THE MINE AT BARYULGIL: WORK, KNOWLEDGE, AND ASBESTOS DISEASE

McCulloch, Jock, The Mine at Baryulgil: Work, Knowledge, and Asbestos Disease. Labour History 92 (2007): 47 pars. 20 May 2012 <http://www.historycooperative.org/journals/lab/92/mcculloch.html>

JOCK MCCULLOCH

In the period from 1945 until the mid-1970s Australia was a major consumer of asbestos products. Today Australia has one of the world's highest rates of asbestos disease. Local manufacture was dominated by James Hardie Industries which also operated a small chrysotile or white asbestos mine at Baryulgil in northern New South Wales. James Hardie has always claimed that the working and living conditions of its Aboriginal employees were good. However, internal company correspondence and the testimony of miners suggest otherwise. Hardie's refusal to protect its workers from a known risk contributed to a high level of occupational morbidity and mortality, as did ineffective state regulations, the non-union nature of the Baryulgil workplace and the community's isolation.

Throughout the twentieth century the Australian asbestos industry was dominated by a single firm: James Hardie Asbestos Pty Ltd. The company, which was founded at the end of the nineteenth century, was one of the first to realize the potential of asbestos cement products. In 1916 it opened the Camellia factory near Sydney to produce building materials. Over the next decade further plants were opened in Perth, Adelaide and Melbourne. Sheltered by tariff barriers and aided by government contracts, James Hardie soon developed into one of the country's most successful businesses. In New South Wales (NSW), Hardie supplied asbestos cement products to the Housing Commission, the Metropolitan Water, Sewage and Draining Boards and numerous Shire councils. Between 1945 and 1954 more than half of the new homes built in NSW were made from Hardie's asbestos cement sheets. Largely because of the company's success in manufacture and marketing, in the three decades after 1945 Australia was the highest per-capita user of asbestos in the world. As a result, Australia now has the world's highest recorded incidence of mesothelioma, the most deadly of the asbestos diseases.

One of the less well known aspects of James Hardie's history concerns a small mine at Baryulgil in northern NSW. The mine, which employed an Aboriginal workforce, was operated by the company from 1953 until 1976. The work and living conditions at Baryulgil were in some ways just as harsh as those endured by black miners in South Africa under apartheid. As a result, the history of Baryulgil can serve as a window onto one of the most lamentable stories of occupational risk in an Australia workplace during the post-war period.

THE INDUSTRY AND THE FIRM

The global asbestos industry was vertically integrated. From the beginning of the twentieth century the larger US and British manufacturers of asbestos-based products, such as Johns-Manville and Turner & Newall, operated mines in Canada and Southern Africa to provide fibre for their metropolitan factories.[3] The industry's peak in Western Europe and North America coincided with what some economists6 have called the 'golden age of capital' (1945–72) and, in that sense, asbestos is an exemplar of modern industrial production and its attendant global divisions of labour. Unfortunately, asbestos causes three life-threatening diseases, namely asbestosis, lung cancer and mesothelioma, a primary cancer of the lining of the lung or the abdominal cavity.[4] Recent estimates put the eventual number of fatalities world-wide from the three diseases at in excess of five million.[5]

James Hardie differed from Johns-Manville and Turner & Newall in that it bought most of its fibre from outside sources.[7] However, from 1955 it did have a share in the chrysotile or white asbestos mine at Cassiar in British Columbia[8] as well as operating the mine at Baryulgil. In contrast to Cassiar, Baryulgil was small. There was never more than 40 in the workforce.[9] The fibre yield was poor and at its peak Baryulgil produced only 400 tones of chrysotile a year, or less than one per cent of James Hardie's needs.[10] Rarely did the mine make a profit.[11] Despite its lack of size, Baryulgil had strategic importance: the mine gave James Hardie a seat on the inquiries run by the Tariff Board which controlled duties on imported asbestos. It also provided a back up in case of a disruption of supplies from overseas.

Until 1970 Baryulgil was the only asbestos mine in eastern Australia and it was staffed by Aboriginal workers living on traditional land. In the late 1970s there was an exposé by the ABC journalist Matt Peacock of the harsh work conditions at the mine.[12] During 1983–84, through the efforts of the community supported by the Aboriginal Legal Service in Redfern, Baryulgil was the subject of a Parliamentary inquiry. It remains the only inquiry of its kind into asbestos mining.[13] During that 1983–84 Inquiry, James Hardie presented a picture of a safe work environment. The company claimed to have made every effort to reduce work hazards at Baryulgil, and even adopted dust thresholds far in advance of the recommended standards.[14] Safety equipment, including respirators, was made available and workers were instructed in its use.[15] According to the company, the plant was well maintained and any problems were the result of breakdown or operator neglect. James Hardie was adamant then (and remains so today) that there has never been a case of asbestos disease at Baryulgil.

The 1983–84 Inquiry followed a tide of litigation that had begun in the US in mid-1970s. A flood of law suits saw the major producers, including Johns-Manville and Raybestos-Manhattan, take refuge in bankruptcy and subsequently reinvent themselves as non-asbestos companies. To protect itself, in 1976 James Hardie sold Baryulgil, and gradually phased out asbestos from its domestic products. Like Johns-Manville, it managed a successful transition and by the 1990s its subsidiary, Amaca Pty Ltd, had become a market leader in the US building materials industry. But it was not so easy for James Hardie to escape its past. On average, James Hardie consumed 70 per cent of the fibre used annually in Australia.[16] Recent estimates put the liability for asbestos disease in Australia at around $A6 billion, of which the major share is attributable to James Hardie.[17] In early 2001 Hardie's management shifted its headquarters to The Netherlands and transferred ownership of Amaca Pty Ltd to a second subsidiary, thereby creating a veil between the parent company and litigants. During that restructuring James Hardie assured the NSW Supreme Court that it would, if necessary, make available up to $A1.85 billion to cover its liabilities. In fact the company left only $A293 million in its Medical Research and Compensation Foundation for future claims.20 James Hardie also failed to inform the NSW or Federal governments about the shortfall. As major users of asbestos insulation in trains, power stations and ships, those governments also face a massive future liability.

As the result of protests by trade unions and victims groups, in March 2004 the NSW government established a Commission of Inquiry into James Hardie's conduct. In his final report the commissioner, David Jackson, found that Hardie's chief executive had mislead the stock exchange about the company's asbestos liabilities being 'fully funded'. Jackson also found evidence that Hardie's management had engaged in deceptive conduct which might justify civil or criminal proceedings. Following Jackson's report, the company entered into negotiations with trade unions and the Asbestos Diseases Society. As a pre-condition for a settlement, James Hardie's new chair, Meredith Hellicar, asked the NSW premier, Bob Carr, to guarantee immunity for herself and other senior executives from criminal prosecution. Carr left office before an agreement was negotiated and it remains to be seen whether criminal charges will be laid. During negotiations, James Hardie argued that while it was the joint or sole owner of the Baryulgil mine, the operating company, Asbestos Mines Pty Ltd, was never under its control and that it would therefore not include the Baryulgil community within the terms of a settlement. The history of the mine and, in particular, the working and living conditions endured by the Aboriginal workforce reveal why James Hardie has never been comfortable in talking about Baryulgil.

THE BARYULGIL MINE

The Banjalang of Baryulgil first came into contact with Europeans in 1840 when Edward Ogilvie established a pastoral empire along the banks of the Clarence River. Ogilvie, who employed Aboriginals on his station, which he named Yulgibar, learned the Banjalang language and is credited with producing its first written grammar.24 At its height Ogilvie's empire employed well over 100 Aboriginals as stockmen and domestic servants. For the Bundjalang, work at Yulbilgar meant that the community could continue to live on traditional land without being subject to the authority of a white reserve manager. However, Ogilvie's empire barely survived his death and the property was gradually reduced in size. By the first decade of the twentieth century Yulgilbar was a run of less than 50,000 acres. With the decline of Yulgilbar, young men began leaving the district in search of work and by 1943 the official population of The Baryulgil Square was fifty-three.

In 1918 chrysotile was discovered less than a mile south-west of The Square and a small quarry was opened. Between 1918 and 1924 it produced 2,500 tones of fibre. In 1940 Wunderlich Ltd began re-developing the site. In 1943 a mill was installed and with it came further improvements in output. In the following year James Hardie, which was anxious to secure a local source of fibre, entered into a partnership with Wunderlich and the Asbestos Mines Pty Ltd. was formed. In 1953 the James Hardie group purchased Wunderlich's share and from then until 1976 Asbestos Mines Pty Ltd was a wholly owned subsidiary. From 1976 until its closure three years later, the mine was owned by Woodsreef Mines Ltd.

Ken Gordon was 13 years old when he started work in 1946 as a 'billy boy' supplying the miners with tea and water. At 15 he went into the quarry to work on the skips. The mine had benches running down both sides of the pit. Drilling was done with jack hammers while explosives were used to dislodge rock from the workface. Following blasting the quarry filled with dust, and it was usual for the miners to re-enter the site before the dust had settled.31 Ore the size of kitchen tables was broken up by hand. The work was hard, with shoeless men using 14lb sledgehammers in summer temperatures of 40° celcius. The richer ore was placed in skips and drawn by horses to the mill.

At the mill the ore was emptied into a crusher, then processed before the fibre and dust were drawn off by exhaust fans. At the end of each day, the fibre was shovelled by hand into hessian bags. The bagged chrysotile was then trucked along the unsealed road to the railhead at Grafton, some 50 miles away. The mill itself was cramped and all the crushing and separation was carried out within a single building. One of the permanent hands would sweep dust from benches, floors and walls. The men employed in the bagging section, Andrew Donnelly, Harry Mundine, Benjamin Oba, Richard Mundine, Albert Priest and Joe Waghorn, all died prematurely.

The fibre was handled manually throughout milling, storage and transport. The hessian bags were porous and often split, thereby making haulage of the product hazardous. Many of the bags used at Baryulgil were re-cycled from the Camellia factory and often contained residues of asbestos. Bill Hindle, who worked as a fitter, recalled that the bags carried the initials EGNEP which referred to the Penge amosite or brown asbestos mine in South Africa. There were also bags from Wittenoom, which contained crocidolite or blue asbestos. Bill Hindle himself died from mesothelioma in December 1984.

The prospect of regular work attracted Aboriginal men from as far away as Brisbane and Cherbourg. The only other work available at that time was on cattle stations but station work is seasonal whereas the mine ran the whole year round. The mine also gave the men access to skilled industrial work. They operated jack hammers, and worked as mill hands, powder monkeys, and as drivers. They did repair work on the machinery and they laid the benches in the quarry. Aboriginal men built the new mill that was opened in 1958. Apart from the manager and the fitter, no European stayed for any length of time.

