that subjects who spent long periods in mining districts merely had greater opportunity for contact with fibres rather than longer periods of actual contact - duration variables may, therefore, be surrogates for exposure per se rather than a measure of length of contact. It is notable that the length of time exposed at work was not important either as a categorical variable (medium and long) nor as a continuous variable (half years of exposure).

Table 3.14a: Duration of asbestos exposure and relative risk of mesothelioma - cancer controls

Duration variable	OR (ß co-efficient)	95% Ci[a]	P
Years of exposure	1.06 (0.054)	1.01 - 1.1	0.013
Half years spent in a mining district	1.12 (0.109)	1.03 - 1.2	0.009
Categorical: mining district			
Long (>120 months)	13.50	1.0 - 181	0.049
Medium (1-<120 months)	1.15	0.2 - 7.4	0.89

[a]Ci = confidence intervals

The possible effect of skin colour on developing mesothelioma was examined by comparing the odds ratios for developing the disease in black and white subjects. For these analyses separate datasets containing either the white subjects or the black subjects were created and skin colour specific odds ratios were calculated. Unfortunately convergence could not be attained for most of the analyses so comparisons are limited to odds ratios calculated for asbestos exposure as a dichotomous variable with unexposed = unlikely or possible and exposed = probable or definite exposure class. Table 3.15 shows odds ratios by dichotomous exposure classes for all subjects irrespective of skin colour and for white and black subjects separately. ORs were similar in black and white subjects and similar to those which were calculated on the dataset inclusive of both black and white subjects.

Tobacco smoking was not associated with mesothelioma either as smoking status (current, ex, never) nor as pack-years, whether adjusted or not for asbestos exposure class.

Table 3.15: Odds ratios (OR) for mesothelioma according to class of asbestos exposure - base level of exposure: unlikely or possible

Asbestos exposure	Cancer and Medical[a] OR	95%CI	n[b]	Cancer controls OR	95% CI	n[b]	Medical Control OR	95%CI	n[b]
Definite or probable	14	6.6 - 32	101	22	6.9 - 7.0	119	14	5.1 - 39	103
Definite or probable - remote	17	6.1 - 47	89	23	5.5 - 92	82	19	4.7 - 80	73
White subjects									
Definite or probable	16	6.8 - 38	51	39	5.4 - 284	66	9.0	2.7 - 29	51
Definite or probable - remote	24	8.2 - 74	34	No convergence		42	8.5	1.9 - 36	34
Black subjects									
Definite or probable	14	5.2 - 39	35	22	3.0 - 163	35	No convergence		35
Definite or probable - remote	9.6	3.4 - 26	26	14	1.8 - 107	26	No convergence		28

[a] = Conditional logistic regression - matching 1:2.
[b] n = number of matched case control sets.

3.6 DIET.

3.6.1 Frequency of consumption

Table 3.16 compares the frequency of consumption of the major vegetables and fruits investigated by case control status, skin colour and region. Region specific comparisons are for white subjects only (the most numerous group) and limited to the three regions with sufficient numbers to make comparisons worthwhile. In reading the table it should be noted that frequency ranges from 1 (never) to 7 (a few times per day); 4 is once a week. It can be seen from the table that cases consumed carotene-fruit slightly less frequently than did the controls (medical controls vs cases $F = 3.46$; $p = 0.064$) and that differences existed by skin colour and region (e.g. black vs white subjects - carotene-fruit $F = 138$; $p < 0.001$ and Johannesburg vs Bloemfontein - homegrown $F = 36$; $p < 0.001$). It is notable that frequency of consumption of cruciferous vegetables is not significantly different by skin colour (white vs black subjects $F = 2.79$; $p = 0.096$). Table 3.17 shows the distribution of asbestos exposure class across carotene-fruit category for cases and controls. A greater proportion of the definite asbestos exposed subjects (cases and controls) were in the high carotene-fruit category than in the low category. In the unlikely exposure class the cases had mostly a low or medium level of carotene-fruit consumption. As can be seen from the table, 91 cases fell into the definite exposure class and of these 43 (47.3%) had a high frequency of

Table 3.16: Consumption of selected dietary constituents by case control status and by skin colour and region

		Homegrown		Cruciferous		Carotene			
						Fruit		Vegetables	
	n	Mean[c]	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Cases	123	2.6	(1.9)	4.3	(1.2)	4.1	(1.4)	4.8	(1.1)
Cancer controls	119	3.1	(2.1)	4.3	(1.2)	4.3	(1.4)	4.7	(1.1)
Medical controls	103	2.6	(1.8)	4.1	(1.2)	4.5	(1.4)	4.7	(1.0)
White Subjects	189	2.9	(2.1)[a]	4.4	(1.0)	4.9	(1.0)[a]	5.1	(0.7)[a]
Black Subjects	111	3.1	(1.8)	4.1	(2.1)	3.2	(1.5)	4.3	(1.3)
Coloured Subjects	45	1.5	(1.2)	4.2	(1.1)	4.2	(1.2)	4.3	(1.3)
Johannesburg[b]	78	2.3	(1.9)[a]	4.4	(1.0)	5.0	(0.9)[a]	5.1	(0.7)
Pretoria[b]	52	3.1	(2.1)	4.3	(1.1)	5.2	(0.9)	5.1	(0.9)
Bloemfontein[b]	33	4.6	(1.7)	4.3	(1.1)	4.5	(0.8)	5.1	(0.6)
Total		**2.8**	**(2.0)**	**4.3**	**(1.2)**	**4.3**	**(1.4)**	**4.7**	**(1.1)**

[a] Differences significant $p < 0.05$.
[b] White subjects only.
[c] Mean = mean of frequency of consumption (never = 1 - few times per day = 7).

Table 3.17: Carotene-fruit consumption categories by exposure class in cases and in medical and cancer controls

Carotene-fruit category		Exposure class				
		Unlikely	Possible	Probable	Definite	Total[a]
Cases	Low	3	1	2	29	35
	Medium	0	6	4	19	29
	High	2	4	7	43	56
		5	11	13	91	120
Medical controls	Low	7	9	5	3	24
	Medium	12	4	2	1	19
	High	15	20	7	15	57
		34	33	14	19	100
Cancer controls	Low	13	9	4	5	31
	Medium	4	9	7	5	25
	High	23	21	5	14	63
		40	39	16	24	119
Cases and controls	Low	23	19	11	37	90
	Medium	16	19	13	25	73
	High	40	45	19	72	176
		79	83	43	134	339

[a] Missing information for 3 cases and 3 medical controls.

carotene-fruit consumption versus 29 (31.9%) in the low frequency category. In the unlikely class the relationship was reversed: 5 cases fell into this exposure class and of these 2 (40%) had a low frequency of carotene-fruit consumption versus 3 (60%) in the high frequency category. This difference was not statistically significant possibly because of the small numbers.

3.6.2 Logistic regression analysis: diet and mesothelioma

Logistic regression analyses were performed with the variables shown in Appendix 2.5. The variables included separate frequency scores (1 to 7) as reported by the patient for all vegetables, homegrown vegetables, cruciferous vegetables, carotene fruit, carotene vegetables, vitamin tablets and salad; two summary scores, namely carotene fruit + carotene vegetables and cruciferous + carotene fruit + carotene vegetables + salads; and two categorical variables (1 = high and low consumption, 2 = high, medium and low consumption) for each of the types of vegetables or fruits. Odds ratios were adjusted for asbestos exposure and calculated for all subjects and for black and white subjects separately. Table 3.18 presents only the dietary variables which produced adjusted ORs and 95% confidence intervals showing an association between the variable and mesothelioma. In reading the table carotene-fruit 2 refers to the high level of consumption using the variable with three consumption levels. Carotene-fruit 1 refers to the high level using the variable with two comsumption levels.

Table 3.18: Statistically significant[a] associations between mesothelioma and dietary constituents

Dietary constituent	Dataset[b]	OR[c]	95%CI		Logistic regression model	Asbestos exposure variable
Carotene-fruit 2[d]	Cancer	0.16	0.03 - 0.86	0.033	Conditional	Exposure class
Carotene-fruit 2[d]	Medical	0.19	0.04 - 0.99	0.049	Conditional	Exposure class
Carotene-fruit 1[e]	Medical	0.23	0.07 - 0.77	0.017	Conditional	Exposure class
Carotene-fruit 1[e]	Both sets of controls[f]	0.36	0.14 - 0.92	0.033	Conditional	Exposure class
Carotene-fruit 1[e]	All white subjects	0.42	0.18 - 0.97	0.042	Unconditional	Exposed/unexposed
Cruciferous 1[e]	All white subjects	1.56	1.01 - 2.40	0.044	Unconditional	Exposed/unexposed

[a] p Value <0.05.

[b] Appropriate cases and controls in each dataset(e.g. cancer = cancer cases and cancer controls).

[c] Odds ratio adjusted for asbestos exposure as specified in column asbestos exposure variable.

[d] Odds ratio calculated with base level of consumption < once per week (i.e. low, medium and high categories).

[e] Odds ratio calculated with base level of consumption ≤ once per week (i.e. low and high categories only).

[f] 303 subjects matched 1 : 2 (i.e. 101 matched sets of 1 case + 1 medical + 1 cancer control).

It can be seen from the table that high frequency of carotene-fruit consumption was associated with a decrease in relative risk of the tumour in the cancer, medical and combined datasets. These analyses were repeated for the white and black subjects (separate datasets were created by skin colour). Convergence was not attained for any variable using the black subject dataset, possibly due to small numbers. In the white subject dataset conditional logistic regression analyses (1:2 matching) did not produce statistically significant associations between diet and mesothelioma but unconditional logistic regression (matching disrupted) did: these are shown in Table 3.18.

In Table 3.19 the detailed results of the analyses of the association between carotene-fruit 2 (i.e. consumption of carotene rich fruit at three levels, namely < once per week, once per week and > once per week) and mesothelioma are presented. Adjusting for exposure class produced larger ORs for exposure and lower ORs ("more protective") for carotene-fruit 2 than in the unadjusted bivariate analyses: an interpretation of this finding is presented in the Discussion. Exposure - response relations were evident for increasing exposure class and increasing level of consumption in the cancer controls.
Indicator variables used to assess interaction between exposure and consumption of carotene fruit were not associated with mesothelioma (95% confidence bounds straddled one and $p > 0.1$).

Table 3.19: Carotene-fruit, exposure class and mesothelioma

Variable	Cancer		Medical	
	OR	95%CI	OR	95%CI
Exposure class - unadjusted				
Definite	40.84	9.2 - 180.6	105.7	10.6 - 1026
Probable	7.49	1.5 - 37.0	10.6	1.2 - 89
Possible	1.74	0.4 - 8.2	10.1	0.9 - 109
Carotene-fruit 2 - unadjusted				
>once/week	0.62	0.3 - 1.5	0.57	0.2 - 1.4
Once/week	0.86	0.4 - 2.0	0.75	0.3 - 2.1
Exposure class - adjusted[a]				
Definite	77.13	12.4 - 480.1	301.9	18.1 - 5040
Probable	12.53	1.9 - 83.1	15.1	1.6 - 144
Possible	1.16	0.2 - 6.4	21.4	1.5 - 314
Carotene-fruit 2 - adjusted[a]				
>once/week	0.16	0.03 - 0.86	0.19	0.04 - 0.99
Once/week	0.31	0.06 - 1.5	0.76	0.2 - 3.9

[a] Adjusted = both terms entered into conditional logistic regression model together.

3.7 COATED FIBRES IN SPUTUM.

As part of the study subjects were asked to provide sputum so that coated fibres could be sought. Three hundred and eighty five subjects were interviewed during the course of the study. Table 3.20 shows that 232 of them (60.3%) could not provide a sputum specimen - this is not surprising given that production of sputum on demand is possible only in subjects with certain medical conditions (e.g. bronchitis or bronchiectasis). In those that could produce sputum 133 (34.5%) had sputum free of fibres while fibres were detected in samples provided by 20 individuals (5.2%). Seventeen of these twenty with coated fibres were cases, two were cancer controls and the remaining person had mesothelioma diagnosed on cytology. It is of interest that in 19 of the 20 subjects with positive sputa, definite or probable asbestos exposure had occurred - the remaining subject was classed possible asbestos exposure. Although these 20 had more months of asbestos exposure than the 133 coated fibre negative individuals this did not reach statistical significance ($F = 1.89$; $p = 0.19$). Surprisingly, neither smoking status nor pack-years of smoking was significantly associated with the capacity to provide sputum ($p>0.05$) although more sputum providers were current smokers (38%) than were non-providers (27%).

Table 3.20: Sputum provision and examination for coated fibres by asbestos exposure and tobacco smoking history in 385 interviewed subjects

	n (%)	Asbestos exposure				Smoking status		
		Definite or probable	Duration (months)			%Current	Pack-years	
			(%)	Mean	(SD)		Mean	(SD)
Coated fibres present	20 (5)	19	(95)	263	(217)	20	10	(11)
Coated fibres absent	133 (35)	71	(53)	169	(201)	41	18	(23)
No sputum provided	232 (60)	105	(45)	112	(173)	27	17	(21)
Total	385 (100)	195	(51)	140	(198)	32	17	(22)

Subjects without asbestos exposure cannot be expected to provide sputum that contains asbestos, but all ninety of the 152 sputum providers who reported definite or probable asbestos exposure could have had coated fibres in their sputum. Yet only 19 (21%) did. Four factors which might explain why some probable or definite asbestos exposed subjects produced coated fibres while others did not are the duration of exposure, the latent period between exposure and sputum collection, the nature of the exposure and the smoking status of the subject. These factors were compared in the 90 asbestos exposed subjects who provided sputum and the results are shown in Table 3.21.

Table 3.21: 90 asbestos exposed[a] subjects who provided sputum

	Coated fibres present				
	Yes (n = 19)		No (n = 71)		p Value
Months of exposure					
Mean (SD)	263	(217)	246	(201)	0.80
Latent period (years)					
Mean (SD)	40	(16.5)	39	(15.8)	0.845
Nature of exposure					
Occupational:direct	17		36		0.002
Other	2		35		
Smoking status					
Ex	11		24		0.178
Never	4		19		
Current	4		26		
Missing information			2		

[a] Asbestos exposed = Definite or probable.

The only factor significantly associated with coated fibres was the nature of exposure: 17 of the 19 positives (89%) reported direct occupational exposure compared to only 51% of the negatives ($Chi^2 = 9.3$, $p=0.002$). In addition, the positives were employed in occupations usually associated with high dust levels (for example asbestos mining in 53% - Table 3.22) whereas the 36 negatives with direct occupational exposure included only 12 (33%) with an asbestos mining history.

In summary, the finding of coated fibres in sputum was strongly associated with a positive asbestos exposure history (19 of the 20 subjects with coated fibres reported asbestos exposure) which was usually occupational in origin (17 of the 20 subjects had occupational asbestos exposure). It was also strongly associated with being a case of mesothelioma but factors such as duration of exposure, years between last exposure and sputum collection and tobacco smoking were unimportant.

Table 3.22: Type of asbestos exposure in subjects with coated fibres in sputum

Subject	Type of exposure	Date of last exposure	Months of asbestos exposure
Cases			
1	Asbestos mining: underground	1963	48
2	Asbestos mining: underground	1974	60
3	Asbestos mining: underground	1959	84
4	Asbestos mining: underground	1952	12
5	Asbestos mining: underground	1989	312
6	Asbestos mining: mill	?	156
7	Asbestos mining: mill	1979	540
8	Asbestos mining: mill	1960's	30
9	Asbestos mining: mill	1968	312
10	Asbestos mining: surface	1956	120
11	Fitter and turner: used asbestos insulation material	?	?
12	Fitter and turner: used asbestos insulation material	1984	384
13	Machine operator: asbestos-cement product manufacture	1981	492
14	Furnace attendant: used asbestos insulation material	1974	420
15	Construction: used asbestos construction materials	1986	84
16	Railroad company: grinder in workshops	?	Nil reported
17	Visted NW Cape asbestos mine	1950	1.5
Cytology only			
1	Machine operator: asbestos brake lining manufacture	1966	138
Control			
1	Lived NW Cape asbestos mining district	1978	432
2	Construction: used asbestos construction materials	1984	60

3.8 REFERENCES.

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CHAPTER FOUR

Discussion

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A. DESCRIPTIVE ASPECTS.

A major objective of this study was to examine asbestos exposure in detail in South African cases of mesothelioma. The cases were not to restricted to particular geographic regions, industries nor medical facilities. The representativeness of the cases with respect to cases diagnosed in South Africa in general is therefore an important issue and is addressed in detail below.

4.1 LIMITATIONS.

4.1.1 Case ascertainment

The number of cases of mesothelioma who should have been included in the study is not known. Nevertheless, it would seem from indirect evidence that a substantial proportion of eligible cases were included. The Zwi study [1987] has been the only one conducted in South Africa specifically to register all cases of mesothelioma diagnosed over a specified time; case collection was thus fundamental to the study and the researchers sought cases from numerous sources including medical practitioners, hospitals (particularly in mining districts), asbestos producers and users, compensation authorities and Panel members [Zwi et al., 1987]. Zwi and colleagues accepted cases without review of the diagnosis and a cytological diagnosis was accepted as was a diagnosis by a surgeon even without direct evidence that histology confirmed the diagnosis. In other words

stringent diagnostic criteria were not applied. The cases could thus be considered roughly equivalent to the potential cases collected during this case-control study. The Zwi study registered 169 cases per year on average (range 152 - 196) for South Africa 1980-1984 compared to 109 potential cases (145 in 16 months) interviewed by us in selected regions only. Thus, although direct data are lacking, available evidence indicates that a substantial proportion of the diagnosed cases of mesothelioma were interviewed. The stringency of the diagnostic criteria applied undoubtedly reduced the number of subjects eventually accepted into the study. In other words case recruitment was reduced due to the high specificity of the diagnostic tests. This should not be seen as a limitation in this study: cases without asbestos exposure were of particular interest so certainty of diagnosis was crucial (otherwise non-exposure could have been explained by subjects not having mesothelioma). In addition, it has been shown that specificity should usually take precedence over sensitivity in case selection for the sake of validity [Brenner and Savitz, 1990].

4.1.2 Representativeness of cases

One of the major aims of this thesis was to describe a series of mesothelioma cases representative of cases diagnosed histologically in South Africa. For a number of reasons representativeness may not have been achieved completely:

4.1.2.1 Regions

1. Case collection was limited to selected geographic regions of South Africa. No study team was successfully established in Natal (as it was then named). Despite training and initiating a team it did not operate successfully and had to be abandoned. The effect of this on case ascertainment is difficult to quantify: Durban has a major harbour which exported asbestos (chrysotile mostly) and the city housed large asbestos product manufactures over the years. On the other hand Natal had no important asbestos mining districts and is the one region without a Panel member (The province is not an important source of cases historically and the Register does not list cases by Natal province). It may be that cases arising from the shipping of asbestos and exposure related to ship maintenance are underrepresented in this series. Cape Town and Port Elizabeth are important harbour towns so this type of case could enter the series. In addition, this type of exposure has not been prominent in South Africa, for example in the Solomons study [1984] only 6 (9%) of the cases with occupational exposure had worked in marine engineering or shipyards.

2. The proportion of cases collected in Kimberley (22/123) was not as large as expected given the importance of this region historically. A proportion of suspect cases was diagnosed clinically and not confirmed by pleural biopsy during the study (Personal communication, Fourie CE , Kimberley: 1989) and thus were not included in the study. It

is likely, therefore, that NW Cape cases (as defined in Table 2.1) are underrepresented in the study. It is difficult to quantify this as neither the Register nor the Zwi study [1989] reported cases by region of diagnosis but it may be substantial given the importance of mesothelioma as a cause of death in the Prieska cohort [Reid et al., 1990]. Records of black and coloured members of the cohort could not be traced but six of 66 deaths in the 399 white cohort members were recorded as due to mesothelioma.

3. Study teams were not established in the NE Transvaal, E Transvaal nor NW Cape mining regions themselves. This was consistent with the location of study teams as described in the Methods: teams were located in cities with the major regional referral hospital or academic hospital complex; the cities were also outside mining districts (otherwise it would have been necessary to assume possible environmental exposure in all of these cases and controls). Pretoria was thus the nearest city to the NE Transvaal and E Transvaal mining districts satisfying these criteria and included the major referral hospitals and Medunsa and Pretoria Medical Schools. Pretoria is about 250kms from the NE Transvaal and E Transvaal mining districts. Kimberley is the nearest city to the NW Cape mining districts and is about 150kms from Kuruman. Cases arising in mining districts had thus to be referred to distant hospitals to enter the study. Nevertheless, given the sophisticated diagnostic and treatment facilities required for the condition and the reliance on specialists such as surgeons, pathologists and

oncologists it seems unlikely that a substantial proportion of diagnosed cases would not have entered a study area, at least through referral of tissue to a pathologist.
Pietersburg is a city in the NE Transvaal with specialist medical services and a branch of the South african Institute for Medical Research (the major pathology service). NE Transvaal cases of mesothelioma could thus have been diagnosed and treated without entering a study area and this would have resulted in a relative underrepresentation of these cases compared to NW Cape cases. A number of factors make this an unlikely source of bias. Special histochemical stains to confirm the diagnosis of mesothelioma were done for the Pietersburg pathologists at the central laboratory in Johannesburg: scrutiny of the record books for these stains showed that no Pietersburg cases were handled over the study period. The Panel collects cases irrespective of the location of the referring pathologist, not one case was referred to the Panel from a Pietersburg pathologist during the study period.
Felix et al. [1994] contend that cases from the Pietersburg laboratories may be underreported as pathologists had identified 16 suspected cases from February 1989 to April 1990.
Given the NW Cape diagnostic practices and the possible underreporting from Pietersburg it is not possible to state confidently that the location of the study teams could not have led to misrepresentation of cases from one or more region but a major regional imbalance of diagnosed cases

that would have satisfied the diagnostic entry criteria is unlikely.

In summary, although it cannot be quantified, it is possible that this series of cases underrepresents cases from the NW Cape (due to non-histologic diagnosis) and from Natal (due to absence of a study team). The effect of this may have been to underestimate the proportion of cases with environmental exposure to Cape crocidolite and those with harbour related exposure (if such cases existed).

4.1.2.2 Site of mesothelioma

The overwhelming proportion of cases (94%) had pleural tumours. This is not much higher than the 86.2% found in the 1347 cases in the Zwi study [1989], but nevertheless significantly different ($Chi^2 = 6.78$; $p = 0.009$). It is also higher than found by Sluis-Cremer and colleagues (Yates corrected $Chi^2 = 5.1$; $p = 0.02$). Sluis-Cremer's series was relatively small (30 cases) and limited to amosite or crocidolite miners; it may thus be an inappropriate comparison group. In the Solomons series [1984] 98% had pleural mesothelioma, similar to the 94% in this case-control study. It may be that peritoneal cases are slightly underrepresented in this case-control study as peritoneal cases make up about 10% of cases in series collected elsewhere, for example the Norwegian cancer registry for 1970-1979 contained 141 cases of which 14 (9.9%) were

peritoneal [Mowe and Gylseth, 1986]. Just under 90% of male mesothelioma cases registered in Great Britain during 1968-1983 were pleural [Jones et al., 1988] and Hillerdal in a review of 4710 published cases [1983] found 9.6% to be peritoneal. A notable exception to the pleural preponderance is the cohort of asbestos insulation workers established by Selikoff in 1967. Four hundred and fifty seven mesothelioma deaths had occurred in this cohort by 1986; 186 were pleural and 271 peritoneal [Ribak and Selikoff, 1992]. Better than usual ascertainment of peritoneal cases is an explanation put forward by the authors for the large proportion of peritoneal cases but additional reasons seem likely.

4.1.2.3 Sex

Women comprised 17% of the cases; this is similar to the 23% found by Zwi et al., [1989] ($Chi^2 = 2.28$; $p = 0.13$), the 22% reported to the Register in 1989 and 1990 and is consistent with what is generally reported. For example, McDonald [1977] reviewed the features of 4539 cases from 22 countries and found that over three quarters had occurred in men.

4.1.2.4 Skin colour

The distribution of cases by skin colour was remarkably similar in this and in the Zwi study: white 55% versus 52% ($Chi^2 = 0.5$; $p = 0.48$); black 32% versus 31% and coloured 13% versus 16% for the case-control and incidence studies respectively. The Register had very similar distributions of cases by skin colour for the years 1990 and 1989: 62% and

32% and 57% and 35% for white and black cases respectively. Possible explanations for the large proportion of white cases, despite this group making up only about one fifth of the population, are presented in some detail by Zwi et al. [1989]. Among them are better access to health care, longer life expectancy and the migrant labour system resulting in some exposed black workers developing disease in neighbouring countries rather than in South Africa.

4.1.2.5 Nature of exposure

Both the Register and the incidence study had a substantial proportion of cases in whom exposure data is incomplete or absent: Register 50% [1990] and incidence study 33% [Zwi, 1989]. In addition, exposure information was collected in a non-standardised manner (as reported to the referring pathologist who then informed the Panel). Consequently it is problematic to compare nature of exposure in the case-control study and these datasets.

Nevertheless, it is interesting that the incidence study found occupational exposure in 60% of the men (versus 70% case-control) and the register in 66% of all cases (versus 58% case-control). Environmental exposure was reported in 10% and 7% of men and 35% and 71% of women in the incidence and case-control studies respectively. Environmental exposure may be undetected unless a detailed residential history is obtained. Such a history was obtained in the case-control study but not in the incidence study; this may explain the greater proportion of environmentally exposed

female cases reported here.

Environmental asbestos exposure is clearly an important cause of mesothelioma in South Africa. Even the 7% in men translates into a large number of cases over time - many hundreds since asbestos mining began. This matter is discussed in more detail section 4.3.5.

4.1.3 Measuring asbestos exposure

Measuring asbestos exposure using a questionnaire has limitations, particularly in quantifying factors such as exposure duration and intensity, since dates, long past, must be recalled and intensity inferred rather than measured. Nevertheless, concordance between job history based exposure indices and lung asbestos fibre retained dose has been shown in a series of 42 subjects selected from Montreal hospitals [Takahashi, et al. 1994] supporting the use of carefully determined exposure indices based on exposure histories in epidemiological studies. Additionally, a number of strategies were adopted in this case-control study to limit misclassification of exposure and particular effort was made to ensure that subjects with exposure would be identified. (See Methods). A number of indicators suggest that this was successful. No case classified in unlikely exposure class had coated fibres in the sputum and 19 of the 20 subjects with coated fibres were classed definite or probable. The remaining case was classed possible, did not recall asbestos exposure but had worked in a Risk occupation for a very long time (38 years). A natural validation study occurred because eight cases were interviewed and then referred to the NCOH occupational medicine clinic so that a compensation claim could be submitted. In all eight cases the class and nature of the asbestos exposure as ascertained by myself during the later consultation were the same as those measured by the interviewer. The high rate of reported asbestos exposure in cases (86.1% if stringent criteria are

applied to 97.6% if any evidence of exposure is accepted) suggests successful documentation of exposure as does the distribution of nature of asbestos exposure shown in Table 3.7. None of the cases, and only five of 222 controls, had worked in a High risk occupation without recalling asbestos exposure.

The measurement of lung fibre loads may have made a substantial improvement to exposure information if this method had been feasible. The nature of the exposure (e.g. details of occupation or residence in a mining district) and details such as duration and date of first exposure cannot be obtained from lung fibre loads, but aspects such as fibre dimentions and retained dose can be explored. It would have been useful to have had lung fibre loads in the cases classed as possible or unlikely asbestos exposure since the finding of very numerous fibres (approaching 1 million per gram of lung tissue) would have been very suggestive of substantial exposure. The lung fibre loads in the short exposure cases would be of interest also. Nevertheless, not all exposure related issues would have been resolved. Even the significance of finding fairly numerous fibres in lung tissue (close to one million fibres per gram of dried lung) may have been problematic in this study given the possibility of environmental exposure: the expected fibre load in rural subjects with short periods of remote environmental exposure would not be greater than that in life-long city dwellers "without exposure". In addition,

lung fibre loads in a proportion of mesothelioma cases are below one million fibres per gram of dried lung. For example, Tuomi [1992] found 10 of 29 cases (34.5%) to be below this limit and a further three (10%) to be close to it (< 1.3 million fibres/gram dry tissue). In the Takahashi study [1994] 12 subjects had an asbestos exposed job history, only three had the generally accepted level of unequivocal occupational exposure (1 million or more fibres per gram dried lung tissue). In other words the cut-off between exposed and unexposed would have been arbitrary even with lung fibre loads, particularly since chrysotile is cleared from the lung over time and mesothelioma may occur many years since last exposure.

Dates and durations of exposure could not be objectively confirmed and must therefore be treated with a degree of caution as should variables derived from them such as latent period.

4.2 AGE.

Over half of the cases were 55 years or younger at diagnosis. This is important as most were of working age and many were likely to have had dependents. The nature of the condition means that sufferers are generally unable to work for more than a few months after diagnosis. This has implications for social security systems (for example, workers' compensation) as speedy resolution of claims is necessary to provide dependents with money.

The younger mean age of the black cases (49.9 versus 58.1 years for white cases) is probably due to selection bias: younger black cases are more likely than older black cases to have access to sophisticated health services and hence are more likely to be diagnosed with mesothelioma. This is particularly likely in migrant workers who, while younger, would have lived in cities or mine compounds but would have returned to resource poor rural areas on retirement.