Baryulgil was a company town run by one of Australia's largest corporations, yet houses at The Square were built by the miners and their families. During the 1950s, a typical house consisted of one large room with a bed, a table and a lamp. The walls were fashioned from flattened kerosene tins and the floors were made from ants' nests which were crushed and wetted to form a rock hard surface. There was no electricity or running water, and no sewerage. The women would wash recycled asbestos bags and make them into floor coverings and bedspreads. Bags were also used to keep out the wind and rain. In the late 1950s families at The Square purchased second-hand cement sheets from Grafton and the housing was gradually improved. There was no medical care and for many years a local woman, Mrs Lucy Daley, acted as a midwife.

Water was a problem at Baryulgil as the creek would alternatively flood or run dry. Most washing was done at the creek, and the women would spend a whole day heating up water over an open fire. There were no cars until the early 1960s. The dirt road to Grafton was at times unpassable, thereby further isolating the community. The general store at The Square was run by Yulgilbar station and there was a mail delivery each week. Bush tucker was a major part of the diet. Men and women trapped echidnas, possums, goannas, and kangaroos. They also caught fish and turtles in the Clarence River.

Linda Walker was born at The Square in 1935. Her father was one of the first men to work on the mine. As a child Linda played in the mill and she recalls that the dust was so thick she couldn't see

more than a few feet.[47] The wages were low and life was hard. Linda's parents built their own house at The Square with timber from the bush. But the community had more freedom than did Aboriginals who lived on the nearby reserves of Mulli Mulli and Tabulum. Linda used to roam everywhere and in some ways she had an idyllic childhood. The people got on well with the graziers who let the children dive for turtles in the river. Linda left school at 14 to help her mother with housework. The major threat to families came from the NSW government policy of forcibly removing children. Mothers warned their children to hide in the bush whenever the Aboriginal Protection Board truck came.[48] Linda Walker's cousin, Pauline Gordon, was on the street in Grafton with her brothers when she was taken by the Board. The boys were sent to Kingela Boys Home, near Kempsey, and the girls were shipped 200 miles away to the Cootamundra Girls Home. Some parents never saw their children again.[49]

THE DUST

The methods of mining asbestos have varied over time and place – from quarries to deep shafts. However, the aim of processing fibre is always the same, namely to preserve the mineral's physical properties. For that reason asbestos is milled dry and the process creates dust. Asbestos mines in Southern Africa, Canada and Australia were always hazardous. Dr Peter Elmes, the consultant physician with Turner & Newall, lamented in 1987:

> By the nature of their operations mine and mine mill operators find it harder than the user industries to meet agreed international standards and consequently are at risk from the environmental lobbies.[50]

The most hazardous jobs at Thetford (Canada), Wittenoom (Western Australia), Penge (South Africa), Shabanie (Zimbabwe) and Baryulgil (NSW), were in the bagging rooms.[51]

The Baryulgil mill was always dusty. There was no mechanical ventilation in the Old Mill, which operated until 1958. As the former manager, Jerry Burke, told the 1983–94 Inquiry: 'When you walked in it was impossible to see anywhere. Even the operator standing beside you was practically invisible'.[52] An Aboriginal miner named Bill Harrington recalled that after each day's work: 'Your skin was still white. You would wash it off and you would go like that afterwards and you would be a black fella walking along with a big white streak'.[53] There were no showers and the men washed in the creek. According Bill Hindle, the New Mill was intended to produce better quality fibre. But when the mill opened production levels were increased so that many of the problems found in the original plant were reproduced. Little attention was paid to containing dusty areas or sealing off trouble spots.[54] Apart from the dust, the work was made difficult by the heat and noise. When Jerry Burke complained to head office he was told that because the mine had a short life, management was unwilling to spend the necessary $70–80,000 on a dust extraction system.[55] At no time did James Hardie issue a warning to the miners about the hazard. Jerry Burke first learned of the danger in 1974 by reading The New Yorker magazine.[56] Linda Walker's father had not heard the word 'asbestosis'. According to her, none of the miners had.[57]

The Square was less than a mile from the mill and the prevailing wind blew dust and fibre over the town, covering the gullies and the creek banks in white powder. According to Jerry Burke:

> The mill generated a lot of dust, you could see it in the sun of an afternoon the dust going out towards the north west This took it over my house and then over towards The Square and all towards Yulgilbar station area.

Rodney MacBeth, an organiser with the Australian Workers Union (AWU), who first visited the mine in 1974, remembers that the town was covered in a white shroud. 'The dust even on still days emanated from the treatment works and settled on everyone and everything in the vicinity.[58] MacBeth knew nothing about asbestos disease. When questioned at the 1983–84 Inquiry as to whether he worried about the dust MacBeth replied:

> Yes, to a certain extent, but when you approached the place on a still day there was always a haze about. To be quite candid the same thing applied to cement works.[59]

Everyone in the community was at risk. The miners returned home at the end of each day with their clothes covered in fibre. Before washing, the women used to beat the clothes on a tree.[60] There was also contamination from the mill waste. The district has a high rainfall and the ground tends to become soggy. To absorb the water, tailings were spread about The Square several times a year.56 Tailings were used around the houses to level the ground and encourage the growth of grass. The dump adjacent to the mine was a playground for the children, and tailings were used at the School as jump pits.[61] The waste was transported in the company truck, a practice that continued until 1977. A study conducted a year after the mine closed found heavy pollution at The Square. According to the report: 'There is no doubt that the residents of Baryulgil are currently being exposed to highly undesirable levels of asbestos dust'.[62]

James Hardie had a reputation at Baryulgil as a bad employer. There was no trade union presence until the late 1960s when most of the miners joined the AWU. Rodney MacBeth would occasionally visit the mine to secure enrolments and mediate disputes with management.[63] Wages at Baryulgil came under the Metalliferous Miners (Open Quarry) Award and although the quarry was over 100-feet deep, according to MacBeth the company never paid 'depth money'. Neil Walker, who worked as foreman, did not receive the above-award payment to which he was entitled.[64] Both Neil Walker and Cyril Mundine, who worked at the mine for many years, were sacked for taking long service leave.[65]

Warwick Sinclair, a former claims officer with the AWU, recalled a problem at the mine in 1962.[66] An AWU officer had come across an Aboriginal community living in harsh conditions. The miners were being underpaid and they were afraid to join the union. The AWU decided to take action on the miners' behalf even though they were not union members. Sinclair visited the James Hardie head office in Sydney and after some consultation the company sent the AWU a cheque for $300, which was back pay for 30 men for 12 months. Although the underpayment had been going on for far longer, it was not possible to seek compensation for more than a one-year period. Sinclair never forgot the heat, the dust and the 'indescribable poverty' he saw at Baryulgil.

During the 1983–84 Inquiry James Hardie emphasised its role as a good employer. Despite the mine's lack of profitability it persevered with Baryulgil in order to preserve jobs for the Aboriginal workforce.[67] There were in fact other reasons why the company kept the mine open. Because it operated Baryulgil, James Hardie was entitled to a seat on Tariff Board inquiries into the asbestos industry. That allowed the company to resist the imposition of duties on imported Canadian and South African fibre upon which its factories relied, while enjoying the protection of a 25 per cent tariff barrier on imported asbestos products.[68] In 1954 James

Hardie's major competitor, the Colonial Sugar Refinery (CSR) instigated a Tariff Board inquiry into asbestos imports. CSR was keen to find a local market for the fibre from its Wittenoom mine and it proposed a 40 per cent protective tariff on imported fibre. As the dominant local manufacturer, James Hardie was CSR's most likely customer, and it hoped to force Hardie to buy its crocidolite. James Hardie's managing director, John Adamson, told the inquiry that overheads were high and in the case of asbestos cement sheets raw materials amounted to 65 per cent of the costs of production.[ ] In 1954 James Hardie imported 26,000 tons of fibre costing £2.09 million. The imposition of the tariff demanded by CSR would have cost Hardie £693,000 a year.[ ] James Hardie won the case and continued to import cheap fibre from South Africa and Canada.

THE STATE

Various government departments, most notably the NSW Department of Mines, shared responsibility for Baryulgil. Until 1964 there was no asbestos legislation in NSW. As a result, Baryulgil fell under The Mines Inspection Act, 1902. That act required inspectors to notify owners of any hazard and specify the measures necessary for its remedy. The legislation refers to the provision of exhaust ventilation and respirators, the vacuum cleaning of workroom surfaces, the use of wet brushes in sweeping floors and benches, and the instruction of workers on occupational safety. There is also reference to showers, lockers and lunch rooms. The code allowed for the periodic testing of work areas and regular medical examinations.[ ] The NSW asbestos regulations of 1964 set a statutory limit for dust of five million parts per cubic foot. With the introduction of the membrane filter method in January 1973, the standard was changed from dust particles to fibre numbers and from that date the limit was set at four million fibres per millilitre. In March 1978 the standard was lowered to two million fibres per millilitre.[ ] Whatever the system of measurement, visible dust always signified a hazard.

In all, Department of Mines officers made some 90 visits to Baryulgil in the period from 1948 until 1979. While their reports contain ample evidence of a serious hazard, the mine was never closed and there were no protests from the Department about conditions. From 1970 the Division of Occupational Health within the NSW Department of Health, carried out dust and fibre counts at the request of the Mines Inspectorate. The final government authority to share responsibility for Baryulgil was the State Pollution Control Commission. The Commission, which was established in the early 1970s, played a passive role. For example, it issued the mine a licence in April 1977 without its officers ever having visited the mine.[ ]

James Hardie is a large company and there was a formal chain of command between head office and Asbestos Mines Pty Ltd. The local manager reported directly to the technical director and decisions about work conditions were made in Sydney. Day to day decisions were the responsibility of Frank Page who was a member of the boards of Asbestos Mines Pty Ltd and James Hardie. Page paid frequent visits to Baryulgil. Items involving capital expenditure were discussed at board level. Such decisions were also discussed with the Industrial Hygiene Section and the Environmental Control Committee.[ ] James Hardie had its own industrial hygiene unit at Camellia which monitored dust levels at the company's factories and issued directives to branch managers, including the manager at Baryulgil. From the late 1960s, samples of dust from the mine were sent to Camellia, where they were examined by the senior technical officers, Mr J. Winters and Dr S.F. McCullagh. The annual X-ray program initiated in that period was co-ordinated by Dr McCullagh. From the early 1970s there was close consultation between the company, the Mines Inspectorate, and the NSW Health Commission. By the company's own admission, it always led government authorities in the adoption and use of sampling techniques.[ ] In that sense James Hardie resembled its major British and US counterparts.

The Department of Mines always took a conciliatory attitude toward conditions at Baryulgil. Its annual report for 1946 refers to the mill, which was supposedly 'being redesigned and particular attention is to be paid to the suppression of dust'. It also mentions 'new dust trunking throughout the mill' and to 'new huts for mine workers that are in the course of construction'.[ ] No such work was ever carried out. Inspections conducted in 1948 and 1952 found high dust counts yet the Mines Inspectorate took no action.[ ] An inspection report from March 1960 refers to the bagging section as dirty and the inspector commented on the absence of respirators.[ ] Again, no action was taken. An inspection in August 1972 revealed a serious dust problem. The report noted: 'All areas except those outside the plant show fibre counts above the statutory 4 fibres per cubic centimetre'.[ ] No notice was issued. The same failure followed an inspection in October 1973 when an officer reported:

> The exhaust at the top of the mill continues to emit a constant stream of dust like a dry wood fire ... the use of hessian bags makes handling of the product a large source of dust.[ ]

The Department of Mines' failure to regulate Baryulgil is not difficult to explain. The mine was small and isolated and before the opening of Barraba in 1970 it was the only asbestos mine in NSW.[ ] Its workforce was Aboriginal and there was no trade union presence. The Department had little expertise in dealing with such a workplace and it was hampered by a lack of trained staff. The Mines Inspectorate also lacked political will. James Hardie was a powerful company with major government contracts. It is likely that the Department of Mines did not want conflict over such a small operation and so it placed its faith in James Hardie to remedy any hazard.

Whatever the Inspectorate's intentions, the regulatory process was corrupted. The mill was always slowed down and the area watered whenever inspectors were due.[ ] Robert Marshall, Chief Inspector of Mines, told the 1983-84 Inquiry that it was normal to forewarn the manager of impending visits in order to maintain good relations with Hardie: 'If we adopt the policy that nobody is to be notified, it is going to create a few hassles', he said.[ ] Dr Francis, from the Department of Health, recalled:

> In the test we did in 1972 when I was there it was obvious that the place had been washed down. The mill, for instance, was wet. The ground was wet. There was no secret made of it. It was quite obvious that it had been hosed down.[ ]

According to James Hardie, the clean ups were simply a matter of etiquette, or 'good housekeeping'. At a mine, just as in a suburban home, it is usual to clean up before the arrival of visitors.[ ]

DISEASE, DEATH AND DENIAL

In pursuing legal action against employers the victims of asbestos disease face various obstacles in proving the cause and extent of their disability.[ ] Asbestosis is a particularly insidious disease which is difficult to diagnose and whose symptoms are often masked by secondary infections such as bronchitis. The general poor health of the Baryulgil community has further obscured the extent of oc-

cupational disease. The health status of Aboriginal people in rural NSW was the subject of a report released during the 1983–84 Inquiry. It gives the life expectancy at birth for an Aboriginal male as 48.1 years, and between 55 and 57 years for a woman. Those figures mean that many miners would have died of other causes before asbestos disease became visible.

James Hardie has always maintained that miners were never exposed to a serious hazard, and that there has been no asbestos disease at Baryulgil. Any illness at The Square, it has claimed, is simply characteristic of Aboriginal communities. Yet the Baryulgil people were living on traditional land largely independent of outside interference, and there was employment. One would expect their health to be superior to that of other Aboriginal communities. Asbestosis is usually associated with at least ten years exposure, yet there is evidence of disease at the mine four years after it opened. An X-ray report on a miner named Preece in 1949 found fibrosis. In 1952 a radiology report on another miner, Harry Mundine, by Dr Pooks from Grafton Hospital, returned the same result. There have also been many premature deaths at Baryulgil. Cyril Mundine, who worked as a jackhammer operator from 1944 until 1966, died in 1969 at 46 years of age. Mundine had been certified with asbestosis by the Dust Diseases Board and at the time of his death he was receiving a disability pension. There was no autopsy and his death certificate gives heart disease as the cause of death. The same ambiguities are found in the case of Andrew Donnelly who died in June 1977. Initially the cause of death was given as lobar pneumonia. A post mortem by Dr K. Murray found asbestosis but cited accelerated hypertension and viral pneumonia as the cause of death. A second report, by Dr R.J. Grobius of the Grafton Base Hospital, gives asbestosis as the primary cause of death and refers specifically to gross disease.

There is plenty of anecdotal evidence of disease at The Square. Jerry Burke and his family lived close to the mill. Burke died from cancer as did both his sons. Linda Walker had seven brothers, six of whom worked on the mine. They did heavy labour but they all died in their 40s and early 50s. They got terribly thin and in Linda Walker's words 'they fell away to nothing'. Linda's sister, who lived at The Square, died at 46 in the same way. Neil Walker spent the last nine years of his life on a disability pension. Four months before his death Neil Walker was re-assessed by the Board at a time when, according to Linda, 'his lungs were gone'. The Board said he may or may not have asbestosis and he was assessed at 30 per cent disability. In the final months of his life he could not walk, he could not sleep and he could not breathe. He was 65 when he died. Among the miners only Cyril Mundine, Neil Walker and Ken Gordon received the dust pension. It is with some justification that the Dust Diseases Board in Sydney, which makes such decisions, is viewed by the Baryulgil people as hostile.

Baryulgil is a close knit community where people have a strong sense of belonging. They also have close connections with other Aboriginal communities in the region. Linda Walker has lost most of her family to the mine: her brothers, her father, her husband, her sister-in-law, and her sister. Those deaths have created a fracture between generations. The children have lost important adults in a community where oral traditions and continuity are paramount. In Linda Walker's words: 'Those deaths broke the children's hearts'.

Following Andrew Donnelly's death, a study of Baryulgil was carried out by the NSW Health Commission. Of the ex-miners in the cohort nearly half had worked for less than one year, while a further third had worked for a period of between one and three years. Most of the long-term employees were dead. The researchers discovered no major differences between the ex-miners and a control group in terms of lung function. However, an analysis of the 67 identified deaths among former miners revealed that 11 per cent were attributed to respiratory disease. The most significant findings were the chronic bronchitis among 70 per cent of former miners and the evidence of X-ray abnormalities including pleural thickening, fibrosis and pleural plaques, all markers of early asbestosis.

Further research conducted in 1981 and 1982 by the Department of Health illustrates the problems in studying subjects drawn from a population suffering from such poor general health. The 1983–84 Inquiry noted that the largely negative findings in the surveys must be viewed in context. Asbestos disease does not manifest readily in such a small population and is rendered even less visible against the backdrop of the appalling health typical of Aboriginal communities. The Banjalang's ethical and religious opposition to autopsies have been a further barrier to knowledge as has the pattern of migrant labour. There was a high turnover at the mine and over a 30-year period hundreds of men worked at Baryulgil. According to Linda Walker many of them died young but because they moved away from The Square asbestos was never recognised as a cause of death.

Over the past two decades, legal discovery in British and US courts has revealed that companies like Johns-Manville and Turner & Newall knew far more about asbestosis and mesothelioma than did regulatory authorities. They knew which parts of the production process were most hazardous, and they had access to employees' medical records, however imperfect these records were. They also commissioned medical research. Unlike the US corporations, James Hardie has mostly settled claims out of court, thereby avoiding a spill of documents into the public domain. There have been two exceptions: there are the documents (the Hardie Papers) tended at the Baryulgil Inquiry in 1983 by the former mine manager Jerry Burke, and there is a cache of in-house correspondence which was tabled during the case of Fred Swift which came before the Dust Diseases Board in Sydney in 1991.

The Hardie Papers consist of correspondence between the mine manager and head office in Sydney covering the period from 1960 to 1974. Those papers show a persistent hazard at the mill, no improvement in conditions over time, and no commitment by management to occupational safety. In February 1960 E.G. Reeve from the Sydney office visited Baryulgil. Reeve was disturbed by the practice of spilling fibre onto the mill floor before it was bagged. He made various suggestions on containing the dust, including enclosure and the introduction of exhaust fans. During his visit Reeve took photographs in the mill but as he explained in a memo to head office: 'The photographic processor did not print the sock cleaning operation presumably regarding it as blank film, which it most certainly is not.' The dust in the mill was so dense it rendered the image invisible. A mine manager's report from April 1969 noted the poor work conditions. In a summary of the dust readings the author comments: 'The only place (within the mill) which is approaching the tolerable limit is the bagging area, which is 213 mpcc'. Much the same conditions are described in a survey carried out between 14 and 17 September 1970. Mr J. Winters, the company's Industrial Hygiene Engineer, noted that the readings at several stations were 'alarmingly high'.

The company's senior medical officer, Dr McCullagh, frequently questioned the reliability of dust counts taken by the Health Department. In one memo Dr McCullagh mentions a survey carried out by Department officers in 1969 which showed only one site above the statutory limit. He noted that the company's own readings taken at that time found only two out of the nine stations satisfactory. The same disregard for Mines Inspectorate data occurs in a report from February 1974. On that occasion, Dr McCullagh remarked: 'The asbestos in the air levels recorded by the Inspector are lower than may correctly be found at the Mine'. The Inspectorate's error was due, he believed, to a lack of competence in using the monitoring equipment, and because during the tests six inches of rain had fallen.

In-house correspondence from February 1972 until October 1976 contains repeated warnings about the dust hazard. One report dated 7 February 1972 presents the following description of the mine:

> Nevertheless, billowing clouds of (fibre) could be seen coming from this building (the mill) and Mr Burke tells me he has, on occasions seen such clouds from distances of several miles.

In a second report, written in the same month, Dr McCullagh comments that despite 'some marginal improvements there is little change and the picture remains gloomy'.

The Swift Papers reveal that like Johns-Manville and Turner & Newall, James Hardie made an effort to keep abreast of medical discovery. A company review dated October 1957 presents an accurate summary of knowledge about asbestosis with citations from the UK literature dating back to 1900. The review also contains reference to research linking asbestos and lung cancer. In July 1966 Dr McCullagh gave a presentation to a manager's conference. He told his audience that asbestos can cause asbestosis, mesothelioma and lung cancer and he explained that there was no treatment for asbestosis and that even slight exposure to asbestos can cause cancer. As dust levels in the industry were reduced McCullagh expected asbestos workers to live longer resulting in more cases of cancer. Asbestos was also suspected of being an environmental hazard for those living near factories. The main danger, he explained, was to those resident within half a mile of the source of exposure, which was the distance between the Baryulgil mill and The Square. McCullagh warned his colleagues that in future James Hardie could face litigation over the siting of its factories.