4.3 ASBESTOS EXPOSURE.

Other studies of mesothelioma have classed subjects by four levels of asbestos exposure, often named, as in this study, as definite, probable, possible and unlikely [Tuomi et al., 1991; McDonald and McDonald, 1980; Zielhuis et al., 1975]. In these studies the occupational history was used to class subjects by exposure: this was not appropriate for a South African study given the importance of asbestos mining here and the subsequent well documented environmental pollution [Felix, et al. 1994]. Because the methods used in other studies could not be applied a standard method was not available and the one shown in Table 2.2 was devised. The definite and unlikely classes appear to have face validity since to be definitely exposed the subject had to report asbestos exposure and to be placed in the unlikely class the subject had to have no evidence of exposure. The major difficulty was in separating probable and possible environmental exposure in subjects who had no recall of

asbestos contact: an arbitrary period of one year of residence in a mining district was selected. Since two cases of mesothelioma which were classed possibly exposed had much less than a year of exposure the success of this method could be questioned. In any event the method has little if any consequences for the descriptive aspect of this study since the exposure details are provided and cases can be reclassified by the reader, but the possible deficiencies need to be born in mind when interpreting the case-control analysis.

The asbestos exposure of the cases is of interest because of the cases without obvious asbestos exposure, the relative importance of the NW Cape, the exposure profiles of cases from the NE Transvaal, the absence of chrysotile exclusive cases and the absence of cases with Incidental exposure (use of asbestos cement garden furniture, spending time in asbestos cement structures and use of asbestos heating panels).

4.3.1 Proportion of cases without documented asbestos exposure

As discussed in Chapter One, the proportion of mesothelioma patients with documented asbestos exposure varies among studies and is determined by factors such as the source of the cases, the source of the exposure information (e.g. the patient - information or lung tissue - a surrogate or

records of work), the competency of history taking and the stringency of evidence for exposure. It is, therefore, problematic to compare studies since one or more of these factors is usually different. This study was rigorous in searching for asbestos exposure (detailed lengthy interviews with the cases themselves) yet, even when lenient criteria for exposure were applied, three cases had no evidence of asbestos exposure (Table 3.5 Unlikely subjects 3, 4 and 5). Asbestos is ubiquitous and one explanation is that these cases were exposed unknowingly, that they failed to recall contact or that general environmental pollution by asbestos or trivial contact is sufficient to cause the disease in a small proportion of cases. The alternative explanation is that a background rate exists or that other agents cause the disease. This study is unable to provide the answer but it would seem reasonable to accept that three out of 123 people could have forgotten or not known about exposure to an agent and that undocumented asbestos exposure had occurred in these individuals.

4.3.2 The relative importance of the NW Cape

In all study areas the majority of cases who had spent time in an asbestos mining district had done so in the NW Cape (Table 4.1). The majority of cases who had mined asbestos had mined NW Cape crocidolite (Table 3.9) and the majority of cases with asbestos exposure exclusively in an asbestos mining district had this exposure in the NW Cape (Table 3.10). Of the twenty two cases with only environmental

exposure, 20 (91%) were exposed in the NW Cape.

Table 4.1: Cases of mesothelioma by study area and number and proportion who had spent time in asbestos mining districts

Study area	NW Cape		NE Transvaal		E Transvaal		OTHER	
	n	(%)[a]	n	(%)[a]	n	(%)[a]	n	(%)[a]
Johannesburg n = 48	14	(29)	10	(21)	6	(13)	3	(6)
Pretoria n = 21	11	(52)	2	(10)	1	(5)	0	
Bloemfontein n = 19	16	(84)	1	(6)	0		0	
Kimberley n = 22	20	(91)	0		0		0	
Cape Town n = 10	3	(30)	0		1	(10)	0	
Port Elizabeth n = 3	0		0		0		0	
Total n = 123	64	(52)	13	(11)	8	(7)	3	(2)

[a]% = % of the study area's cases who had spent time in the mining district.

Explanations for this preponderance of cases with NW Cape mining district experience are:

1. That these districts mined much more asbestos than the other districts.
2. That the nature of the mining operations led to contamination of a much larger area.
3. That they generated much more dust thus exposing more people to more dust.

The first suggestion is easiest to examine. Table 4.2 shows that it was only in about 1960 that crocidolite production exceeded that of amosite and that amosite and chrysotile production was substantial throughout the 60's and early to mid 70's. (Given the long latent period for mesothelioma more recent data are not of real interest).

It is true that NW Cape crocidolite mining took place over a wide geographic area (Table 2.1) but extensive contamination of the NE Transvaal has been well documented [Felix et al., 1994]: that pollution by asbestos of surrounding villages and the environs was extensive (for example, at least nine mills operated in the Mafefe district each with a large asbestos waste dump); and that disease due to environmental exposure was common in mining areas (for example 389 of 611 randomly selected adults from Mafefe had a history of environmental asbestos exposure and 34% of these 389 individuals had pleural disease). E Transvaal (chrysotile) communities have not been studied, the extent of environmental pollution experienced by these communities and of asbestos related disease in them is not known.

Table 4.2: Asbestos production and estimated number of miners by fibre type

Source of information	Asbestos production[a]				Number of asbestos miners		
Webster, 1973	Production of amphibole asbestos						
	1940	1945	1950	1955			
Cape crocidolite	7	8	15	35			
Amosite	18	17	42	50			
Hart, 1988	Production of asbestos fibre						
	1960	1970	1975				
Crocidolite	71	137	165				
Amosite	62	97	88				
Chrysotile	27	53	100				
Myers, 1987	Percent of asbestos production						
	1977	1983					
Crocidolite	53	40					
Amosite	18	18					
Chrysotile	29	42					
du Toit, 1993	Approximate production (%)				Estimated number of asbestos miners (% of all asbestos miners)		
	1960	1970	1975		1960	1970	1975
Cape crocidolite	70	138	168				
Amosite	63	100	88				
Chrysotile	30	50	100 (29)		2600 (17)	1200	1500
Felix, 1994					Number of asbestos miners		
					1960s - 1970's	1970	
Cape crocidolite					12000 - 14000	7000	
Chrysotile					No estimates		

[a] Hart and du Toit in metric kilotons, Webster in short kilotons.

Dust levels in and around NE Transvaal mines and mills were very high (dust counts taken in the Penge mill remained well above 12 fibres/ml until after the second half of the 1970's) [Felix et al. 1994]. Published studies of fibre levels in E Transvaal chrysotile mines are sparse, the only readily available data are from Slade's thesis [Slade, 1931]. The thesis provides convincing evidence of uncontrolled dust levels (the concentration of dust in the atmosphere was such that objects were rendered indistinguishable at a distance of a few yards) and of high disease rates (of 100 chrysotile mill workers examined, 74 had an abnormal finding consistent with asbestosis [Felix et al., 1994]).

Given the contamination of mining regions in the NE Transvaal, the high dust levels in chrysotile mines and that the NW Cape is a sparsely populated region, it is untenable that the preponderance of NW Cape cases can be explained merely by a preponderance of individuals exposed in the NW Cape.

4.3.3 NE Transvaal cases

Table 3.9 shows that seven cases (6% of all cases) had worked on asbestos mines in the NE Transvaal and Table 3.11 that an additional case had spent 228 months in NE Transvaal mining districts. This case had had no occupational exposure but had taught in asbestos-cement classrooms for over 40 years. Hence at least eight cases (6.5%) could be attributed to asbestos mining in the NE Transvaal. It is notable that

three cases (2.4%) were from a single amosite mine (Penge). One was from a Transvaal crocidolite mine while for the other three miners mixed amosite and crocidolite exposure appeared likely.

Mesothelioma as a consequence of amosite exposure is well documented in experiments on baboons [Webster et al., 1993], in occupational cohorts [Ribak et al., 1989; Sluis-Cremer et al., 1992] and in individual cases with confirmation of amosite in lung tissue [Stein et al., 1989] and in series of cases [Webster, 1973; and Acheson et al., 1981]. The Webster study found only two cases out of 232 with amosite exclusive exposure.

It is of interest that peritoneal mesothelioma has been relatively more common in some studies of amosite exposed subjects than in it is in most other series of mesothelioma cases [Webster et al., 1993; Ribak et al., 1989]. This was not true of the Acheson cases - five workers with mesothelioma were reported in a factory using mainly amosite and some chrysotile: four were pleural and one peritoneal. Only one of the three Penge miners in this study had a peritoneal mesothelioma and of the seven peritoneal cases two had exclusively NW Cape environmental exposure, two worked on Cape blue mines and two had mixed or unspecified exposure. As mentioned above underreporting of Pietersburg cases and possible underascertainment of peritoneal cases may have occurred so the lack of association between amosite and peritoneal mesothelioma in this study may be due to relative underrepresentation of these cases.

In summary, despite the relatively small proportion of cases and the lower odds ratios NE Transvaal exposure (amosite and crocidolite) is still an important source of cases.

4.3.4 Paucity of chrysotile cases

No case with a history of chrysotile mining entered the study (Table 3.9), nor did a case with exclusively environmental exposure to chrysotile (Table 3.11). Although no case could be said to have had good evidence of chrysotile exclusive occupational exposure, two reported contact with this material, and little if any work with amphiboles. One of these spent 369 months in chrysotile mining districts and three months on an asbestos mine in the NE Transvaal - he had amphiboles isolated from pleural biopsy tissue. The other case (subject 2 Table 3.5) is intriguing: despite repeated questioning for clinical and compensation purposes the only historical source of asbestos exposure was to chrysotile which began only four years prior to diagnosis. Lanphear and Buncher, [1992] reviewed 21 articles to estimate the minimum latent period for mesothelioma of occupational origin. Applying strict histologic and exposure criteria before accepting cases into the study produced an observed probability of zero for mesothelioma occurring within a decade of first exposure. Other researchers have reported disease within shorter latent periods but actual first exposure may have preceded reported first exposure in some or all of these cases. In any event, four years (as reported by this case) is a very

short latent period and does not lend itself to causal interpretation. An amphibole, probably tremolite, was seen in pleural material examined by scanning electron microscopy: this may have been a contaminant of the chrysotile to which she was exposed.

One explanation for the absence of chrysotile exclusive cases is that production and use of the material in South Africa was so limited that the small number of exposed individuals has resulted in a paucity of cases. Table 4.2 presents data on asbestos production and the estimated number of miners by fibre type. Hart [1988], du Toit [1993] and Myers et al. [1987] estimate chrysotile production at about 30% of total asbestos production by the end of the 1970's. In the early 60's production was closer to 20% [Hart, 1988; du Toit, 1993]. Substantial numbers of miners worked in chrysotile production as can be seen by du Toit's estimates, although the number was fewer than on Cape crocidolite mines [Felix et al., 1994]. It seems unlikely from these data that scarcity of exposed workers is an adequate explanation for the absence of cases. Adequate dust control on chrysotile mines is another possible reason but this is intuitively unconvincing and not supported by available data. One study has been published on respiratory disease in South African chrysotile miners and, although it was long ago, dust levels and disease rates were very high [Slade, 1931]. Dust control may have been better on chrysotile than on amphibole mines in subsequent decades but there is no published evidence to confirm this and dust

control was unlikely to have been sufficient to eliminate the mesothelioma risk (had one been present). Australia and South Africa are unique in that both countries mined significant amounts of both chrysotile and crocidolite. The Australian experience of mesothelioma is, therefore, of interest (although chrysotile mining was only about one tenth of crocidolite mining in Australia). The Australian mesothelioma surveillance programme had registered 726 cases with an exposure history by 1987 [Ferguson et al., 1987] - only two of these had been exposed to chrysotile (at Baryulgil mine) and the authors note that chrysotile was not the only fibre type to which these two cases were exposed.

In summary, the great preponderance of crocidolite cases followed by amosite and then chrysotile cases (in this study no convincing case was identified) is consitent with the view that that there is a fibre gradient in mesotheliomagenic potential (crocidolite > amosite > chrysotile). This South African experience of a preponderance of crocidolite cases without convincing chrysotile cases will not be shared in countries with different asbestos mining and usage profiles. Roggli and colleagues [1993] used scanning electron microscopy to examine fibre type in 94 cases of mesothelioma; amosite was identified in 81% of samples, chrysotile in 21% and crocidolite in only 16%. The authors conclude that the results do not support the notion that most mesotheliomas in

the United States are due to crocidolite asbestos. The country of origin of the chrysotile might be a determinant of the relative contribution of each fibre type to country-specific case-loads. Lippman [1994] has summarised the mesothelioma yields in rat inhalation studies and found them to be highly dependant on fibre type. The percentage of mesotheliomas was 0.6% (1/169 rats) for Zimbabwean chrysotile, 2.5% (13/520) for the various amphiboles as a group and 4.7% (9/193) for Quebec chrysotile.

Thus findings in South Africa should be generalised to other settings with caution.

4.3.5 Nature of asbestos exposure

Four aspects of the nature of asbestos exposure are particularly important.

1. Firstly, the large proportion of cases with purely environmental exposure is unique to south Africa. Australia is the only other country to have mined crocidolite in significant amounts and it has maintained a mesothelioma surveillance programme since 1979. Ferguson et al., [1987] presented exposure data on 726 cases collected from 1/1/1980 to 31/12/1985. Environmental exposure had occurred in 43 of these cases (6%) and in only six of these (less than 1%) was environmental exposure due to residence in an asbestos mining region (Wittenoom, the crocidolite district). This is about one case per year - a sharp contrast to the findings

of this study.

Other mining countries do not report environmental mesothelioma to any extent; for example, McDonald and McDonald, [1980] examined the exposure histories of 480 cases of mesothelioma in the USA and Canada. Neighbourhood exposure (i.e. exposure recorded as exclusively residence within 20 miles of a chrysotile mine) was found in one USA case and in none of the Canadian cases.

2. The second important feature is the absence of trivial exposure in cases. No case with Incidental exposure to asbestos cement products (e.g. in domestic use) or residence near a dockyard, railway station or asbestos using factory was documented. Of course, such exposure could have led to some of the cases since a clear history of asbestos exposure was not obtained from all the of them. Nevertheless, it would appear that in South Africa this type of exposure contributes little to the current case load.

3. The importance of mining in generating cases is shown clearly in Tables 3.9, 3.10 and 3.11. The cases with purely environmental exposure are important - 15 of the 22 were exposed as a direct consequence of mining related activity and not as a consequence of general pollution of the district. This should strengthen claims for financial compensation in these cases since an attributable company or mine can be identified for most of them.

4. The fourth aspect is the difference in asbestos exposure profiles in men and women. In general, a greater proportion of men than women with mesothelioma report asbestos exposure and this is usually occupational [McDonald, 1985]. A greater proportion of women cases have non-occupational exposure (i.e. neither direct nor indirect exposure at work) and it has been suggested that this can be used as an indicator of the impact of environmental asbestos exposure, especially if field studies are done to estimate the contribution of occupational exposure to the case load in women [McDonald, 1985]. In other words, since there is a stronger environmental signal in female cases, one could monitor the mesothelioma trends in women, adjust for occupational exposure and have an estimate of the impact of environmental asbestos.