James Hardie issued the first in a series of bulletins to senior management on asbestos and health in June 1971. Most of the material originated from the Asbestosis Research Council in the UK, of which James Hardie was an associate member. There was also literature from Johns Manville, and the Swiss conglomerate, Eternit SA. In addition, a James Hardie medical officer kept a watch on three dozen or so journals published in the Pacific rim.

CONCLUSION

James Hardie's involvement at Baryulgil came to an end in September 1976 when it sold the mine. The buyer, Woodsreef, which at that time was mining at Barraba, was interested not in Baryulgil but in extending its existing leases. Although it worked Baryulgil for only a brief period after its closure, Woodsreef graded the site, fenced the pit, removed the old mill and planted trees on the tailings dumps. In addition, between 1977 and 1983 state and federal authorities spent $3.5 million at Baryulgil to solve the problems left behind by Asbestos Mines Pty Ltd. In 1983 most of the people at The Square agreed to move to a new site at Mulabugilmah, some three miles away along a dirt road. The Square is important to community identity and in the past 20 years most of the people have moved back to The Square. The general store is used by both communities and it provides a mail service and a bank. Those older members who remain are not concerned about the tailings. They have lived with that problem all their lives.

The 1983–84 Inquiry concluded that James Hardie should have been aware of the dangers of asbestos long before Baryulgil opened and therefore was under an obligation to protect the workforce. It also noted that its own deliberations had been hindered by James Hardie's refusal to provide medical records or to allow Dr McCullagh to give evidence. Yet the Inquiry offered little criticism of the company and its final report offers little insight into James Hardie's behaviour. There is no explanation as to why Hardie, which was so well informed about asbestos disease, chose to keep that knowledge to itself. The testimony of miners was given little credence even though the Hardie Papers, which the Committee accepted as authentic, substantiated their claims about work conditions and environmental pollution. Perhaps most surprising of all, the Inquiry found no evidence of widespread occupational disease. Some of the Banjalang elders, including Neil Walker, spoke at the 1983–84 Inquiry but the community never saw the final report and they were told nothing about the outcome. It was as if the Inquiry had never taken place. In any case over the past 20 years men and women have continued to die prematurely. During the current negotiations over a settlement, James Hardie has resisted the inclusion of Baryulgil, forcing the community to initiate legal action in the NSW High Court in March 2006.

Work conditions at Baryulgil were similar to those faced by black workers on South African mines under apartheid. That in turn raises the question as to how that could have happened in Australia? James Hardie was under no pressure from trade unions or regulatory authorities to improve conditions. The miners were Aboriginal, they had low expectations of employers and they were largely isolated from the outside world. In truth, their choice was to work for Asbestos Mines Pty Ltd, or to work for no one. There were in addition technical factors peculiar to asbestos which meant that the mills were particularly hazardous. Turner & Newall and Johns-Manville found that it was impossible to eliminate dust and still produce fibre cheaply. As a result, around a third of mill workers in South Africa, Swaziland, Zimbabwe, and Canada developed asbestosis. Baryulgil was different in the sense that the mine's output and profitability were of little importance to the operating company. Its reason for running the mine was to maintain a seat on the Tariff Board rather than to produce large quantities of chrysotile. Consequently, there were none of the pressures on production which contributed so much to the dust in South Africa and Canada. The Hardie Papers show that the threat of occupational disease at Baryulgil was simply irrelevant to the company's senior management.

The 1983–84 Inquiry rejected claims by the Aboriginal Legal Service that James Hardie had exploited an Aboriginal community. In its final report it noted that conditions at Wittenoom, the site of Australia's worst occupational disaster, where the workforce was white, were just as bad. Presumably James Hardie would have treated white miners in the same way and therefore the issue of race is not relevant to labour relations at Baryulgil. That conclusion is contradicted by the Swift Papers which suggest

that conditions at the mine were worse than at James Hardie's metropolitan factories. But it is consistent with the company ethos identified by the Jackson report.

In the US, Canada and South Africa, the asbestos industry benefited from poor and sometimes complicit state regulation. That in turn has led to the delayed costs of mining and manufacture being shifted onto the public purse. In South Africa, the post-apartheid state is still paying for the reclamation of mines in the Northern Cape abandoned by British companies in the 1980s. Until the Jackson Inquiry, the same happened in Australia. What changed the attitude of federal and state governments, which for so long had shared an interest in James Hardie's success, has been the spiralling costs of litigation from publicly owned power stations, railways, and shipyards. On a small scale Baryulgil presents a window into the conduct of James Hardie. It also presents a microcosm of the global industry. It is a story of low wages, hazardous work conditions, and environmental pollution. It is also a story of the protracted struggle by a community for recognition of its losses.

Jock McCulloch teaches in the School of Global Studies at RMIT University. He is the author of several books on asbestos mining in Australia and Southern Africa, the most recent one with Geoff Tweedale, The Global Asbestos Industry and its Fight for Survival (forthcoming). He is currently writing a history of silicosis among South African gold miners

<jock.mcculloch@rmit.edu.au>

ENDNOTES

* This article has been peer reviewed for Labour History by two anonymous referees. The author would like to thank the people of Baryulgil and especially Ken and Pauline Gordon and Linda Walker for their help.

1. For a history of the company see Geoffrey Hagan, James Hardie Industries 1880–1980, unpublished BA Hons thesis, Macquarie University, 1980. See also Gideon Haigh, Asbestos House: The Secret History of James Hardie Industries, Scribe Publications, Carlton North, 2006
2. Hagan, James Hardie Industries, p. 32
3. 'Asbestos and James Hardie', Annexure J in Report of the Special Commission of Inquiry into the Medical Research and Compensation Foundation, D.F. Jackson, Commissioner, (NSW Government: Sydney), September 2004, p. 16
4. Ibid., p. 117
5. See Geoffrey Tweedale, Magic Mineral to Killer Dust: Turner & Newall and the Asbestos Hazard, Oxford University Press, Oxford, 2000; and Jock McCulloch, Asbestos Blues: Labour, Capital, Physicians and the State in South Africa, James Currey: London, 2002
6. Stephen A. Marglin and Juliet B. Schor (eds), The Golden Age of Capitalism: Reinterpreting the Postwar Experience, Clarendon Press, Oxford, 1990.
7. In addition to those three diseases, asbestos has been implicated in cancers of the liver, brain and mammary glands. See Barry Castleman, Asbestos: Medical and Legal Aspects, 5th ed., Aspen Law and Business Books, New Jersey, 2005
8. Joe LaDou, 'An International Review of Occupational and Environmental Asbestos Issues: Funding of International Agencies', Paper presented at The Chrysotile Debate, Canadian Asbestos Conference: A Global Problem, House of Commons, Ottawa 12–14 September 2003
9. L. Noakes, Asbestos, supplement Department of Supply and Shipping Mineral Resources of Australia, Summary Report, No. 17 July 1945.
10. There were three major commercial varieties of asbestos, namely chrysotile (white), and amosite (brown) and crocidolite (blue) which are known as amphiboles. Over 90 per cent of the asbestos used during the twentieth century was chrysotile. See Suzanne LeBlanc, Cassiar: A Jewel in the Wilderness, Caitlin Press, Prince George, 2003
11. Submission by Hardie Trading (Services) Proprietary Ltd. Submission to the Inquiry into the Effects of Asbestos Mining on the Baryulgil Community, House of Representatives Standing Committee (hereafter 1983–84 Inquiry), November 1983, p. 9. Copies of submissions made and evidence given at the Inquiry are in the author's possession. See Endnote 34 for the citation of the published report
12. Mr James Kelso, evidence before the 1983–84 Inquiry, 2 December 1983, Sydney, p. 39.
13. Ibid., p. 38
14. See Matt Peacock, Asbestos: Work as a Health Hazard, Australian Broadcasting Commission, Sydney, 1978
15. The only parallel, the Beaudry Commission in Canada, was also concerned with manufacture. See R. Beaudry, G. Lagace, L. Jukau, Rapport Final, Comite d'Etude sur La Salubrite dans L'Industrie de L'Amiante, Le Comite, Quebec, 1976
16. Submission by Hardie Trading (Services) Proprietary Ltd. Submission to the 1983–84 Inquiry, p. 4
17. Ibid.
18. 'Asbestos and James Hardie', Annexure J, p. 121
19. 'In the Shadow of the Corporate Veil: James Hardie and Asbestos Compensation', Research Note, no. 12, 10 August 2004, Parliamentary Library, Canberra, Australia
20. See Bob Burton, 'Fund for patients with asbestos induced diseases may run out', British Medical Journal, no. 328, 27 March 2004, p. 728
21. Report of the Special Commission of Inquiry into the Medical Research and Compensation Foundation, D.F. Jackson, Commissioner, September 2004.
22. 'Trailed by Asbestos', The Australian, 7 December 2005
23. 'Black Workers Miss Hardie Payouts', Australian, 21 March 2005
24. George Farwell, Squatters' Castle, The Story of a Pastoral Dynasty, Lansdowne Press, Melbourne, 1973, pp. 136. For an account of the colonial period see Malcolm David Prentiss, Aborigines and Europeans in the Northern Rivers Region of New South Wales, 1823–1881, MA thesis, Macquarie University, 1972
25. Author's interview with Lucy Daley, Baryulgil, 15 October 1984
26. See the Annual Report of the Aborigines Welfare Board for the Year Ending 30 June 1944, Parliament of New South Wales, Appendix B, p. 19
27. For a history of the early period, see Jock McCulloch, Asbestos: Its Human Cost, University of Queensland Press, St Lucia, 1986, pp. 131–137
28. Summary of Report of the Department of Mines, 1954 Second Session Parliament of New South Wales, Government Printer, Sydney, 1965, p. 9.
29. Submission by Hardie Trading (Services) Pty Ltd to the 1983–84 Inquiry, November 1983, p. 8
30. Author's interview with Ken Gordon, Grafton, 29 September 2005
31. Ibid.
32. Author's interview with Mr Neil Walker, Baryulgil, 22 October 1984.
33. William Hindle, evidence before the 1983–84 Inquiry, 7 February 1984, Sydney, pp. 223–237
34. Ibid., p. 235
35. The Effects of Asbestos Mining on the Baryulgil Community, Report of the House of Representatives Standing Committee on Aboriginal Affairs, Australian Government Publishing Service, Canberra, 1984, pp. 7.22–30.
36. Author's interview with Mr Neil Walker, Baryulgil, 22 October 1984
37. Author's interview with Linda Walker, The Square, Baryulgil, 29 September 2005.
38. Author's interview with Pauline Gordon, Grafton, 29 September 2005
39. Ibid.
40. Ibid.
41. Author's interview with Linda Walker, The Square, Baryulgil, 29 September 2005
42. Ibid.
43. Ibid.
44. 'Visit to Shabanie and Gaths Mines, Zimbabwe, March 1987, Dr P. Elmes, 14 April 1987', Turner & Newall Papers, 0301/1537–1540, Manchester Metropolitan University, Manchester
45. On the history of mining and milling see McCulloch, Asbestos Blues; Lloyd Tataryn, Dying for a Living: The Politics of Industrial Death, Deneau & Greenberg, Toronto, 1979; and Andrea Peacock, Libby, Montana: Asbestos and the Deadly Silence of an American Corporation, Johnson Books, Boulder, 2003
46. Jerry Burke, evidence before the 1983–84 Inquiry, Sydney, 7 February 1984, 1984, p. 122.
47. Bill Harrington, evidence before the 1983–84 Inquiry, Sydney, 7 February 1984, p. 109.
48. William Hindle, evidence before the 1983–84 Inquiry, Sydney, 7 February 1984, pp. 223–237
49. Jerry Burke, evidence before the 1983–84 Inquiry, Sydney, 7 February 1984, p. 126.
50. Ibid., p. 151
51. Author's interview with Linda Walker, The Square, Baryulgil, 29 September 2005.
52. Jerry Burke, evidence before the 1983–84 Inquiry, Sydney, 7 February 1984, p. 159
53. Rodney MacBeth, evidence before the 1983–84 Inquiry, Sydney, 7 February, 1984, p. 215
54. Ibid., p. 210.
55. Pauline Gordon, evidence before the 1983–84 Inquiry, Baryulgil, 6 February 1984, p. 109