The detailed exposure histories obtained in this study provided an opportunity to estimate the contribution of occupational exposure in women. Table 3.7 shows nature of asbestos exposure in 21 women. One worked on a Cape crocidolite mine and one had indirect occupational exposure from asbestos insulated pipes in a dry-cleaner. Fifteen women (71%) had lived in asbestos mining districts, 14 in the NW Cape and one in the NE Transvaal. The Domestic-use case had been exposed to insulation material at home and had visited construction sites as a pay clerk. Three had poor evidence of exposure: one had lived in Kagiso in Krugersdorp (an OTHER district); one had contact with chrysotile at work four years prior to diagnosis and had visited the E

Transvaal for three weeks in the 1960's; the third reported no exposure. In summary two cases (9.5%) could be attributed to occupational activity, one (5%) either domestic or domestic and indirect occupational, and the remainder (86%) to non-occupational contact. The Zwi study [1989] presents female cases by exposure category: an exposure history was not obtained in 38% of cases and exposure details were provided by the referring agent who usually obtained it second-hand. Nevertheless, it is interesting that 9.7% of the women had "Occupational only" as the exposure category; the same proportion as in this case-control study.
The findings support McDonald's view that mesothelioma rates in women reflect, in large measure, the non-occupational impact of asbestos exposure and that secular trends in rates in women would be important to monitor the epidemic in South Africa. The occupational contribution to the case load may change over time, with a likely increased entry of women into workplaces contrasting with a reduction in the use of asbestos: the proportion of cases with occupational exposure would have to be determined from time to time.

4.3.6 Duration of exposure and latency

The data on duration of exposure and date of first exposure could not be validated and, given the long latent period, may not be reliable. In addition, the exact date of first exposure (and hence latent period and duration) was unknown for many of the cases (and controls) who spent time in mining districts and for subjects classed possible asbestos

exposure. For these reasons duration related aspects were not a particularly useful variable for analysis. The median latent period of 38.0 years for the cases with occupational exposure is somewhat longer than the 32 years reported for occupational mesothelioma by Lanphear and Buncher [1992].

4.3.7 Exposure to non-asbestos agents

It could be anticipated that South Africa, having mined crocidolite and amosite for decades, would be a problematic country in which to investigate the association between agents other than mineral fibres and mesothelioma. The cases due to amphibole exposure would be expected to overwhelm the contribution to the caseload (should one exist) from non-asbestos agents. In addition, collecting a series of "non-asbestos exposed" cases would be difficult as the possibility of unrecalled, incidental or short duration environmental exposure as an explanation for the disease could not be excluded with confidence. Another possibility is that the pathologic criteria for mesothelioma diagnosis included asbestos exposure, thus cases without this exposure but with exposure to other agents would not have come to light.

The findings of this study confirm this expectation. Only 17 cases did not have definite or probable asbestos exposure and in many of these some asbestos contact was not excluded. Only two of the 17 had had exposure to putatively non-asbestos causing agents: one had worked with glass fibre but had worked intermittently on construction sites as a pay

clerk over a 54 month period. The other had worked with yttrium but reported nine 10-day visits to the NW Cape (Koegas) from 1979-1987.
It can be concluded that, although agents other than asbestos as a cause of mesothelioma could not be excluded, their contribution to the caseload in South Africa, if one exists, is negligible.

4.3.8 Asbestos exposure in controls
The ubiquitous use of asbestos is shown by the exposure experiences of the medical and cancer controls. Only about one third of each group was classed unlikely (Table 3.4) and 21% and 18.5% of medical and cancer controls respectively had good evidence of occupational contact with the agent (Table 3.7).
The possible exposure class should be interpreted with caution in both sets of controls. The likelihood that these subjects actually had significant asbestos exposure may be small given that over 50% of the possibly exposed controls comprised subjects who had worked in Risk occupations without recall of exposure (Table 3.7).

To summarise the descriptive aspects of this study: there is no convincing evidence that limitations in study design or implementation meant that study objectives could not be achieved; the NW Cape is by far the most important source of cases of mesothelioma but the NE Transvaal contributes a large number of cases; the paucity of chrysotile exposed

cases is notable as is the importance of environmental exposure and the scant contribution to the case load made by incidental asbestos exposure and putatively non-asbestos causes.

B CASE-CONTROL ASPECTS .

The second major objective of this study was to examine the relationship between risk of mesothelioma and asbestos exposure using a prospective study design. In general the risk of mesothelioma following asbestos exposure was high and an increasing risk with increasing exposure was found (for example, class of exposure). The risk following environmental exposure was higher in crocidolite than in amosite exposed subjects. It is unlikely that bias arising from methodological or analytic factors could explain the findings given the very substantial odds ratios and consistency with other studies. Nevertheless, a number of important sources of bias deserve attention.

4.4 LIMITATIONS.

The approach to bias adopted here follows a recently described theoretical approach in which a more uniform approach to bias was propounded [Steineck and Ahlbom, 1992]. On this conception bias follows the research process. Confounding is inherent in the study base. the selection of the study subjects engenders misrepresentation, the measurement of exposure and outcome engenders misclassification and errors in the handling of data and inappropriate modelling engenders analysis deviance. This gives complete coverage of all potential biases conceptualised in mutually exclusive analytic compartments

which map one to one to the stages of the research process viz. identification of the study hypothesis, selection of study population and sampling, measurement methods, and analysis of results.

4.4.1 Confounding

Confounding variables should not be of concern theoretically, if asbestos is the only cause of mesothelioma (for example where fibrous zeolites are absent). However, since a background rate has not been disproved and since misclassification of exposure can result in cases apparently arising spontaneously or from non-asbestos causes, confounding variables may be considered a potential source of bias. These potential confounding variables have not been identified, however, and confounding in this study was considered a relatively minor source of bias except in the consideration of diet and mesothelioma which is discussed in detail below.

4.4.2 Representativeness of controls

4.4.2.1 The study base

A primary study base with a defined population from which cases arose and from which a random selection of controls could be made was not possible in this study due to logistical constraints (e.g. the size of South Africa and poor telephone coverage) and cost considerations. Instead a

secondary base design using referral hospitals as the source of cases and controls was adopted. The underlying assumption in control selection is that the controls were individuals who would have been interviewed as cases had they contracted mesothelioma rather than the control disease. The controls should, therefore, be individuals who have a condition which would route them along the same referral pathways as would having mesothelioma. The strategy to achieve this in this case-control study was to ensure that controls required specialist diagnostic or treatment facilities and that the condition was sufficiently serious to make treatment at a peripheral medical centre unlikely (all factors which apply to mesothelioma). The cancer controls by the nature of their diseases and because they were selected from specialist treatment units probably satisfied these conditions. It is less clear that this applied to the medical controls also although they had to have been in-patients for five days or longer to ensure that the disease was serious enough to have resulted in referral pressures as for mesothelioma. Residential details were obtained from cases and controls so it was possible to determine whether subjects were residents of the study area or referred in from outside. The proportion of cases and controls referred into study areas was similar, for example 33.4% of Johannesburg cases were not current residents of the Johannesburg study area compared to 30.4% of the medical controls ($Chi^2 = 0.05$; $p = 0.8$). This provides some support for the contention that the strategy was successful.

No data are available on asbestos exposure profiles in South Africa so a standard against which to measure the representativeness of the exposure experience of the controls is not available. Studies from elsewhere may make poor references as environmental exposure from mining is not as important a factor as it is in South Africa, thus almost all asbestos exposure in non-South African studies is occupational exposure. Criteria to assign subjects to exposure classes vary among studies further complicating comparison. In addition, exposure profiles need to be gender-specific given the exposure differences between men and women. These concerns need to be remembered in interpreting Table 4.3 which presents cases and controls by exposure class from a number of studies conducted in Europe, Canada and Australia. The asbestos exposure experience of the cancer controls from this study was not unusual in that the proportion with definite exposure (20% for men and women together) is similar to that found by Ashcroft (21%) and McDonald (19%).

Table 4.3: Summary of mesothelioma case-control studies presenting subjects by exposure class

		Cases (%)				Controls (%)			
		Definite	Probable	Possible	Unlikely	Definite	Probable	Possible	Unlikely
Ashcroft, 1973 (Tynside)		80	15	-	5	21	20	-	59
Chiappino, 1985 (Lombardy)		23				8			
Ferguson, 1987[a] (Australia)		45	7	17	26				
McDonald, 1973[b] (Canada)		20	-	20	60	3	-	23	74
McDonald, 1980 (Canada)		46				19			
Mowe, 1985 (Norway)		-	79	14	7				
Rees, 1995		75	11	10	4	20	13	33	34[c]
(South Africa)	men	81	7	10	3	24	13	35	29
	women	48	33	10	10	5	14	24	57
Rubino, 1972 (Piedmont)		22				2			
Tuomi, 1991									
(Helsinki)	men	24	27	22	27	0	27	30	43
	women	0	0	7	93	0	0	7	93
Zielhuis, 1975 (Netherlands)		54	18	8	21	8	10	8	75

[a] 5% missing information. 17% possible = 11% pssible occupational + 6% environmental exposure. Register of cases, not a case-control study.

[b] Definite + probable combined into one exposure class.

[c] Cancer controls.

- Exposure class not used by the authors e.g. Mowe did not have a definite class.

Indices of the representativeness of controls internal to the study are likely to be better measures than data derived from other studies for the reasons cited above. The very similar distributions of class and nature of asbestos exposure for the cancer and medical controls is striking and given the large number of categories (14 for nature of exposure) it is unlikely that this arose by chance. This provides indirect evidence that both sets of controls are representative, in terms of asbestos exposure profiles, at least of hospital inpatients in the selected cities.
The cancer controls included 22 subjects with gastrointestinal malignancies, associated in some reports with asbestos exposure [Homa et al., 1994]. The asbestos exposure classes of these 22 controls were 18% definite, 9% probable, 50% possible and 23% unlikely; not significantly different to the exposure classes of the medical controls shown in Table 3.4 ($Chi^2 = 2.79$; $p = 0.42$) suggesting that this subgroup of cancer controls was not biased towards greater exposure.

4.4.2.2 Nonparticipation

Nonparticipation by cases and controls may introduce bias as nonparticipants may differ from participants with respect to crucial factors such as exposure experience and this may differ for cases and controls [Austin et al., 1994]. For example, mesothelioma cases with occupational exposure may participate more readily than nonexposed cases and all

controls if compensation benefits drive participation. For two reasons nonparticipation was probably not an important source of bias in this study. Firstly, for ethical reasons, the exact purpose of the study was not explained to potential cases and controls so no exposure related benefits could be anticipated. Secondly, nonparticipation rates were low. Twenty seven eligible potential cases did not become cases but only one of them refused the interview (Results 3.1.1 Case ascertainment) so exposure related nonparticipation seems unlikely.

Nonparticipation among controls was rare: for example, only one control refused in the Johannesburg area and one interview was terminated when it became evident that the subject was confused. This experience was shared by the other teams who could recall either no refused interviews or a maximum of two (Pretoria) so that nonparticipation of controls was under 10 (<4.5%) for all study teams combined.

4.4.3 Misclassification

4.4.3.1 Exposure

Nondifferential misclassification of exposure could occur as subjects (whether cases or controls) had to recall distant exposure. Such nondifferential underreporting of exposure may bias effect estimates toward the null. This issue is discussed in detail above (4.1.3 Measuring asbestos exposure) but the most convincing evidence that this did not occur is the high rate of reported exposure in the cases: it is not possible that asbestos exposure was underreported in a significant number of cases since at least 86% reported exposure.

Differential misclassification of exposure due to recall bias is a theoretical consideration although infrequently demonstrated to be substantial in practice [Austin et al., 1994]. In this study a number of strategies to control for this bias were adopted (See Methods 2.5); these together with the paucity of hard evidence showing recall bias significantly affecting relative risk estimates, particularly very large ones as found in this study, reduces concern regarding this potential source of bias.

Non-blind interviewers preferentially seeking asbestos exposure in cases could theoretically have occurred in this study as it would appear that blinding was only partially successful. Although not formally measured in other regions, both of the Johannesburg interviewers knew after a few months that the study was about mesothelioma and could

estimate whether the subject was a case or control by the nature of the ward (e.g. cardiothoracic = mesothelioma and medical = control). Nevertheless, the questionnaire was rigidly structured (few open-ended questions) to an extent that interviewer bias is unlikely to have had a mechanism for expression even if present. Training of interviewers emphasised the requirement for a standardised approach to the interview. The fairly high rate of asbestos exposure in the controls (Table 3.4) is indirect evidence that underreporting of exposure in controls did not occur to a significant extent.

4.4.3.2 Diagnostic bias

Mesothelioma is a problematic tumour histologically and it is possible that a few cases were not mesothelioma despite the fairly stringent case definition. Usually misclassification of diagnosis reduces true effect estimates since a false positive case is less likely to have been exposed than a true case where a real effect is present. This is not the case for mesothelioma and asbestos as exposure per se may influence the pathologist to diagnose mesothelioma. The strategy to counter this diagnostic suspicion bias in this study was to collect potential cases before the pathologist had exposure information and confirm the diagnosis blind of exposure data. To do this, potential cases were interviewed for the study as soon as the diagnosis was suspected and before an exposure history was taken and passed onto the diagnosing pathologist. The

reviewing pathologists confirmed the diagnosis blind of exposure information. This strategy was successful in the main as only 22 of the 123 cases (18%) had provided an exposure history prior to the study interview. Eighteen of the 22 reported definite or probable exposure and all 18 were CEA negative making substantial diagnostic misclassification based on exposure driven influence unlikely.

4.4.4 Analysis deviation

Analysis deviance is an unlikely source of substantial bias in this study given the careful data handling and minimal modelling. Adjustment of odds ratios in analysis to account for confounding was not a feature of the study, consequently almost all of the relative risk calculations were bivariate analyses using an asbestos exposure variable and one outcome (mesothelioma). Inappropriate modelling was, therefore, of little concern.

In summary, due to improved study design (e.g. non-reliance on surrogates for exposure information), minimal evidence of recall bias and the stringency of diagnosis, there is little room for substantial bias. In any event, bias would have to be profound to alter significantly the very large ORs found in this study.

4.5 MEASURES OF RELATIVE RISK.

The odds ratios calculated in this study were larger than those generally reported in other case-control studies of mesothelioma. Table 4.4 summarises findings from six previous studies and, although large risks were found in some (for example 46 for insulation workers [McDonald and McDonald, 1980] and 50.9 for women [Muscat and Wynder, 1991]), odds ratios were generally smaller than those shown in Table 3.14. One explanation is that the other studies generally relied on exposure information obtained from surrogates or records (i.e. not from the cases and controls themselves). This probably resulted in nondifferential underascertainment of exposure which would bias estimates to the null. A second explanation is the extensive mining, transport and use of crocidolite in South Africa which would increase the risk in exposed South African cases relative to cases studied elsewhere.

Odds ratios could not be calculated for cases exposed to chrysotile exclusively since no such cases were identified but Table 3.14 shows larger relative risks for environmental exposure in the NW Cape than in the NE Transvaal. The large relative risks associated with Cape crocidolite mining, insulation work and work with asbestos cement products is notable.

Table 4.4: Estimates of relative risk in case-control studies of mesothelioma

Source	Nature or class of exposure	Case/Control	Odds ratio	95%CI
McDonald, 1980	Insulation workers	27/1	46.0	
	Asbestos production and manufacture	25/7	6.1	
Mowe, 1985	1 000 000 fibres/gm dried lung	14/28	8.5	2.3 - 31.1
Schenker, 1986	Regular exposure vs none		21.4	8.7[a]
	Intermittent vs none		2.3	0.5
	Any vs none		7.2	3.3
Cicioni, 1991	Higher exposure probability		2.5	1.2 - 4.8
	Lower exposure probability		2.0	1.2 - 3.4
Muscat, 1991	Men: employment in asbestos related industries		8.1	4.9 - 13.5
	Women: self-reported exposure		50.9	21.7 - 119.8
Rees, 1995	Definite	cancer controls	40.8	9.2 - 109
	Probable	119/119	7.5	1.5 - 37
	Possible		1.7	0.4 - 8.2
	Definite	medical controls	105	10.6 - 1026
	Probable	103/103	10.5	1.2 - 89
	Possible		10.0	0.9 - 108
Tuomi, 1991	Definite		17.7	3.4 - 253[b]
	Probable		3.0	0.9 - 10.6
	Possible		1.0	0.4 - 2.7

[a] Lower confidence interval
[b] 90% confidence intervals

Odds ratios by skin colour are presented in Table 3.16. This issue could not be examined adequately due to the small number of subjects in each exposure sub-category. Given the clear influence of nature of exposure (Table 3.14) a comparison of risk would have had to control for this factor which was not possible with the small number of subjects in each category.

C DIET AND MESOTHELIOMA.

The objective of this component of the study was to examine the possible protective effect of dietary constituents found to be important in a previous study [Schiffman, et al. 1988]. Schiffman and co-workers studied 37 cases of mesothelioma and 37 controls and found that cases reported less frequent consumption of homegrown produce, cruciferous vegetables and all vegetables combined and that an estimate of usual carotene intake was lower in cases. A reduction in risk with increasing consumption of vegetables, especially cruciferous vegetables, was found also. Except for the protective effect of carotene, this thesis did not confirm the Schiffman findings. There were no statistically significant differences in frequency of consumption of any of the constituents although cases reported less frequent use of carotene rich fruit. Increasing consumption of carotene fruit was found to be protective for mesothelioma when adjusted for asbestos exposure class with an exposure response gradient (Table 3.18).

4.6 CONFOUNDING: DIET AND MESOTHELIOMA.

Increasing consumption of carotene fruit was found to be protective for mesothelioma but this was only evident after adjusting for asbestos exposure. This finding is consistent with negative confounding in that the protective effect was not apparent in bivariate analyses prior to adjusting for

asbestos exposure and the adjusted relative risks of mesothelioma were larger than the unadjusted risks in each asbestos exposure class. The interpretation of these analyses is not straight-forward. If asbestos is the only and specific cause of mesothelioma then it is impossible theoretically for carotene to protect from mesothelioma in the unexposed (since they are not at risk) thereby removing one of Rothman's three criteria for confounding [1986]. In this study carotene as an effect modifier was investigated using a multiplicative term in the regression analysis and effect modification was not demonstrated. If effect modification does not explain the findings then, in this extreme case of an unusually specific cause for a rare condition, the prevailing concept of confounding may not be adequate to cover all scenarios in which confounding may occur. This is a topic for further methodological investigation. Additionally, the adjusted effects of carotene on mesothelioma are relatively large effects with ORs ranging from 4 to 6. This extent of confounding can only take place in the presence of a very strong confounder. These findings are consistent with epidemiologic expectation but they illustrate the importance, especially in the presence of known strong confounders, of making the correct modelling decisions in multivariate analyses. It is all to easy to imagine dietary factors being dropped from a multivariate analysis because of the absence of a crude effect on mesothelioma. The important lesson here is that simple bivariate analyses should not be relied upon in

variable selection for modelling.

Although negative confounding is the focus of the preceding discussion effect modification was not excluded by the multiplicative interaction terms used in the regression analyses since non-multiplicative effects are possible as well.

4.7 LIMITATIONS.

The dietary findings should be interpreted with some caution because of limitations in the thesis methodology and because of the problems inherent in dietary questionnaires and in the application of the case-control method in investigating associations between diet and disease. Nevertheless, it should be remembered that most of these potential limitations would obscure the association between diet and mesothelioma, finding such an association, therefore, deserves attention. An important factor which should be explored futher, is that the asbestos with the highest ORs for mesothelioma (Cape crocidolite) is mined in the driest area with the least fruit farming. A spurious association between increased mesothelioma risk and low consumption of fruit, i.e. an apparent protective effect of increased consumption, could thus be present in the dataset.

4.7.1 Limitations in thesis methodology

The asbestos aspect of the questionnaire was long and the dietary component was limited to seven semi-quantitative

questions. Consequently a detailed evaluation of dietary habits was not possible and quantitative measures such as usual portions per week were unavailable.

The Research Institute for Nutritional Diseases (RIND) was consulted in compiling the lists of important cruciferous vegetables and carotene containing fruits and vegetables but these lists are flawed. Data on the diets of South Africans by cultural group were unavailable (Personal communication, Langenhoven, Ml, RIND, 1988), consequently vegetables usually eaten, major sources of carotene and frequently consumed cruciferous vegetables may have been omitted and differences between cases and controls not detected.

Seven variables reported by the subject, two derived variables and 14 categorical variables (Appendix 2.5) were examined for an association with mesothelioma. A protective effect arising by chance is possible merely due to the analyses of numerous variables. Against this are the relatively large ORs with the exposure response gradient shown for carotene-fruit and the restriction of constituents to those found to be important in another study.

4.7.2 Questionnaires and diet

The difficulty in assessing usual dietary patterns by questionnaire is often emphasised. In this case subjects were expected to report how often they had eaten various items, on average, over the past five years; clearly a difficult request in the best of circumstances. In this study circumstances were far from ideal as subjects were

unwell and many of the controls had chronic diseases which may have led them to alter usual dietary habits in response to the illness (for example 10 of the medical controls were diabetic).

These limitations are substantial. Nevertheless, the dietary data have some face validity. It is not unreasonable to assume that homegrown produce would be consumed more frequently in the more rural regions. This was the case with the Bloemfontein subjects significantly more frequent consumers of homegrown produce (Table 3.16) than those in the larger urban centres of Johannesburg and Pretoria. It is also reasonable to assume that the more expensive foods would be consumed more frequently by white subjects since they are relatively advantaged financially. This was the case: whites subjects reported significantly more frequent consumption of carotene rich fruit than the other groups with consumption of the cheaper cruciferous vegetables equally frequent (Table 3.16).

4.7.3 Case-control studies and diet

The case-control design may be inherently problematic in studying nutritional factors and disease [Austin, et al. 1994]. The selection of appropriate controls is complicated by factors which alter dietary habits (such as illness) and case-control studies are not well suited for detecting weak associations (odds ratios < or = 1.5) [Austin et al., 1994]. This is particularly relevant for the study of diet and cancer since associations, in general, are likely to be weak

and subtle. Also, there may be a tendency for many cancer patients to improve their diets after diagnosis thus resulting in misclassification of exposure and a weakening of the effect estimates.

4.8 CONCLUSION.

Most of the limitations described above would bias the study toward a lack of association between diet and mesothelioma. Nevertheless, a protective effect of more frequent consumption of carotene containing fruit was found and, therefore, warrants further attention, particularly since, in general, epidemiologic reports of the past decade reinforce the conclusion that fruit and vegetable consumption is linked to reduced cancer risks [Council of Scientific Affairs, 1993]. A specific hypothesis has been generated and an investigation designed to estimate carotene intake and to compare intake in cases of mesothelioma and appropriate controls (for example with diseases unlikely to lead to an alteration in diet) is indicated.

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CHAPTER FIVE

Summary of Conclusions and Recommendations

Contents Pages

This is the first case-control study of mesothelioma in South Africa which examined asbestos exposure in detail in cases not restricted to a particular geographic region or industry. The study is important mainly because South Africa has mined the three major commercial varieties of asbestos in significant quantities and the relative contribution made to the case load by each fibre type could be estimated. In addition, the relative importance of particular industries and of environmental exposure could be ascertained. Available information indicated that the cases were fairly representative of cases diagnosed histologically in South Africa although NW Cape and Natal cases and peritoneal cases were probably underrepresented. Black South Africans made up a disproportionately small subset of cases probably due to poor access to diagnostic services.

5.1 TIMEOUS RESOLUTION OF COMPENSATION CLAIMS.

Over half the cases were 55 years or younger at diagnosis and could be expected to have dependants. The South African compensation system for non-mining industry usually fails to resolve compensation cases within a reasonable period. The mean number of months from submission of a claim to first payment of compensation for NCOH occupational lung disease cases was 15.6 (range 2 - 37 months) [Goodman et al., 1994]. This is patently unacceptable for mesothelioma cases with dependants, medical costs and probable unemployment within months of diagnosis. The compensation authorities need to

recognise the special situation of mesothelioma sufferers and respond timeously to submissions for compensation. Submissions of cases of mesothelioma are opportunities to monitor the efficiency of the system in resolving claims and this presents an opportunity for health systems research.

5.2 IMPROVING EXPOSURE DATA.

Two methodological issues related to exposure measurement are of interest. The strategy to improve exposure data by encouraging subjects to report information remembered post interview was not useful: in only one case did this lead to a revision of questionnaire data. No support for this strategy was provided by this study but a modified approach may be justifiable in a different context, for example where literacy levels of subjects are known to be high. An appropriate modification may be to counter poor subject motivation by having interviewers telephone the subject post interview. Coated fibres in sputum, however, proved to be a useful tool for validation of exposure assessment as 19 of 20 positive sputum samples were provided by subjects with definite or probable asbestos exposure. Using questionnaire data as the gold standard coated fibres had a positive predictive value for exposure of 95% and a specificity of 98%. Unfortunately the sensitivity at 21% was low. Coated fibres have specificity for naturally occurring mineral fibres [McDonald et al., 1992], persist over time and are detectable with routinely available and simple techniques.

These factors and the findings of the study support a recommendation for the use of this technique to validate asbestos exposure data collected by questionnaire. It would be an unreliable method of exposure assessment on its own because of the high rate of false negatives and the inability of most subjects to provide sputum on demand.

5.3 PUTATIVE NON-ASBESTOS AGENTS: CAUSATIVE AND PROTECTIVE.

This study was unable to show that agents other than mineral fibres are not associated with an increased risk of mesothelioma. It did show that putative non-asbestos agents plus a possible background rate together could make a scant contribution to the case load. This is important as an assumption of asbestos exposure would be correct in the overwhelming majority of cases and it would seem reasonable to provide some form of compensation to all cases since the cause is almost certainly due to direct or indirect industrial activity. This contention is supported by the exposure histories of most of the people with environmental exposure. The current system of restricting compensation to only those cases who have a history of occupational exposure and documentation from an employer should be revised, particularly since the number of claims per year from these cases would be small. The scientific search for other mesotheliomagenic agents should continue nevertheless.

The protective effect of increasing consumption of carotene

containing fruit deserves further investigation. A prerequisite for a valid study would be the identification of the important sources of carotene in South African diets for each cultural group and for each region. If this information is difficult to obtain it would be necessary to limit the study to selected regions and possibly selected cultural groups. Appropriate controls would be a key issue. Controls with acute conditions (and thus unlikely to have influenced diet) which are not known to be related to diet may be most appropriate. One strategy would be to have two sets of controls, one with traumatic injuries or acute surgical conditions and one with acute medical conditions. Methodological considerations around confounding in extreme cases of unusually specific causes of rare conditions requires investigation.

5.4 AMOSITE.

The relative importance of Cape crocidolite should not mask the impact of identifying three cases in 16 months from a single amosite mine (Penge). This together with the contention by Felix et al. [1994] that mesothelioma is underdiagnosed in the NE Transvaal provides motivation for case-finding strategies in the area. Cross-sectional surveys are inappropriate for a rare disease with short life expectancy following diagnosis so alternatives are necessary. One approach would be to allocate the task to the regional health authority which would be in a position to

identify cases by encouraging pathologists to submit suspect tissue for expert review. Cases could be identified by establishing diagnostic and compensation submission services for asbestos related disease in the major regional hospital and by providing information about the condition and the service to the community and local medical practitioners.

5.5 CHRYSOTILE.

One explanation for the absence of convincing chrysotile exclusive cases is that South African chrysotile is uncontaminated by a significant quantity of fibrous tremolite or that if tremolite is present, its morphology is such that the hazard is small or nonexistent. This issue has been examined superficially [Rees et al., 1992] but deserves greater investigation. An examination of the fibre content of the lungs of deceased chrysotile miners will provide data on the cumulative tremolite exposure over time. The size and shape of tremolite fibres, if found in the lung tissue, should be recorded.

Another explanation for the paucity of these cases is a relatively low level of environmental pollution together with limited awareness of the disease in the community and in local medical practitioners. This combination of fewer exposed individuals and relative underdiagnosis warrants attention.

5.6 ASBESTOS CEMENT AND INCIDENTAL EXPOSURE.

The large relative risk of mesothelioma associated with the manufacture or use of asbestos cement products is of concern given the widespread use of these products in the construction industry and the generally poor hazard control in place on construction sites. The absence of cases with incidental exposure (e.g. use of asbestos cement furniture and heating panels) is a more positive finding.

5.7 ENVIRONMENTAL CASES AND COMPENSATION.

Contamination of the environment by mining related activity is an important factor in generating cases as shown by the 22 cases with exclusively environmental exposure. These twenty two cases had no other asbestos exposure. A further eight had environmental exposure and had worked in a Risk occupation without recall of contact with asbestos. If these eight are included in the environmental exposed group then 30 out of 123 cases were associated with this type of exposure. None of these cases is eligible for financial compensation nor for payment of medical expenses. One remedy (mentioned above) would be to provide compensation to all cases under the present workers' compensation systems by waiving the requirement to identify an attributable employer. This is likely to meet with resistance from the compensation fund managers which suggests that strategies to create a dedicated fund should be pursued as well.

5.8 WOMEN.

Women with mesothelioma provide a means of monitoring secular disease trends due to environmental pollution. This would be a fairly simple task using a national mesothelioma register. It is regrettable that the register maintained by the NCOH Pathology department has been discontinued. The register was a substantial task in its previous form because all cases were subject to histologic confirmation by a panel of pathologists, some of whom were not resident in Johannesburg. A less rigorous approach, possibly with review of a sample of submitted cases by a local panel, is likely to be sustainable and cheaper and this should be investigated. The local cancer register (a national register of all types of cancer diagnosed by pathologists) could be utilised but the poor exposure data and anonymous registration may limit the utility of this database.

5.9 STRENGTH OF ASSOCIATION.

The relative risks for mesothelioma (as odds ratios) were generally large probably due to the type of exposure (amphiboles, and crocidolite in particular) and because of the prospective method of exposure assessment resulting in reduced exposure misclassification. The nature of asbestos exposure was an important determinant of level of risk and this needs to be considered in studies of mesothelioma which compare specific groups.