56. Chris Lawrence. Aboriginal Legal Service, evidence before the 1983–84 Inquiry, Sydney, 2 December 1983, p. 41

57. Ibid.

58. K.C. Cross, 'An Investigation of Degree of Asbestos Pollution in the Vicinity of Baryulgil and Yulgilbar Gap, NSW'. Document Prepared on Behalf of the Department of Aboriginal Affairs, 13 October 1980, p. 6

59. Rodney MacBeth, evidence before the 1983–84 Inquiry, Sydney, 6 February 1984, p. 208

60. Author's interview with Neil Walker, Baryulgil, 20 October 1984

61. Author's interview with Linda Walker, The Square, Baryulgil, 29 September 2005

62. Letter from Mr Warwick Sinclair to Mr Cecil Patten, Aboriginal Legal Services, Redfern 14 May 1983.

63. James Kelso, evidence before the 1983–84 Inquiry Sydney, 10 February 1984, p. 36.2

64. See Official Transcript, Tariff Board Inquiry Re Asbestos Fibre, Commonwealth of Australia, 2 June 1954. A copy is in the author's possession.

65. Testimony of John Thyne Adamson, Managing Director of James Hardie & Com., Tariff Board Inquiry Re Asbestos Fibre, Commonwealth of Australia 2 June 1954 Official transcript, p. 132

66. Ibid p. 132

67. The legislation was based on state regulations from Victoria. See 'Safety in Industry', series of lectures delivered to inspectors of Factories, Victoria by K.A. Kinnish, Victorian Department of Labour, Government Printer, 1954 p. 40

68. For an account of the legislation see McCulloch, Asbestos: its Human Cost, pp. 144–149

69. Jerry Burke, evidence before the 1983–84 Inquiry, Sydney, 7 February 1984, p. 333.

70. James Kelso, evidence before the 1983–84 Inquiry, Canberra, 2 May, 1984, p. 1781

71. 'Asbestos and Aborigines', submission by Public Interest Advocacy Centre to the 1983–84 Inquiry, 9 February, 1984, p. 623

72. James Kelso, evidence before the 1983–84 Inquiry, Sydney, 7 February, 1984, p. 351.

73. See Castleman, Asbestos and Tweedale, Magic Mineral.

74. Reports of the Department of Mines, New South Wales, for the year 1946, Joint Volumes of papers presented to the Legislative Council and Legislative Assembly, Vol. III, p. 18. Sydney, Government Printer 1950, p. 27

75. Aboriginal Legal Service, submission part 3 to the 1983–84 Inquiry, 28 June, 1984, Sydney, p. 2297

76. 'Exposure to Asbestos Dust in Crushing Plant and Quarry at Asbestos Mines Pty Ltd, Baryulgil' Scientific Division of Occupational Health, 24 May, 1960, signed A.T. Jones Scientific Officer, quoted in submission by New South Wales Department of Health, the 1983–84 Inquiry, 10 February, 1984, Sydney, p. 8.

77. Minute paper from Inspector of Mines, 'Inspection and Dust Sampling Asbestos Mines Pty Ltd', 1 February, 1973, quoted in transcripts, the Inquiry, 10 February, 1984, Sydney

78. Minute paper, Department of Mines, 19/12/73, subject Asbestos Mines Pty Ltd, Baryulgil, inspection and dust sampling results, October 1973 signed Inspector of Mines (Special duties).

79. The Barraba mine was operated by the Chrysotile Corporation of Australia Pty Ltd and at its peak in the late 1970s it employed over 400 people See McCulloch, Asbestos, p. 153

80. Author's interview with Ken Gordon, Grafton, 29 September 2005

81. Robert Marshall, evidence before the 1983–84 Inquiry, 10 February, 1984 Sydney, p. 1068

82. Dr Evan Francis, evidence before the 1983–84 Inquiry, 10 February 1984, Sydney, p. 1071

83. Mr James Kelso, evidence before the 1983–84 Inquiry, 10 February, 1984, Sydney, p. 24.

84. See for example N.J. Wikely, Compensation for Industrial Diseases, Dartmouth Publishing, Aldershot, 1993 and Castleman, Asbestos.

85. A. Julienne, L. Smith, N. Thomson and A. Gray, 'Summary of Aboriginal Mortality in New South Wales Country Regions, 1980–1981', NSW Department of Health, State Health Publication No (IDS) 83–168, (Sydney) 1983, p. 9

86. James Kelso, evidence before the 1983–84 Inquiry, Canberra, 30 May 1984, p. 1755

87. Radiology Report of Mr A. Preece by Dr A. Sharland, 15 January 1949, Grafton Base Hospital, cited in submission by the Aboriginal Legal Service before the 1983–84 Inquiry, Yellow Book vol. 2, document 1.

88. Dr Pooks, Radiology Reports on A. Preece and H. Mundine, 2/4/52, the 1983–84 Inquiry, Yellow Books, vol. 2, document 2.

89. Death Certificate, Cyril Mundine cited in the 1983–84 Inquiry, 10 February 1984, Sydney, p. 37.1

90. James Kelso, evidence before the 1983–84 Inquiry, Sydney, 10 February 1984, p. 37.4.

91. Post-mortem Report, Andrew Donnelly signed Dr K.D. Murray, 17/6/1977, Grafton Base Hospital cited as Document Number 8a, Submission by Aboriginal Legal Service before the 1983–84 Inquiry, Yellow Books, Volume 2

92. Document, review of the Death Certificate of Andrew Donnelly Dr R.J. Grobious, Grafton Base Hospital 20 January 1984 Submission by Aboriginal Legal Service before the 1983–84 Inquiry, Yellow Books vol. 2

93. Author's interview with Linda Walker, The Square, Baryulgil, 29 September 2005.

94. Ibid.

95. Ibid.

96. 'An Examination of the Aboriginal Miners of the Baryulgil Asbestos Mine', Respiratory Laboratory of the Division of Occupational Health, NSW, 1977

97. 'A Re-examination of the Health of the Miners and Ex-miners from the Baryulgil Asbestos Mine', Respiratory Laboratory of the Division of Occupational Health, NSW, 1981; 'Further Examinations of Baryulgil Asbestos Miners', Respiratory Laboratory of the Division of Occupational Health, NSW, 1982.

98. The Effects of Asbestos Mining on the Baryulgil Community, pp. 7.19–30.

99. See Castleman, Asbestos, pp. 581–698 and Tweedale, Magic Mineral, passim

100. See Fred Swift versus James Hardie & Comp. Pty et al, The Dust Diseases Tribunal (NSW), Matter DDT 74 of 1991

101. Memo to head office, E.G. Reeve Chief Draftsman 28/2/66, Hardie Papers, in author's possession

102. L.C. Denmead, Mine manager's Report for fortnight ending 1/4/69, dated 2/4/69 Hardie Papers 89a, in author's possession

103. 'Report on the Industrial Hygiene Survey, 14–17 September, 1970', J. Winters, Industrial Hygiene Engineer, 16/10/70 Hardie Papers 5 in author's possession

104. Letter to from Dr S.F. McCullagh, Medical Officer, to manager, Baryulgil subject Industrial Hygiene, Baryulgil, 6 November, 1970 Hardie Papers 4, in author's possession.

105. Memo from Dr S.F. McCullagh, 21 February, 1974, subject Department of Mines Inspection 11, October 1973, to Head Office, Hardie Papers 20, in author's possession

106. Letter (confidential) from Dr S.F. McCullagh, subject Industrial Hygiene Baryulgil, Medical Officers Inspection, 7 February, 1972 Hardie Papers, 13, in author's possession.

107. Letter from Dr S.F. McCullagh to head Office, 29 February, 1972, subject Dust Counts for February Hardie Papers, 47, in author's possession

108. A Report Concerning the Incidence of Asbestosis and The Nature of the Present Day Dust Exposures at the Camellia Factory of J. Hardie & Co. Ltd.

24 October 1957 Swift Papers A copy is in the author's possession.

109. Extract from Notes of Talk by Dr McCullagh to James Hardie Factory Managers Conference, July 11 1966 Swift Papers A copy is in the author's possession.

110. Biological Effects of Asbestos Bulletin, 1 June 1971, James Hardie & Company Ltd, Swift Papers A copy is in the author's possession

111. For an account of the management of the mine during the Woodsreef period see Mr David Barwick, Chairman and Managing Director of Woodsreef Mines Ltd, evidence and submission before the 1983–84 Inquiry, Sydney, 28 June, 1984, pp. 2119–2150

112. The Effects of Asbestos Mining on the Baryulgil Community, p. 2.29

113. Ibid., pp. 1.24–25

114. Ibid., p. 1.33.

115. See Castleman, 'Asbestosis in Canada' in Castleman, Asbestos, pp. 21–38. Jock McCulloch 'Dust, Disease and Labour at Havelock Asbestos Mine, Swaziland', Journal of Southern African Studies, vol. 31, no. 2, June 2005, pp. 251–266, and Jock McCulloch, 'Asbestos Mining and Occupational Disease in Southern Rhodesia/ Zimbabwe, 1915 to 1998', History Workshop Journal, no. 56, 2003, pp. 131–152

116. Testimony of John Thyne Adamson, Managing Director of James Hardie & Com. Tariff Board Inquiry Re Asbestos Fibre, Commonwealth of Australia, 2 June 1954, Official transcript, p. 132

117. See Jock McCulloch 'The Mine at Wittenoom: Blue Asbestos, Labour and Occupational Disease' Labor History, vol. 47, no. 1, February 2006, pp. 1–19

118. The Effects of Asbestos Mining on the Baryulgil Community, p. 1.31

Int. J. Cancer: **122,** 2337–2344 (2008)

Cancer incidence among women and girls environmentally and occupationally exposed to blue asbestos at Wittenoom, Western Australia

Alison Reid[1]*, Jane Heyworth[1,2], Nicholas H. de Klerk[1,3] and Bill Musk[1,4]

[1]*Occupational Respiratory Epidemiology, School of Population Health, University of Western Australia, Crawley, WA, Australia*
[2]*Faculty of Medicine, Dentistry and Health Science, University of Western Australia, Crawley, WA, Australia*
[3]*Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia, Perth, Western Australia*
[4]*Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia*

The impact of crocidolite exposure on the health of former Wittenoom miners and millers (largely male) has been well documented. Less is known about the health outcomes of the 2,968 women and girls who lived (N = 2,552) and worked (N = 416) in the blue asbestos milling and mining town of Wittenoom between 1943 and 1992. Quantitative exposure measurements were derived from dust studies undertaken over the lifetime of the mine and mill and the township. Incident cancers were obtained from the Western Australian (WA) Cancer Registry and the National Cancer Clearing House. Standardized incidence ratios (SIRS) compared Wittenoom females with the WA female population. Exposure-response relationships were examined using a matched case-control study design. There were (47) mesothelioma and (55) lung cancer cases among the 437 cancers in the Wittenoom females over the period 1960–2005. When compared to the WA female population, Wittenoom women and girls had higher rates of mesothelioma and possibly lung cancer. Mesothelioma incidence rates are increasing with the incidence rate of 193 per 100,000 in the period 2000–2005 being more than double that for the period 1995–1999 at 84 per 100,000. A significant exposure-response relationship was present for mesothelioma, but not for lung cancer. Forty years after the asbestos mine and mill at Wittenoom were closed, there is a high toll from cancer among the former female residents of the town and company workers.

Key words: women; cancer incidence; asbestos

The impact of crocidolite exposure on the morbidity and mortality of Wittenoom miners and millers (largely male) has been well documented.[1–3] Less is known about the impact of exposure on the health outcomes of the 3000 women and girls of Wittenoom, who comprised both asbestos workers employed by the Australian Blue Asbestos Company (ABA), and former residents of the Wittenoom township who were not employed directly in the asbestos industry.

This study was undertaken because the results from studies of men may not be pertinent or adequate to characterize the risks among women[4] and cannot be used to examine breast or gynecological cancers. There may also be gender specific responses to asbestos exposure that cannot be determined solely through an examination of male subjects. Susceptibility and carcinogenicity may vary by gender, and the nature and patterns of exposure to asbestos may differ by gender.

Most studies examining asbestos exposure and health outcomes among women have confined their attention to mortality rather than incidence of cancer. This appears most appropriate where the period between diagnosis and death is relatively short (e.g., for malignant mesothelioma and lung cancer), but it relies on the accuracy of cause of death recording and coding which may be contentious for malignant mesothelioma.[5–8] These earlier studies examining cancer mortality and asbestos exposure in women have reported excess mortality from lung and respiratory cancers and malignant mesothelioma. There has been some suggestion that ovarian cancers are also in excess but small numbers make interpretation difficult.[6,7,9]

The women of Wittenoom have been exposed virtually exclusively to crocidolite and quantitative measures of their exposure have been estimated.[2,10] Their sources of asbestos exposure were mixed; for some it was occupational whilst for others it was from the general environment and from the domestic environment in the home where ABA workers' clothes were worn and washed. The aim of this article is to examine cancer incidence in the Wittenoom women, compare it with the Western Australian (WA) female population and examine exposure–response relationships.

Methods

Blue asbestos was mined and milled at Wittenoom Gorge in WA between 1936 and 1966. The township of Wittenoom that developed as a result of the mine and mill was initially located in Wittenoom Gorge, 1 km away from the mine. As the population grew it moved to the flats of the Fortescue River, 12 km from the mine. The State and Commonwealth governments actively encouraged the development of Wittenoom and provided housing for the ABA workers and their families and various township amenities. Asbestos tailings from the mine were distributed throughout the town: on roads and footpaths; on the school playgrounds; on the racecourse; and in the back yards of houses, in an attempt to minimize the fine, irritating dust rising from the red sandy dirt.[10,11] A chronology of events that occurred at Wittenoom is presented in Table I.

Wittenoom workers' and residents' cohorts

Establishment of the Wittenoom workers cohort has been described elsewhere.[2] Briefly, crocidolite (blue asbestos) was mined at Wittenoom gorge in Western Australia from 1936 until 1966. From 1943 until 1966 the principal leases were mined by a single company, ABA which employed over 6,000 people, mostly for short periods (Table I). From employment records a cohort of 6,493 males and 416 (6%) female employees was assembled. Most of the women who worked for ABA were not employed in mining or milling roles but instead worked in the company shop, hotel or offices. When the cohort was assembled vital status was determined for 73.2% of men and 58.0% of the women.[2] To the end of 2000 the vital status of more than 70% of the former female workers was known.

A further cohort were identified from various sources as being former residents of the township of Wittenoom.[11,13] These sources and the percent of people they identified included: state primary school records (22%), admission and out-patient records from the Wittenoom hospital and General Practitioner (20%), the State Electoral Roll for the Pilbara district (12%) questionnaires sent to ABA workers (14%), participants of a cancer prevention program

***Correspondence to:** Occupational Respiratory Epidemiology, School of Population Health, M431, University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia. Fax: +61-8-6488-1611.
E-mail: alison.reid@uwa.edu.au
Received 12 July 2007; Accepted after revision 5 November 2007
DOI 10.1002/ijc.23331
Published online 20 December 2007 in Wiley InterScience (www.interscience.wiley.com).

TABLE I - CHRONOLOGY OF EVENTS[1] THAT OCCURRED AT WITTENOOM, WESTERN AUSTRALIA

1936	Crocidolite deposits "discovered" and pick and shovel mining commenced
1943	Australian blue asbestos company takes over the principal leases
1946	Establishment of residential settlement in Wittenoom Gorge about 1km downstream from mine and mill
1946	Mines Department Inspector describes dust conditions at Wittenoom as 'terrific'.
1947	Building of town of Wittenoom at entrance to Wittenoom Gorge commenced, 10km from the mine and mill
1948	Town named Wittenoom
1948–1951	Dust levels in mine and mill regularly monitored at 6–8 times "safe" levels.
1950	Wittenoom has 150 houses and population over 500
1958	New "cleaner" mill opens
1960	First mesothelioma case in a worker diagnosed.
1965	Local council warned that the tonnes of asbestos tailings spread around the town could even threaten tourists.
1966	October 8th. Air sampling program using long running thermal precipitators commenced
1966	December 1st. Asbestos mine and mill closes due to economic reasons. Population declines rapidly
1978	November. Government decides to phase out the town of Wittenoom.
1980–83	Some Wittenoom streets closed
1985	December 18th. primary school closed
1992	Government owned buildings demolished and new residents discouraged

[1]Taken from the report of the select committee appointed to inquire into Wittenoom.[12]

and associated publicity (18%) and Wittenoom birth records (4%). Other sources included records from the Catholic Church, Wittenoom burial records, employment lists from the school, hotel, police, hospital and banks and information from the Asbestos Diseases Society of WA (10%). In total 18,553 records collected identifying 5,097 individuals not employed directly in asbestos mining or milling.[10,11]

Between 1991 and 1993 a questionnaire was sent to all former residents of Wittenoom traced to an address in Australia, (N = 3,244, 64%), excepting those participating in a cancer prevention program (N = 641, 13%) from whom the information had already been collected. Date, length and place of residence at Wittenoom, occupation at Wittenoom, whether lived with an asbestos worker or washed the clothes of an asbestos worker, smoking and past medical history as well as demographic information were collected.[14]

After consideration of questionnaire responses, 438 subjects were deleted from the cohort for various reasons; denied living at Wittenoom (n = 209, 48%), no details on date of birth or duration of residence (n = 152, 35%), lived at Wittenoom for less than one month (n = 22, 5%) and 55 (12%) were duplicate records.[14] Therefore follow up status at the end of 1993 was; 2,173 (47%) returned a questionnaire, 641 (14%) were participating in the cancer prevention program, 51 (1%) had permanently departed Australia, 460 (10%) were dead, 785 (17%) had not returned a questionnaire and 549 (11%) were not traced since leaving Wittenoom.[13] Where the person remained untraced, did not return a questionnaire or was dead: if they were related to an ABA worker, then dates and place of residence were assumed identical to that of the worker. For those unrelated to an ABA worker, dates of residence were assumed the same as other family members provided that at least one family member had known exposure. Dates of residence were taken as those found on the various sources used to establish the cohort for all other residents.[10,13] If the untraced person was the wife of an ABA worker and known to have lived with that worker, it was assumed that she washed his clothes. The residents' cohort was considered complete when comparisons between it and the population of Wittenoom recorded at various census dates showed a close correspondence.[11]

Work has continued on the development of this cohort since 1993 and this accounts for differences in the number of persons from those earlier articles.[10,11,13] To the end of 2000 there were 2,608 women and 2,160 men in the residents' cohort.[15]

Women at Wittenoom

All women from both cohorts without a death record and who were not attending a cancer prevention program,[16] were searched for in the Marriage Register of WA to determine if a change of surname had occurred. The search commenced from the year they were last known to be alive. Death certificates of any spouse or birth, death and marriage certificates of children were sought in an attempt to obtain the wife or mothers' maiden name and date of birth. From this search we obtained authenticating information for 235 women previously thought lost to follow up. Fifty six women were excluded because they had insufficient identifying information (missing date of birth, first name etc.) or because they were residents of Wittenoom for less than 1 month. The final cohort therefore consisted of 2,968 women, 416 former workers and 2,552 former residents. As at the end of 2004, 556 women (19%) were known to have died, 1,762 women (59%) were alive and 650 women (22%) were lost to follow up. Women were defined as lost to follow up if there was no "passive" contact since 1999 and were not known to be dead.