5.10 CONCLUSION.

This study confirms the very strong relationship between asbestos exposure and mesothelioma and has met the stated objectives of differentiating this effect with respect to the nature of asbestos exposure. The relative importance of environmental exposure was established, a response to individuals who contract mesothelioma through this kind of contact is required urgently. Incidental contact with asbestos contributed little to the case load. The influence of other putative factors has shown important results with respect to diet. This has both preventive implications and implications for further research into dietary factors and mesothelioma and for methodological considerations related to confounding.

5.11 REFERENCES.

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APPENDIX 2.1: INTERVIEWER'S GUIDE

Welcome! you have been selected to be one of the interviewers in a case-control study about the relationship between diet, exposure to dusts and certain illnesses, that is being run by investigators at the National Centre for Occupational Health.

Whew! take a minute to catch you breath after reading that mouthful and I'll explain what it all means.

Let's start at the end of the sentence .....

* **Occupational Health** - is a section of health care that is concerned with injuries and diseases caused by exposure to harmful substances eg. fibreglass, chronic back pain caused by repetitive work in uncomfortable positions and workplace accidents.

* **The National Centre for Occupational Health (NCOH)** - is based in Johannesburg. It has existed for many years and is concerned with many issues related to occupational health. There is a large staff of doctors, scientists and administrative personnel. The primary purpose of the centre is to conduct research into occupational disease. There is also a clinic where workers with suspected occupational disese are diagnosed and referred for treatment.

* **.... the relationship between diet, exposure to dusts and certain illnesses...** - often research is concerned with the relationship between different factors eg. diet and heart attacks. This type of research tries to find out WHAT the causes of disease are. We think that exposure to dusts and fibres cause certain illnesses and that substances in the diet might protect one from these illnesses. We have designed this study to determine the causes of these illnesses in order to help prevent them.

* **A case-control study** - is an excellent type of study for testing ideas about the suspected relationship between different factors. Cases (persons with one of the diseases) are compared with controls (persons without one of the diseases being studied) to see whether they have different exposures to suspected causes of the disease.

  More about all of the above later.

  As you can see, there is a lot involved in this study. There is quite a wad of reading to get through. Most of it is straightforward and we hope interesting. We think that you will be able to read it through in one sitting (it should take about two hours). But take two sittings if you need to. Don't worry if there are points that you find hard to understand immediately - ask your team coordinator, ----------, or write EACH question down to ask us when we come to your centre.

* We don't expect you to be experts when we meet but we do expect:
  a) that you have read the **whole** package through at least **once.**
  b) that you have read the **questionnaire** through at least **twice.**
  c) some questions from each person.

* A date will be set for us all to meet - the team coordinator, yourself, the other interviewer from your area and the NCOH research team. On that day we will:

  - discuss the project and the main issues related to it
  - answer all your questions (maybe ask some as well)
  - do training in interviewing techniques
  - role-play/practice doing an interview

- we will ensure that you will be fully prepared and 100% confident for your interviews.

You will be paid for the training day; the amount will equal the payment for 2 interviews.

INTRODUCTION TO THE STUDY

The **objectives** of our study are to look at:

1. the relationship between **diet** and **certain cancers.**
2. the **relationship between exposure to dusts, fibres and certain cancers.**
3. specifically, the **relationship between asbestos exposure and cancer and other illnesses.**

This study centres around a detailed interview (here's where you come in) about the person's past environmental and occupational history. You will be trained to administer a structured questionnaire in a sympathetic and thorough way. The questionnaire is the only means which we have to record the diet and exposure to various substances in each individual. To use this questionnarie properly, there are a few simple but extremely important rules that all interviewers must follow. We will deal with most of them later.

I will introduce you to one of the most important rules now....

It is important the you do **NOT KNOW WHICH PEOPLE ARE CASES OR CONTROLS** and that you do not try to find out! (We call this interviewer BLINDNESS). If you ignore this you may introduce something called BIAS into the study. Bias can take many different forms. If you know that someone whom you are interviewing has one of the diseases being studied, you might treat them slightly differently. Perhaps you would encourage them to recall exposure more than if they are "just" controls (ie. people without the disease). Even if you feel sure that you, yourself, would not be influenced, the rest of the scientific world will not accept it and the whole study could be discredited.

There is also the ethical issue with regards to the patient's diagnosis. Often people are unaware of their diagnosis, they may not have been informed or they may not want to know. Hearing the questions may throw up a range of further questions for them. The best response is always to gently refer them to their doctor. No matter what your personal views are with regards to patients knowing their own diagnosis - if you begin to discuss diagnosis, you could put the entire study in jeopardy. You may also have to embark on a painful process with the patient that you will not be able to follow through in a supportive way. In this instance, ignorance might not be bliss but it is EXTREMELY IMPORTANT!

IMPLEMENTATION OF THE STUDY

Many centres in SA have been selected for the study ie. Cape Town, Johannesburg, Pretoria, Kimberley, Bloemfontein, Durban, Port Elizabeth.

We will be starting in most of these areas in November 1988. Other areas may be added later.

Each area will have its own team coordinator (a doctor and 2 interviewers (yourselves). We are not sure at this point exactly how many interviews each interviewer will need to do.

THIS IS HOW THE STUDY WILL RUN STEP-BY-STEP

a) the local team coordinator will get telephonic consent from suitable patients for the study
b) s/he will get consent from all staff concerned with caring for the patient and inform them that you are coming
c) s/he will inform you of the patient's name, hospital and ward
d) you will go to the hospital, get written consent from the patient(s) to question them and conduct the interview.

- you will not know who are cases or controls **REMEMBER DO NOT TRY TO FIND OUT**
- you will ask **everyone** the same questions
- each interview will take about 1-1.5 hours
- you will be paid for doing the interview
- transport costs will also be paid
- no interview will take place more than 50 km away from the referral centre i.e. one of the towns in the study
- patients will also be asked to give us 2 sputum specimens - the exact method of collecting sputum will be explained later.

Please read through the **questionnaire** now (without reading the user's quide) and make a note of any unclear sections or questions that you have. You will be asked to read the questionnaire once more.

THE QUESTIONNAIRE

You should have read through the questionnaire at least once and you may have noticed some of the following:

- how structured it is
- how lengthy it is
- how repetitive it is

let me explain....

The structure

The questionnaire is what we call the "measurement tool" of the study. This means that it needs to be as accurate as any diagnostic instrument and as reliable. Therefore, the questionnaire must accurately measure exposure to the substances being studied as well as record other important information.

Questions can be asked in an open-ended or closed-ended way - in this questionnaire we have used both types of question. A **closed-ended** question offers a limited number of options as answers.

Eg. Did you ever stay/work near a mill? Answer: Yes
No
Unsure

Another type of close-ended question does not have yes/no as its answer but presents you with a finite set of options to choose from

Eg. How old are you? Answer: a) 0 - 20
b) 21 - 40
c) 41 - 60
d) older than 60

We use closed-ended questions when we are confident that the patient's answers will fall into one of the categories offered. **Open-ended** questions are used when one is not sure of all the possible options. It is also an opportunity for the person to state something in his/her own words.

Eg. "What were you father's occupations when you lived with him?"

We cannot possibly list all the possible answers. They could range from pilot to miner to unemployed.

Now imagine the variety of answers to this question -

Eg. "What did you learn from your father while you lived with him?"

Here the range of answers is even broader - it could include information about the father/child relationship, cricket-games, pipe-smoking etc.

The repetition

Let's look at 2 sections of the questionnaire that appear to repeat each other: question 6.1 & 6.2. If you look carefully, you will see that 6.1 is an open-ended question that asks people to list and explain all the jobs that they've done. Question 6.2, however, asks for similar information in a closed-ended way. We use this method to check:

a) that the person has not forgotton about certain key occupations that we are interested in.
b) whether there are discrepancies between the two answers. Question 6.2 acts as a memory jogger or prompt that we've inserted to ensure that no important information has been left out.

The length

It is not surprising that the questionnaire is long - The study is large and ambitious in that it hopes to examine the relationship between exposure to various substances and disease. To do this we need to cast our net (the questionnaire) very wide to bring in as much information as possible. So we ask questions about all of the situations in which people are exposed to hazardous substances. Each area has been dealt with separately in order to retain as much detail as possible and ensure that the answers are clear and unambiguous.

As you can see from the above, the design and phrasing of the questionnaire is not coincidental or haphazard. Much thought, many expert opinions and long hours have gone into ensuring that it is logical and consistent. We have tried to make it clear enough to allow all the relevant information to be captured without the interviewer having to explain further.

THE INTERVIEW

Earlier on, we spoke about certain important rules for you to follow to be a successful interviewer. The next few paragraphs will deal with the more important aspect of these interviewing techniques.

* All the people being interviewed have a serious illness. You need not feel hesitant about asking a sick person so many questions. In fact, in the test interviews for this study, we found people very willing to answer questions.

  It does mean, however, that the interviewers must be sensitive to a number of factors eg. tiredness, difficulty talking, anxiety, tearfulness. If necessary, allow the person to take a break or reassure them but remember not to get involved in discussion about diagnosis or treatment.

* Try to create a relaxed atmosphere but remember not to enter into lengthy discussions about the questionnaire. Being relaxed does not necessarily mean being chatty.

* You must have a good grasp of the questionnaire and of the objectives of the sutdy, this will be gained by reading through this package and further discussion on the training day.

* The person being interviewed must understand what is required of him/her. On the first page of the questionnaire are some tasks that you must complete before beginning the questionnaire. You do not have to use our exact words for this introduction. Rather use them as a guide for yourself, as well as an indication to us that the points were made. We feel that these 9 points are useful for the establishment of a relaxed environment where the patient is clear about the procedure.

* Once the interview has started, you may only read out the questions as they appear on the page and record the answers as given. It is essential that you read every word on the page (except the words which are highlighted on your copy of the questionnare). This is essential to ensure standardization (that all of the interviews are conducted in the same way). You may, however, use your initiative as an interviewer to explain a specific question if the patient does not understand (general questions must be dealt with before the interview begins). We have purposefully made the questions simple so they should not require much explanation.

* Always try to give the person sufficient time to complete their answers before you explain or go onto the next question. Don't rush.

* As an interviewer you must not influence the answers at all, <u>explaining is not the same as prompting.</u>

So, in summary the golden rules are - to keep the interview relaxed, while making sure that it is conducted in a standardised way without distressing the patient.
The final task for now is to read the questionnaire through again with the "user's guide". The other articles are further reading about study method and design, they are for your interest only.

There will be plenty of time to discuss any problems and answer questions at our training day. We are looking forward to meeting you all and hearing you comments and questions. I hope that this package has held your interest and that you are feeling confident and eager to begin.

Thanks

KIM GOODMAN
DAVE REES
(NCOH)

APPENDIX 2.2: STAINING FOR CARCINOEMBRIONIC ANTIGEN (CEA)

Method

Cut wax sections at 4 microns
Place overnight in incubator at 37°C
Place into 60°C incubator for 30 min
Dewax slides in xylene
Hydrate slides through graded alcohols (100% : 95%)
Trypsinize slides in prewarmed trypsin for 15 min
Quench (endogenous peroxidase) slides in quenching solution for 30 min
Rinse in phospahte buffered saline (PBS)
Place slides into normal horse serum for 20 min
Wipe off excess horse serum (do not rinse)
Add primary antibody for 30 min
Rinse well in PBS
Place on secondary antibody for 30 min
Rinse well in PBS
Place into ABC reagent for 30-60 min
Rinse well in PBS
Place into DAB solution for 5 min
Rinse in running tap water for 10 min
Counterstain in Mayers haematoxylin for 5 min
Wash in tap water
Blue sections in Scotts TWS
Rinse in tap water
Dehydrate slides through graded alcohol (95% :100%)
Place in xylene
Mount with entellan.

Results of staining

Positive tumour cells - brown staining
Nuclei/background - blue

CHECK LIST

This is a checklist for you, please ask the following questions in your own words

Tick each square provided when you have completed that task

Please return this sheet with the completed questionnaire

1. Hullo, my name is _____ [ ]

2. I work for a health research group and I'd like to ask you some questions. [ ]

3. I would like you to take part in a scientific study to establish whether diet or the exposure to some dusts, fibres and other substances in the environment, the home, as part of a hobby or at work, are associated with one or a number of illnesses. [ ]

4. We have chosen a group of in-patients at this hospital and other hospitals around the country because we want to compare their different illnesses with the things that they have been exposed to. You have been scientifically selected from the in-patients of this hospital. [ ]

5. We are asking you to :
   a) spend about one hour answering questions about yourself, your family and your work.
   b) give us some sputum/phlegm samples to study. [ ]

6. Do you have any questions so far? [ ]

7. You may refuse to answer any questions if you choose. You'will not be treated any differently if you do. [ ]

8. All information will be kept confidential, so don't feel embarassed about telling me anything. [ ]

9. This is a consent form. It says in writing what I have just told you, please sign it to show that you have understood what I have told you and that you agree to participate. [ ]

Card 1 [ ] 2
Pat [ ][ ][ ][ ] 7

CASE - CONTROL STUDY: INTERVIEW QUESTIONNAIRE

1. INTERVIEW DATA

1.1 Interviewer: name ..... [ ][ ] 9

1.2 Date of interview (dd/mm/yy): ____/____/19____ [ ][ ]-[ ][ ]-[ ][ ] 15

1.3 Hospital name and address: .....

.....

..... [ ][ ][ ] 18

postal code ..... [ ][ ][ ][ ] 22

1.4 Hospital ward no.: .....

2. PATIENT DETAILS

2.1 Hospital number ..... [ ][ ][ ][ ][ ][ ][ ][ ] 30

2.2 Surname .....

2.3 First names .....

2.4 Present address .....

.....

.....

postal code ..... [ ][ ][ ][ ] 34

tel.no ..... [ ][ ][ ][ ][ ][ ][ ] 39 46

2.5 Other contact address .....

.....

.....

postal code ..... [ ][ ][ ][ ] 50

tel.no ..... [ ][ ][ ][ ][ ][ ][ ] 55 62

Sex (tick one): female [1]
male [2] ☐ 63

Race (tick one): white [1] black [2]
coloured [3] asian [4] ☐ 64

Date of birth (dd/mm/yy): ___/___/___ ☐☐-☐☐-☐☐ 70
Present age : [ ][ ] yrs ☐☐ 72

Card 2 ☐☐ 2
Pat ☐☐☐☐☐ 7

I.D. no. ..... ☐☐☐☐☐☐☐ 14
☐☐☐☐☐☐ 20
☐☐ 22

Home language .....

Card 2 [ ][ ]
Pat [ ][ ][ ][ ]

EXPOSURE HISTORY

I am going to ask you a lot of questions about yourself. These questions are mostly about where you have lived and the work you have done during your life.
If you get tired please tell me and we will have a rest. You may be unable to remember all the things I ask you about. If you cannot remember, please tell me.

3. ENVIRONMENTAL EXPOSURE

3.1 The next few questions deal with all the places that you have lived

a) Where were you born ?

Town/Township/Village ..... [ ][ ][ ] 10

Magisterial District ..... [ ][ ][ ] 13

Province (or country, if not born in RSA):

..... [ ][ ] 15

b) Where did you spend most of your childhood?

Town/Township/Village ..... [ ][ ][ ] 18

Magisterial District ..... [ ][ ][ ] 21

Province (or country, if not RSA):

..... [ ][ ] 23

From 19___ to 19___ [ ][ ] yrs [ ][ ]-[ ][ ]-[ ][ ] 29

c) Where else did you stay for 2 months or longer as a child ?

i) Town/Township/Village ..... [ ][ ][ ] 32

Magisterial District ..... [ ][ ][ ] 35

Province (or country, if not RSA):

..... [ ][ ] 37

From 19___ to 19___ [ ][ ] mnths [ ][ ] 39
[ ][ ] yrs [ ][ ]-[ ][ ]-[ ][ ] 45

ii) Town/Township/Village 48

Magisterial District 51

Province (or country, if not RSA):

..... 53

From 19___ to 19___ [ ][ ] mnths 55
[ ][ ] yrs 61

3.2 Please list all the other places where you stayed for more than 3 months (this includes hostels).

i) Town/Township/Village 64

Magisterial District 67

Province (or country, if not RSA):

..... 69

Card 4 2
Pat 7

From 19___ to 19___ [ ][ ] mnths 9
[ ][ ] yrs 15

ii) Town/Township/Village 18

Magisterial District 21

Province (or country, if not RSA):

..... 23

From 19___ to 19___ [ ][ ] mnths 25
[ ][ ] yrs 31

iii) Town/Township/Village 34

Magisterial District 37

Province (or country, if not RSA):

..... 39

[ ][ ] mnths 41
From 19___ to 19___ [ ][ ] yrs 47

iv) Town/Township/Village 50

Magisterial District 53

Province (or country, if not RSA):

..... 55

[ ][ ] mnths 57
From 19___ to 19___ [ ][ ] yrs 63

v) Town/Township/Village..... 66

Magisterial District 69

Province (or country, if not RSA):

..... 71

Card 5 2
Pat 7

[ ][ ] mnths 9
From 19___ to 19___ [ ][ ] yrs 15

vi) Town/Township/Village 18

Magisterial District 21

Province (or country, if not RSA):

..... 23

[ ][ ] mnths 25
From 19___ to 19___ [ ][ ] yrs 31

3.3 As an adult or a child, did you ever spend time in any of the following areas?

a) The NW Cape eg. Prieska, Kuruman, Danielskuil, Pomfret, Postmasburg, Vryburg, Koegas

Yes [1]
No [2]
Unsure [3] ☐ 32

b) The NE Transvaal eg. Penge, Burgersfort, Pietersburg, Mafefe, Bewaarkloof

Yes [1]
No [2]
Unsure [3] ☐ 33

c) The Eastern Transvaal eg. Msauli, Barberton, Badplaas, Havelock

Yes [1]
No [2]
Unsure [3] ☐ 34

---- if yes to 3.3 a,b or c ----------

i) What was the name of the (nearest) town\township? ☐☐ 36

.....

ii) During what years did you stay there?

19___ to 19 ___ ☐☐-☐☐ 40

19___ to 19 ___ ☐☐-☐☐ 44

iii) How long did you stay there? [ ][ ] mnths ☐☐ 46
[ ][ ] yrs ☐☐ 48

(COMPLETE BELOW IF MORE THAN ONE TOWN)

---- if yes to 3.3 a,b or c ----------

i) What was the name of the (nearest) town\township? ☐☐ 50

.....

ii) During what years did you stay there?

19___ to 19 ___ ☐☐-☐☐ 54

19___ to 19 ___ ☐☐-☐☐ 58

iii) How long did you stay there? [ ][ ] mnths ☐☐ 60
[ ][ ] yrs ☐☐ 62

3.4 Did you ever spend time <u>near</u> a dockyard?
eg. stay or work or for some other reason

Yes [1]
No [2]
Unsure [3] ☐ 63

--- if yes/unsure ---

a) Explain briefly how you spent the time .....

..... ☐☐ 65

b) What was the name of the dockyard?

..... ☐☐ 67

c) What was the name of the (nearest) town\township?

..... ☐☐ 69

Card 6 ☐☐ 2
Pat ☐☐☐☐☐ 7

d) During what years? 19___-19___ 19___-19___ ☐☐-☐☐ 11

19___-19___ 19___-19___ ☐☐-☐☐ 15

19___-19___ 19___-19___ ☐☐-☐☐ 19

19___-19___ 19___-19___ ☐☐-☐☐ 23

19___-19___ 19___-19___ ☐☐-☐☐ 27

☐☐-☐☐ 31

e) For how many months/years in total? [ ][ ] mnths ☐☐ 33
[ ][ ]yrs ☐☐ 35

f) Did you stay/work within.....(tick one)

0,5 km [1]
1 km [2]
5 km [3]
more than 5 km [4] of the dockyard? ☐ 36

3.5 Did you ever spend time <u>near</u> a mill (where substances are ground eg. grain or minerals)?
eg. stay or work or for some other reason

Yes [1]
No [2]
Unsure [3] ☐ 37

--- if yes/unsure ---

a) Explain briefly how you spent the time .....

..... ☐☐ 39

b) What was the name of the mill?..... ☐☐ 41

c) What substance was milled? ..... ☐☐ 43

d) What was the name of the (nearest) town\township?

..... ☐☐ 45

e) During what years? 19___-19___ 19___-19___ ☐☐-☐☐ 49

19___-19___ 19___-19___ ☐☐-☐☐ 53

19___-19___ 19___-19___ ☐☐-☐☐ 57

☐☐-☐☐ 61

☐☐-☐☐ 65

☐☐-☐☐ 69

Card 7 ☐☐ 2
Pat ☐☐☐☐☐ 7

f) For how many months/years in total? [ ][ ] mnths ☐☐ 9
[ ][ ] yrs ☐☐ 11

g) Did you stay/work within.....(tick one)

0,5 km [1]
1 km [2]
5 km [3]
more than 5 km [4] of the mill? ☐ 12

3.6 Did you ever spend time <u>near</u> a **mine or mine dump** ?
eg. stay or work or for some other reason

Yes [1]
No [2]
Unsure [3] ☐ 13

--- if yes/unsure ---

a) Explain briefly how you spent your time .....

..... ☐☐ 15

b) What was the name of the mine/minedump?

..... ☐☐ 17

c) What kind of mine produced the dump?

..... ☐☐ 19

d) What was the name of the (nearest) town\township?

..... ☐☐ 21

e) During what years? 19___-19___ 19___-19___ ☐☐☐-☐☐ 25

19___-19___ 19___-19___ ☐☐☐-☐☐ 29

19___-19___ 19___-19___ ☐☐☐-☐☐ 33

☐☐☐-☐☐ 37

☐☐☐-☐☐ 41

☐☐☐-☐☐ 45

f) For how many months/years in total? [ ][ ] mnths ☐☐ 47
[ ][ ] yrs ☐☐ 49

g) Did you stay/work within.....(tick one)

0,5 km [1]
1 km [2]
5 km [3]
more than 5 km [4] of the mine/minedump? ☐ 50

3.7 Did you ever spend time <u>within 500m</u> of a railway station?
eg. stay or work or for some other reason

Yes [1]
No [2]
Unsure [3] ☐ 51

--- if yes/unsure ---

a) Explain briefly how you spent your time .....

..... ☐☐ 53

b) What was the name of the railway station?

..... ☐☐ 55

c) What was the name of the (nearest) town\township?

..... ☐☐ 57

d) During what years? 19___-19___ 19___-19___ ☐☐-☐☐ 61
19___-19___ 19___-19___ ☐☐-☐☐ 65
☐☐-☐☐ 69

Card 8 ☐☐ 2
Pat ☐☐☐☐☐ 7

19___-19___ 19___-19___ ☐☐-☐☐ 11
☐☐-☐☐ 15
☐☐-☐☐ 19

e) For how many months/years in total? [ ][ ] mnths ☐☐ 21
[ ][ ] yrs ☐☐ 23

4. <u>HOME LIFE</u>

The next few questions concern your family.

4.1 What were your mother's occupations when you lived with her?

a) ..... b) ..... ☐☐ 25
☐☐ 27

c) ..... d) ..... ☐☐ 29
☐☐ 31

4.2 What were your father's occupations when you lived with him ?

a) ..... b) ..... ☐☐ 33
☐☐ 35

c) ..... d) ..... ☐☐ 37
☐☐ 39

The next 2 questions are to find out whether you were ever exposed to dust or fibres at home.

4.3 Did you ever stay with a person who brought dust or fibre into the house on his/her clothes? (from work or a hobby or leisure-time activity)

yes [1]
no [2]
unsure [3] ☐ 40

---- if yes/unsure ----

a) Who was the person? ..... ☐☐ 42

b) For how many months/years in total did you live with this person? [ ][ ]mnths ☐☐ 44
[ ][ ]yrs ☐☐ 46

c) During what years did you live with this person when s/he was bringing dust/fibres into the the house ?

19___ -19___ ☐☐-☐☐ 50
19___ -19___ ☐☐-☐☐ 54
19___ -19___ ☐☐-☐☐ 58

d) What was the nature of the dust/ fibre ?

.....

..... ☐☐ 60

Card 9 ☐☐ 2
Pat ☐☐☐☐☐ 7

(COMPLETE BELOW IF MORE THAN ONE PERSON)

---- if yes/unsure ----

a) Who was the person? ..... ☐☐ 9

b) For how many months/years in total did you live with this person? [ ][ ]mnths ☐☐ 11
[ ][ ]yrs ☐☐ 13

c) During what years did you live with this person when s/he was bringing dust/fibres into the the house ?

19___ -19___ ☐☐-☐☐ 17
19___ -19___ ☐☐-☐☐ 21
19___ -19___ ☐☐-☐☐ 25

d) What was the nature of the dust/ fibre ?

.....

..... ☐☐ 27

4.4 Were you ever exposed to dust or fibres in a hobby or leisure-time activity?

yes [1]
no [2]
unsure [3] ☐ 28

---- if yes/unsure ----

a) What was your hobby or activity?

..... ☐☐ 30

b) What was the dust or fibre ? .....

..... ☐☐ 32

c) How often did you do this? (approximately)

more than once/ week [1]
about once/ week [2]
about once or twice/month [3]
less than once/month [4] ☐ 33

d) During what years were you exposed?

19___-19___ ☐☐☐-☐☐ 37
19___-19___ ☐☐☐-☐☐ 41
19___-19___ ☐☐☐-☐☐ 45

e) For how many months/years in total were you exposed to dust or fibre ?

[ ][ ] mnths ☐☐ 47
[ ][ ] yrs ☐☐ 49

(COMPLETE BELOW IF MORE THAN ONE HOBBY)

---- if yes/unsure ----

a) What was your hobby or activity?

..... ☐☐ 51

b) What was the dust or fibre ? .....

..... ☐☐ 53

c) How often did you do this? (approximately)

more than once/ week [1]
about once/ week [2]
about once or twice/month [3]
less than once/month [4] ☐ 54

d) During what years were you exposed?

19___-19___ ☐☐☐-☐☐ 58
19___-19___ ☐☐☐-☐☐ 62
19___-19___ ☐☐☐-☐☐ 66

e) For how many months/years in total were you exposed to dust or fibre ?

[ ][ ] mnths ☐☐ 68
[ ][ ] yrs ☐☐ 70

5. OCCUPATIONAL EXPOSURE

The following questions are about all the jobs you have done during your life. Please start with your first job and finish with your last. We need information about the type of work you did, how long you worked at that job, and whether you were exposed to dust while doing it.

5.1 JOB TITLE	EMPLOYER	WORK DONE (Brief description of work and workplace)	DATE STARTED - DATE ENDED	YEARS WORKED OR MONTHS	WERE YOU EXPOSED TO ASBESTOS		
					YES	NO	UN-SURE
1	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
2	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
3	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
4	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
5	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
6	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
7	.....	....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]

(SEE NEXT PAGE FOR MORE OCCUPATIONS)

	JOB TITLE	EMPLOYER	WORK DONE (Brief description of work and workplace)	DATE STARTED - DATE ENDED	YEARS WORKED OR MONTHS	WERE YOU EXPOSED TO ASBESTOS		
						YES	NO	UN-SURE
8	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
9	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
10	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
11	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
12	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
13	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]
14	.....	.....	.....	19__ - 19__	[ ][ ]m [ ][ ]y	[1]	[2]	[3]

if yes/unsure to exposure to asbestos in any of the jobs mentioned
put the correct job number into a highlighted block

	[ ]	[ ]	[ ]	[ ]	[ ]
a) In this job, over which years were you exposed to asbestos?	19__ - 19__ 19__ - 19__ 19__ - 19__	19__ - 19__ 19__ - 19__ 19__ - 19__	19__ - 19__ 19__ - 19__ 19__ - 19__	19__ - 19__ 19__ - 19__ 19__ - 19	19__ - 19__ 19__ - 19__ 19__ - 19__
b) For how many years/ months in total were you exposed?	[ ][ ]mnths [ ][ ]yrs	[ ][ ]mnths [ ][ ]yrs	[ ][ ]mnths [ ][ ]yrs	[ ][ ]mnths [ ][ ]yrs	[ ][ ] mnths [ ][ ]yrs
c) How often were you exposed?					
every day = 1	[1]	[1]	[1]	[1]	[1]
most days/week = 2	[2]	[2]	[2]	[2]	[2]
once or twice/week = 3	[3]	[3]	[3]	[3]	[3]
less than once/week = 4	[4]	[4]	[4]	[4]	[4]
d) Please tell me how you were exposed to the asbestos					

I am now going to list some jobs in which you might have been involved. If yc have, please tell me when you worked at these jobs and for how many years in total.