Case ascertainment

The cohort was linked to the WA Cancer Registry, to ascertain incident cancers from 1982 to December 2005. Cancers diagnosed prior to 1982 were obtained by manually searching printed computer records of all cancer registrations in Western Australia, as well as searches of hospital admission records at all public hospitals in Australia. Pathologists throughout Australia, and other state and territory cancer registries were sent a list of names of all cohort members and asked to search their records. Completeness of cancer registrations for cancers other than mesothelioma before 1982 are not known, therefore any cancer diagnosed before that period have not been included in the standardized incidence ratios (SIR). The WA Mesothelioma Registry, which assesses and verifies all cases of mesothelioma diagnosed in the state, was established in 1960.[17] Incident cancers among women not resident in Western Australia were obtained from each state and territory Cancer Registry *via* the National Cancer Clearing House, and mesotheliomas from the Australian Mesothelioma Register.[18] The end of follow-up for each state and territory were: Tasmania and South Australia 1999, Northern Territory 1998, Australian Capital Territory, New South Wales, Queensland and Victoria 1997. Cancers were defined using the International Classification of Diseases for Oncology, Second Edition.[19] Data quality checks at the cancer registries are carried out on a continual basis. Pathology coding and entry into database are checked by a second staff member and unusual cases are flagged according to the International Agency for Research into Cancer (IARC's) "Check" routine. Completeness is ascertained by comparisons with reports from radiation oncologists and the hospital morbidity data system which records all details of hospitalizations in Western Australia.[17]

Asbestos exposure assessment

The Mines Department of WA conducted several surveys of dust exposure in the mine and mill between 1948 and 1958 measuring the concentration of particles per cubic centimetre using a koniometer. The upper measurement limit of 1,000 cm^3 was often exceeded and anecdotal evidence suggests that operations were shut down before the inspections commenced. In 1966 airborne

respirable fibers greater than 5 μm in length were measured in various workplaces in the mine and mill and in the township using a Casella long running thermal precipitator.[20] Fiber concentrations ranged from 100 fibers/ml (f/ml) in the bagging room down to 20 f/ml in the mine. Cumulative exposure, measured in fiber per ml years (f/ml years) was calculated for each former worker by adding over all his/her jobs the product of his/her estimated fiber concentration (derived from the dust surveys) and the length of time spent in each job obtained from the ABA employment records.[2] An additional amount was added to the workers exposures reflecting 16 more hours of residential exposure each day and a two day weekend.

In 1973 personal and fixed positional monitors were used to measure environmental levels in the township, and further measurements were taken in 1977, 1978, 1980, 1984, 1986 and 1992.[10] On the basis of these measures residents not working directly with asbestos were assigned an intensity of exposure of 1.0 fiber/ml of air from 1943 to 1957, when an old "dirty" mill was in operation and then 0.5 f/ml from1958 when a new "cleaner" mill was in operation until the time that the mine and mill closed in 1966 (Table I).[10,13] Interpolation between the dust surveys that used personal monitors allocated exposures from 0.5 f/ml in 1966 to 0.010 f/ml in 1992. The township of Wittenoom did not close with the demise of the asbestos mining and milling operation, although there was a significant decline in population at that time.[15] The State Government began to phase out the town from 1992 when some of the buildings were demolished and services withdrawn (Table I). Duration of residence was combined with intensity of exposure to provide a measure of cumulative exposure. Cumulative exposure was then adjusted by a factor of 4.2 to account for 24 hr a day/7 day a week exposure.

The estimates of asbestos exposure have been validated internally by showing an agreement with lung fiber burdens[21] and a clear relationship between all asbestos-related diseases and exposure-response has been repeatedly documented in the cohort.[2,22–24] Further, Hodgson and Darnton, found Wittenoom exposures comparable to exposures reported from other crocidolite mines and found the Wittenoom lung cancer risk (R_L) similar to that from other studies.[25]

Analysis

SIRs were calculated as the ratio of the observed cancers to expected cancers. Confidence intervals were assessed by treating the observed number as a Poisson count with expectation equal to the particular expected numbers. Expected numbers of cancers were estimated using age-period and cause-specific cancer incidence rates for the WA female population in 5-year periods from 1982 to 2005, provided by the WA Cancer Registry. For the period 1960–1981 the population age and cause-specific cancer incidence rates for 1982–1984 were used to estimate expected cancers as period specific rates were unavailable. However, cancers diagnosed before 1982 were not included in the SIR analysis. For mesotheliomas, age and period specific incidence rates for the WA female population in 5-year periods from 1982 to 2005 were used to calculate expected numbers. For mesotheliomas diagnosed prior to 1982 incidence rates for the period 1982–1984 were used as period specific rates for 1960–1981 were not available. The usual method for calculating expected cancers would lead to a probable overestimate of risk,[2] given that 22% of the women were lost to follow up and the nearly complete ascertainment of cancers in WA. Therefore two methods were used to derive expected cancers, to show minimum and maximum estimates of effect, based on differing censoring dates. The first method assumed that all women who were not diagnosed with a cancer, not known to be dead, and not known to have migrated were cancer-free at the end of 2004 or, if they were residents of other Australian states, they were cancer-free until their respective state end of follow up date. This method tends to overestimate the person-years at risk and therefore provides a minimum estimate for SIR. The second method censored women at their date last known to be alive if they were not diagnosed with a cancer, known to be dead or to have migrated. This method tends to underestimate person-years at risk and therefore gives an upper estimate of SIR. Both methods censored women at age 85 years if they were not known to have a cancer or to have died before that age.

Mesothelioma incidence rates were derived in 10 year periods of time since first exposed to asbestos at Wittenoom and for each 5 year period from 1960, by dividing the number of cases in each time span by the number of person-years at risk in the same time span and multiplied by 100,000. Those women who were lost to follow up were censored at their date last known to be alive.

Exposure-response relationships were examined using a nested case-control analysis. Cases were those women who were diagnosed with a cancer of interest during the study period. Controls were all those not known to have been diagnosed with the same cancer by the year of diagnosis of the case and who were the same age as the case, in 5 year age-bands. Conditional logistic regression related asbestos exposure to cancer outcome. Asbestos exposure measurements were not normally distributed and so were transformed to their natural log. All analysis was undertaken using Stata 9.0.[26]

Results

Descriptive results

There were 437 incident cancers in 387 women among the Wittenoom women between 1960 and 2005. The age at diagnosis ranged from 10 to 99 years. Cases were more likely to arrive at Wittenoom in the 1940s and 1950s, and to be older on their arrival than women who remained cancer free although their duration of residence at Wittenoom was not significantly different (Table II). There was no difference in duration of residence between case and non cases, with 45% of all women staying at Wittenoom for 1 year or less. Twenty percent of former ABA workers compared with 12% of former residents were diagnosed with a cancer. Cases had a greater intensity of asbestos exposure and a greater cumulative asbestos exposure than non cases. Among former residents, 72% of those who developed a subsequent cancer had lived with an ABA asbestos miner or miller and 35% reported washing the clothes of an ABA worker.

Incidence of cancers

For all the Wittenoom women combined, the incidence of all cancers, malignant mesothelioma and cancer of the lung, trachea and bronchus was greater than that of the WA female population irrespective of which censoring method was used. The incidence of mesothelioma was 55–77 times greater than in the WA female population. The SIR for lung cancer was 80% to 254% higher among the Wittenoom women than women in the WA population. Regarding smoking status we have limited information. For all women we have smoking information on 59% of whom 53% reported being an ever smoker. Applying Axelson's adjustment to our data, we estimate that the lung cancer SIR is raised by a factor between 1.4 and 1.5 due to confounding by smoking.[27,28] Therefore SIR1 might be adjusted down to 1.27 and SIR2 to 1.75.

Among former ABA workers, the incidence of mesothelioma and lung cancer was raised, compared to the WA female population irrespective of which censoring method was used (Table III). Thirty four percent of former workers responded to a smoking questionnaire in 1979 and 49% reported currently smoking. Applying Axelson's adjustment attenuated the lung cancer SIR1 to 1.92 and SIR2 to 2.91. All cancers incidence was increased with SIR2 (women lost to follow up censored at their date last known to be alive). Cervical cancer was between 90% and 250% greater among the Wittenoom workers than the WA female population, but this was not statistically significant.

Among former residents of Wittenoom, the incidence of mesothelioma, all cancers and lung cancer was increased compared to the WA female population, irrespective of which censoring

TABLE II – RESIDENTIAL AND ASBESTOS EXPOSURE CHARACTERISTICS FOR ALL CANCER CASES AND NON CASES AMONG THE WOMEN FROM WITTENOOM

	Cases *N* (%)	Non cases *N* (%)	Total *N* (%)	*p*-value
Year of arrival at Wittenoom				
1940s	22 (6)	95 (4)	117 (4)	
1950s	184 (48)	907 (35)	1,091 (37)	
1960s	147 (38)	1,174 (45)	1,321 (45)	
1970s	31 (8)	382 (15)	413 (14)	
Unknown	3 (1)	23 (1)	26 (1)	
Total	387	2,581	2,968	$p < 0.001$
Age of arrival at Wittenoom				
<15 years	65 (17)	1,157 (45)	1,222 (41)	
15–39 years	252 (65)	1,164 (45)	1,416 (48)	
40+ years	67 (17)	227 (9)	294 (10)	
Unknown	3 (1)	33 (1)	36 (1)	
Total	387	2,581	2,968	$p < 0.001$
Duration of residence at Wittenoom				
Less than 1 year	175 (45)	1,162 (45)	1,337 (45)	
One to less than 3 years	91 (24)	691 (27)	782 (26)	
Three to less than 5 years	62 (16)	390 (15)	452 (15)	
Five years or more	57 (15)	310 (12)	367 (12)	
Unknown	2 (1)	28 (1)	30 (1)	
Total	387	2,581	2,968	$p = 0.328$
Average Intensity of exposure (f/ml)				
<2 f/ml	128 (33)	908 (36)	1,036 (35)	
2 to <5 f/ml	235 (61)	1,572 (62)	1,807 (62)	
5 to <10 f/ml	15 (4)	51 (2)	66 (2)	
10+ f/ml	6 (2)	21 (1)	27 (1)	
Unknown	3 (0)	29 (1)	32 (1)	
Total	387	2,581	2,938	$p = 0.049$
Cumulative exposure (f/ml years)				
<10 f/ml years	302 (78)	2,161 (85)	2,463 (84)	
10 to <20 f/ml years	54 (14)	257 (10)	311 (11)	
20 to <30 f/ml years	16 (4)	82 (3)	98 (3)	
30 to <40 f/ml years	8 (2)	31 (1)	39 (1)	
40+ f/ml years	5 (1)	21 (1)	26 (1)	
Unknown	2 (0)	29 (1)	31 (1)	
Total	387	2,581	2,968	$p = 0.038$
Worker	84 (20)	332 (80)	416	
Resident	303 (12)	2,249 (88)	2,552	$p < 0.001$
Live with ABA worker[1]	219 (72)	1,462 (65)	1,681 (66)	$p = 0.012$
Wash clothes of ABA worker[1]	107 (35)	459 (20)	566 (22)	$p < 0.001$