Card 17 [ ][ ] 2
Pat [ ][ ][ ][ ] 7

5.2 Have you ever been involved in any of the following ?

JOB	Y	N	U	MONTHS/ YEARS	
A Insulation work	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	9 12
B Working with furnaces	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	14 17
C Manufacturing asbestos cement products	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	19 22
D Working with boilers	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	24 27
E Wearing heat protective clothing	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	29 32
F Selling asbestos	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	34 37
G Construction site work	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	39 42
H Demolishing buildings	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	44 47
I Working in a factory using asbestos	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	49 52
J Working for the navy/ merchant navy	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	54 57
K Repairing/servicing motor vehicles more than once a month	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	59 62
L Helping manufacture asbestos-containing articles	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	64 67
				Card 18 Pat [ ][ ][ ][ ]	2 7
M Working in a power station	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	9 12
N Working with the manufacture of batteries	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	14 17
O Working in the plastic industry	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	19 22
P Using asbestos rope or asbestos gaskets	[1]	[2]	[3]	[ ][ ]m [ ][ ]y	24 27

Q Working in the rubber industry	[1] [2] [3]	[ ][ ]m [ ][ ]y	29 32
R Manufacturing brake linings or clutch plates	[1] [2] [3]	[ ][ ]m [ ][ ]y	34 37
S Transporting asbestos	[1] [2] [3]	[ ][ ]m [ ][ ]y	39 42
T Working for a railway company	[1] [2] [3]	[ ][ ]m [ ][ ]y	44 47
U Insulation of hot water pipes	[1] [2] [3]	[ ][ ]m [ ][ ]y	49 52
V Working with steam locomotives (train engines)	[1] [2] [3]	[ ][ ]m [ ][ ]y	54 57
W Working with sugar-cane	[1] [2] [3]	[ ][ ]m [ ][ ]y	59 62

5.3 Did you ever work as a .....

Card 19 2
Pat 7

JOB	Y N U	MONTHS/ YEARS	
A Boiler maker	[1] [2] [3]	[ ][ ]m [ ][ ]y	9 12
B Fitter and\or turner	[1] [2] [3]	[ ][ ]m [ ][ ]y	14 17
C Stevedore	[1] [2] [3]	[ ][ ]m [ ][ ]y	19 22
D Marine/civil engineer	[1] [2] [3]	[ ][ ]m [ ][ ]y	24 27
E Plumber/plumber's assistant	[1] [2] [3]	[ ][ ]m [ ][ ]y	29 32
F Welder/welder's assistant	[1] [2] [3]	[ ][ ]m [ ][ ]y	34 37
G Building carpenter/ building carpenter's assistant	[1] [2] [3]	[ ][ ]m [ ][ ]y	39 42
H Electrician/electrician's assistant	[1] [2] [3]	[ ][ ]m [ ][ ]y	44 47
I Paint manufacturer	[1] [2] [3]	[ ][ ]m [ ][ ]y	49 52

If the answer is YES/UNSURE to any of the options in question 5.2 or 5.3, please go back to question 5.1 and check that the occupation has been included in one of the jobs listed there.

5.4 Did you ever work with .....?

a) Fibreglass — yes [1] / no [2] / unsure [3] — ☐ 53

if yes/unsure

i) In which year did you first work with the fibreglass? 19___ — ☐☐ 55

ii) For how many months/ years did you work with the fibreglass? [ ][ ]m or [ ][ ]y — ☐☐ 57 / ☐☐ 59

iii) Did you work in a fibreglass factory while the fibreglass was being made? yes [1] / no [2] — ☐ 60

b) Other manufactured mineral fibres? (MMF) eg.ceramic fibres. yes [1] / no [2] / unsure [3] — ☐ 61

if yes/unsure

i) Which MMF did you work with ? — ☐☐ 63

.....

ii) In which year did you first work with the MMF? 19___ — ☐☐ 65

iii) For how many months/years did you work with the MMF? [ ][ ]m or [ ][ ]y — ☐☐ 67 / ☐☐ 69

iv) Did you work in a MMF factory while the fibres were being made ? yes [1] / no [2] / unsure [3] — ☐ 70

Card 20 ☐☐ 2
Pat ☐☐ 7

c) X Rays? yes [1] / no [2] / unsure [3] — ☐ 8

if yes/unsure

i) In which year did you first work with the x-rays? 19___ — ☐☐ 10

ii) For how many months /years did you work with the x-rays? [ ][ ]m or [ ][ ]y — ☐☐ 12 / ☐☐ 14

Did you ever work with .....?

d) Radioactive material ? yes [1] / no [2] / unsure [3] ☐ 15

if yes/unsure

i) What was the radioactive material ?

..... ☐☐ 17

ii) In which year did you first work with it? 19___ ☐☐ 19

iii) For how many months/ years did you work with the radioactive material? [ ][ ]m or [ ][ ]y ☐☐ 21 / ☐☐ 23

e) Beryllium? yes [1] / no [2] / unsure [3] ☐ 24

if yes/unsure

i) In which year did you first work with the beryllium 19___ ☐☐ 26

ii) For how many months/ years did you work with the beryllium [ ][ ]m or [ ][ ]y ☐☐ 28 / ☐☐ 30

f) Nickel? yes [1] / no [2] / unsure [3] ☐ 31

if yes/unsure

i) In which year did you first work with the nickel? 19___ ☐☐ 33

ii) For how many months/ years did you work with nickel? [ ][ ]m or [ ][ ]y ☐☐ 35 / ☐☐ 37

5.5 Were you ever treated with radiotherapy? (ie. X-ray treatment) yes[1] / no [2] / unsure [3] ☐ 38

if yes/unsure

i) What were you treated with ?

..... ☐ 39

ii) When were you treated ? 19___-19___ ☐☐-☐☐ 43

iii) For how long were you treated? [ ][ ]m or [ ][ ]y ☐☐-☐☐ 47

6. I am now going to ask you some questions about the food you usually ate before you were admitted to hospital.

6.1 Over the past 5 years how often, on average, did you eat vegetables (this does not include rice or potatoes)

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐48

6.2 Over the past 5 years how often, on average, did you eat home grown vegetables (that is, vegetables grown by yourself, a friend or a neighbour).

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐49

6.3 Over the past 5 years how often, on average, did you eat any of the following groups of vegetables ?

-A.
- Broccoli
- Brussels sprouts
- Cabbage
- Turnip
- Radish
- Cauliflower
- Kale (Kail)
- Other cabbages (eg. red cabbage, pickled cabbage)

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐50

6.4 Over the past 5 years how often, on average, did you eat any of the following groups of fruit?

-B.
- Apricot
- Mango
- Paw-paw
- Sweet melon (yellow)
- Dried peaches or apricots
- Raisins
- Loquots

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐51

6.5 Over the past 5 years how often, on average, did you eat any of the following groups of vegetables?

-C.

Carrots (cooked, raw or with other vegetables)
Pumpkin
Yellow squash
Spinach
Sweet potato
Imifino (wild greens)
Marog (wild greens)

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐52

6.6 Over the past 5 years how often, on average, did you take vitamin tablets?

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐53

6.7 Over the past 5 years how often, on average, did you eat any of the following groups of vegetables?

Lettuce
Tomato
Leavy green salads
Other green vegetables (not mentioned above)

(TICK THE CORRECT BLOCK)

NEVER	FEW TIMES A YEAR	ABOUT MONTHLY	ONCE A WEEK	FEW TIMES A WEEK	DAILY	FEW TIMES A DAY
1	2	3	4	5	6	7

☐54

7. OTHER ASBESTOS EXPOSURE

7.1 Did you ever live or work near ?

	Y	N	U	
a) an asbestos using factory ?	[1]	[2]	[3]	☐ 55
b) a store of asbestos?	[1]	[2]	[3]	☐ 56

if yes/unsure

a) What kind of factory was it? ☐☐ 58

.....

b) What type of asbestos store was it? ☐☐ 60

.....

c) What was the name of the :

factory ? ..... ☐☐ 62

.....

store of asbestos? ..... ☐☐ 64

.....

d) During what years did you stay or work near the

Card 21 ☐☐ 2
Pat ☐☐☐☐☐ 7

Factory ? 19___ -19___ 19___ -19___ ☐☐-☐☐ 11
19___ -19___ ☐☐-☐☐ 15

Store ? 19___ -19___ 19___ -19___ ☐☐-☐☐ 19
19___ -19___ ☐☐-☐☐ 23
☐☐-☐☐ 27
☐☐-☐☐ 31

e) For how many months/years in total did you live?

near this factory [ ][ ]m ☐☐ 33
[ ][ ]y ☐☐ 35

store of asbestos [ ][ ]m ☐☐ 37
[ ][ ]y ☐☐ 39

f) Did you live or work within

of the factory ?		of the store ?	
0,5 km	[1]	0,5 km	[1]
1 km	[2]	1 km	[2]
5 km	[3]	5 km	[3]
more than 5 km	[4]	more than 5 km	[4]

☐ 40
☐ 41

7.2 Have you had any exposure to asbestos you have not already told me about ? (eg. did you work or live or play in a building with an asbestos ceiling or some other asbestos)

yes [1]
no [2]
unsure [3] ☐ 42

if yes/unsure

How were you exposed ? .....

..... ☐☐ 44

7.3 Have you had any exposure to any other dust, fibre or substance (at work, home or in the environment) that you think is important and that you have not already told us about ?

yes [1]
no [2]
unsure [3] ☐ 45

if yes/unsure

a) What was the name of the dust, fibre or substance?

..... ☐☐ 47

b) How were you exposed ? .....

..... ☐☐ 49

8. Have you ever been questioned about exposure to dust or fibres at work or in the home before?

yes [1]
no [2]
unsure [3] ☐ 50

if yes/unsure

a) Who asked the questions? ..... ☐☐ 52

.....

b) When did they ask the questions? 19___ ☐☐ 54
19___ ☐☐ 56

9. TOBACCO SMOKING

9.1. Do you smoke ? yes [1] / no [2] ☐ 57

If **yes**, go to question 9.7
If **no**, carry on here

9.2 Have you ever smoked as much as one cigarette per day for a year ? yes [1] / no [2] ☐ 58

If **no**, go to question 10
If **yes**, carry on here

Ex-smokers

9.3 What did you smoke? commercial cigarettes [1]
hand-rolled cigarettes [2]
pipe [3] ☐ 59

9.4 How old were you when you started smoking?
[ ][ ] yrs ☐☐ 61

9.5 How old were you when you stopped smoking?
[ ][ ] yrs ☐☐ 63

9.6 In the past, on average, how much did you smoke per day?
number of commercial cigarettes [ ][ ] ☐☐ 65
number of hand-rolled cigarettes [ ][ ] ☐☐ 67
grams of pipe tobacco [ ][ ][ ] ☐☐☐ 70

Go to question 10 now

Card 22 ☐ 2
Pat ☐☐☐☐☐ 7

Present smokers

9.7 What do you smoke? commercial cigarettes [1]
hand-rolled cigarettes [2]
pipe [3] ☐ 8

9.8 How old were you when you started smoking?
[ ][ ] yrs ☐☐ 10

9.9 How much do you smoke per day at present?
number of commercial cigarettes [ ][ ] ☐☐ 12
number of hand-rolled cigarettes [ ][ ] ☐☐ 14
grams of pipe tobacco [ ][ ][ ] ☐☐☐ 17

9.10 In the past, on average, how much did you smoke per day?
number of commercial cigarettes [ ][ ] ☐☐ 19
number of hand-rolled cigarettes [ ][ ] ☐☐ 21
grams of pipe tobacco [ ][ ][ ] ☐☐☐ 24

WE HAVE FINISHED NOW, THANK YOU FOR TAKING PART IN THIS INTERVIEW !

10. GENERAL

The following questions are to be completed by the interviewer only.

10.1 Co-operation of subject? (tick one)
good [1]
fair [2]
poor [3] ☐ 25

10.2 Additional comments (if no sputum obtained please explain)

.....

.....

.....

.....

.....

10.3 Language of interview ..... ☐☐ 27

10.4 Home language of interviewer ..... ☐☐ 29

Remember to tell the person these 2 things when you have finished the interview.

Tick each square provided when you have completed that task.

1. I am leaving this letter and this stamped, addressed envelope with you. If you remember anything that you have not told me, please write it on the bottom of the letter and ask someone to post it for you. [ ]

2. Here are 2 containers for sputum specimens. We want you to cough the phlegm from your chest into these containers. Please give me one specimen now and then one tomorrow. (We need all the sputum that you produce over the whole day, if possible). Then ask the sister to put it in this stamped, addressed envelope and send it to us. We want you to post the container in the envelope to us even if you did not have any sputum. (I have spoken to the sister and physiotherapist and asked them to help you) [ ]

3. Have you remembered to label the sputum containers. [ ]

APPENDIX 2.4: ASBESTOS EXPOSURE VARIABLES

Classes

Definite	As presented in Table 2.2.
Probable	"
Possible	"
Unlikely	"
Definite-remote	As presented in Table 2.2
Probable-remote	but 10 years or more since first exposure -
Possible-remote	classified unlikely if more recent
Unlikely-remote	exposure.

Nature

Occupational

Direct	Direct exposure at work reported.
Indirect	Co-workers used asbestos.
High risk	5.2 A,C,F,L,M,P,R,S,U or V Appendix 2.3.
Risk	5.2 All others or 5.3 except sugar-cane Appendix 2.3.
Uncertain	Subject reported uncertain exposure at work.

Environmental

Mining	Spent time in any district shown in Table 2.1 except OTHER district.
Other	Lived within 1 km of an asbestos using factory, dockyard or store of asbestos.
OTHER	The fourth set of districts in Table 2.1.

Domestic

Clothes	Exposed to contaminated workclothes.
Use	Used asbetos or products at home.

Incidental — Used asbestos cement heating panels or garden furniture or lived/worked in an asbestos cement structure.

Crocidolite — Spent time in NW Cape mining districts or occupational contact with large diameter asbestos cement pipes or battery cases or reported direct contact with crocidolite.

APPENDIX 2.5: Variables used in analysis of diet and mesothelioma

As reported by patient	Questionnaire section number	
1. Allvegetables	6.1	Frequency score 1 to 7 based on questionnaire data.
2. Homegrown	6.2	Frequency score 1 to 7 based on questionnaire data.
3. Cruciferous	6.3	Frequency score 1 to 7 based on questionnaire data.
4. Carotene-fruit	6.4	Frequency score 1 to 7 based on questionnaire data.
5. Carotene-vegetables	6.5	Frequency score 1 to 7 based on questionnaire data.
6. Tablets	6.6	Frequency score 1 to 7 based on questionnaire data.
7. Salads	6.7	Frequency score 1 to 7 based on questionnaire data.

Derived	Calculation
1. Carotsum	6.4 + 6.5
2. Allsum	6.3 + 6.4 + 6.5 + 6.7

Factored	Method
1. Method 1[a]	Base level once per week or less; high ≥ once per week.
2. Method 2[a]	Base level < once per week; medium = once per week; high > once per week.
3. Carotene-group	Carotsum divided into three approximately equal groups: base level, medium and high.
4. All-group	Allsum divided into three approximately equal groups: base level, medium and high.

[a]Allvegetables, homegrown, cruciferous, carotene-fruit, carotene-vegetables and salads factored according to both method 1 and 2.

GW 1/6.2.8

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Appendix 2.6 : The consent form

Reference:

Inquiries:

I have been informed that the NCOH is conducting a study into the relationship between various substances and illness. The purpose of the study is to establish whether diet or exposure to various dusts, fibres and other substances in the environment, in the home, as part of a hobby or at work, are associated with one or a number of illnesses.

I understand that I have been scientifically selected from the in-patients of this hospital to be interviewed for this study.

I fully agree to take part in this study understanding that it involves :

1. being interviewed for + 1 hour concerning information about the environmental and occupational history of myself and my family members

2. having my medical and laboratory records reviewed

3. providing sputum specimens for the conductors of the study.

I understand that my participation is entirely voluntary and that I may refuse to answer any questions if I choose, or may withdraw my consent to participate at any time without penalty or without in any way affecting the health care I receive. I understand there are no special risks involved in being a participant, and that, even though I may not benefit individually, it is expected that other people will benefit from the knowledge gained from the study.

I understand that the information collected about me will be treated in a confidential manner and that I will not be personally identified in the reporting of the results. My answers will be combined with the others interviewed to make totals.

I understand that I may ask any questions I have about the study now. If I have further questions about this study, I may contact

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Participant's signature and date Investigator's signature