[1]Residents only.

method was used. Sixty percent of residents returned a questionnaire in the early 1990s and 26% reported currently smoking compared with 20% in the Australian female population. Applying Axelson's adjustment attenuated the lung cancer SIR1 to 1.11 and SIR2 to 1.47. Former workers had greater SIRs for mesothelioma, all cancers, lung cancer and cervical cancer compared to former residents.

Including those cancers ($n = 36$) diagnosed before 1982 and their respective person years at risk attenuated SIR1 to 0.96 (95%CI 0.87–1.06) and SIR2 to 1.23 (95%CI 1.11–1.36) for all cancers among all women (not shown). For the period 1960 to 1981 SIR1 was 2.50 (95%CI 0.52–7.31) and SIR2 was 3.25 (95%CI 0.67–9.53) for ovarian cancer among former workers. Inclusion of these 3 ovarian cases increased the SIR1 for the period 1960–2005 to 1.25 (95%CI 0.34–3.21) and SIR2 to 1.73 (95%CI 0.47–4.43). All other SIRs were moderately attenuated if the cases diagnosed prior to 1982 were included.

Mesothelioma among workers and residents

There were 47 cases of malignant mesothelioma (46 pleural). The first woman was diagnosed in 1975 and the youngest was aged 27.5 years. The proportion of ABA workers with mesothelioma was double that of the residents 2.5% and 1% respectively. There was no significant difference in age of arrival ($p = 0.069$) at Wittenoom for workers or residents with mesothelioma or year of arrival ($p = 0.168$) although residents stayed longer at Wittenoom than workers ($p = 0.003$). The median length of stay at Wittenoom for a worker was 2.2 years (IQR 0.4–2.7 years) and for a resident 4.5 years (IQR1.9–6.4 years). Therefore cumulative asbestos exposure was significantly greater for residents, median 12.2 f/ml years (IQR 5.8–25.5 f/ml years), than for workers, median 3.6 f/ml years (IQR 0.89–14.4 f/ml years). There was no difference in the intensity of asbestos exposure between workers and residents who subsequently developed mesothelioma; workers median 1.7 f/ml (IQR 1.4–5.3 f/ml), compared with residents 3.1 f/ml (IQR 2.1–4.2 f/ml), although the exposure measurements were derived differently for workers and residents (see Methods section). The first case of mesothelioma in a worker occurred 24.6 years after first exposure to asbestos (e.g., arrival date in Wittenoom) and 23.5 years in a resident. The time from first exposure to onset of mesothelioma ranged from 23.5 years to 51.8 years (median 38 years) and was shorter for workers (median 34.1 years, IQR 27.1–38.6 years) than for residents (median 39.3 years, IQR 34.7–43.6 years). The incidence rate among workers appears to have peaked 30–39 years after first exposure, with only one case occurring more than 40 years after first exposure. For residents, peak incidence occurred after more than 40 years. At every 5-year period after 1975 the incidence rate was greater among workers than residents and appears to be still increasing (Table IV). The doubling of mesothelioma cases among the former workers and their shorter latency period compared to the residents suggests that the asbestos exposure measurement for the workers underestimates their actual exposure.

TABLE III – STANDARDIZED INCIDENCE RATIOS FOR MALIGNANT MESOTHELIOMA, 1960–2005 AND SPECIFIC CANCERS 1982–2005 FOR WOMEN FROM WITTENOOM

Cancer	ICDO-2 Code	Observed	SIR1[1] (95%CI)	SIR2[2] (95%CI)
All women				
1960–2005				
Malignant mesothelioma	C384, C481–C482 and M9050–M9055	47	55.9 (41.1–74.4)	77.0 (56.6–102.5)
1982–2005				
All cancers[3]	C000–C809	330	1.12 (1.00–1.25)	1.51 (1.35–1.68)
Lung, trachea and bronchus	C330–C349	45	1.84 (1.30–2.38)	2.54 (1.80–3.29)
Breast cancer	C500–C509	82	0.89 (0.69–1.08)	1.19 (0.93–1.44)
Ovarian cancer	C560–C569	10	0.98 (0.37–1.58)	1.30 (0.49–2.11)
Cervical cancer	C530–C539	12	1.13 (0.49–1.77)	1.42 (0.62–2.23)
Corpus uterine cancer	C540–C549	12	0.98 (0.43–1.54)	1.32 (0.58–2.07)
Colorectal cancer	C180–C209	31	0.76 (0.49–1.03)	1.03 (0.67–1.40)
Workers				
1960–2005				
Malignant mesothelioma	C384, C481–C482 and M9050–M9055	11	64.7 (32.3–116)	82.7 (41.3–148)
1982–2005				
All cancers[3]	C000–C809	65	1.13 (0.86–1.41)	1.66 (1.26–2.06)
Lung, trachea and bronchus	C330–C349	15	2.88 (1.42–4.34)	4.36 (2.15–6.57)
Breast cancer	C500–C509	13	0.78 (0.36–1.21)	1.11 (0.51–1.72)
Ovarian cancer	C560–C569	1	0.50 (0.01–2.80)	0.72 (0.02–4.01)
Cervical cancer	C530–C539	3	1.89 (0.39–5.51)	2.48 (0.51–7.25)
Corpus uterine cancer	C540–C549	2	0.81 (0.10–2.91)	1.16 (0.14–4.20)
Colorectal cancer	C180–C209	6	0.68 (0.14–1.22)	1.04 (0.21–1.87)
Residents				
1960–2005				
Malignant mesothelioma	C384, C481–C482 and M9050–M9055	36	52.9 (37.1–73.3)	76.6 (53.6–106)
1982–2005				
All cancers[3]	C000–C809	265	1.12 (0.99–1.26)	1.48 (1.30–1.66)
Lung, trachea and bronchus	C330–C349	30	1.57 (1.01–2.13)	2.09 (1.34–2.84)
Breast cancer	C500–C509	69	0.91 (0.69–1.12)	1.21 (0.92–1.49)
Ovarian cancer	C560–C569	9	1.11 (0.39–1.84)	1.43 (0.50–2.37)
Cervical cancer	C530–C539	9	1.01 (0.35–1.67)	1.23 (0.43–2.03)
Corpus uterine cancer	C540–C549	11	1.13 (0.46–1.79)	1.48 (0.61–2.36)
Colorectal cancer	C180–C209	25	0.78 (0.48–1.09)	1.03 (0.63–1.44)

[1]Minimum estimate—censored at earliest of: date of diagnosis, date of death, date aged 85 or end-date of state cancer registry follow-up.–[2]Maximum estimate censored at earliest of: date of diagnosis, date of death, date aged 85 or date last known to be alive.–[3]For women with multiple cancers—first diagnosed cancer included in this analysis.

TABLE IV – MALIGNANT MESOTHELIOMA INCIDENCE RATE, PER 100,000 PERSON YEARS, BY TIME SINCE FIRST EXPOSURE AND YEAR OF DIAGNOSIS AMONG THE WITTENOOM WOMEN

Time since first exposure	All women		Workers		Residents	
	Observed	Rate[1] (95% CI)	Observed	Rate[1] (95% CI)	Observed	Rate[1] (95% CI)
0–19 years	0	–	–	–	0	–
20–29 years	8	35 (17–70)	3	101 (33–314)	5	25 (10–60)
30–39 years	20	119 (77–184)	7	304 (145–637)	13	90 (52–154)
40+ years	19	256 (163–401)	1	114 (16–811)	18	275 (173–436)
Year of diagnosis						
1960–64	0	–	0	–	0	–
1965–69	0	–	0	–	0	–
1970–74	0	–	0	–	0	–
1975–79	3	24 (8–76)	1	63 (9–446)	2	19 (5–75)
1980–84	4	33 (12–88)	1	67 (9–476)	3	28 (9–88)
1985–89	5	42 (18–102)	1	71 (10–503)	4	39 (14–103)
1990–94	14	127 (75–214)	3	236 (76–733)	11	112 (62–203)
1995–99	8	84 (42–168)	1	94 (13–664)	7	83 (39–174)
2000–05	13	193 (112–332)	4	542 (203–1444)	9	150 (78–288)

[1]Women lost to follow up censored at date last known to be alive.

Exposure-response relationships—mesothelioma

The risk of mesothelioma stratified by worker and resident status and adjusted for time since first exposure and age, significantly increased with every unit increase in log fiber ml years (Table V). Among workers the risk increased 75% for every unit of log fiber ml year. For residents this risk was almost 3-fold. The risk of mesothelioma increased for those residents who had washed the clothes of OR = 1.68 (95%CI 0.66–4.29) or lived with OR = 2.57 (95%CI 0.96–6.84) an ABA asbestos worker (not shown).

Lung cancer

The risk of lung cancer stratified by worker and resident status and adjusted for time since first exposure and age increased with every unit of log fiber per ml years but not significantly. The risk of lung cancer increased in those residents who lived with an ABA worker OR = 2.61 (95%CI 1.09–6.21). There was no increase in lung cancer risk among those residents who washed the clothes of an ABA worker, OR = 1.14 (95%CI 0.46–2.81). Among the 55 cases of lung cancer, 14 were adenocarcinomas, 7

TABLE V – EXPOSURE-RESPONSE RELATIONSHIPS[1] BETWEEN CUMULATIVE ASBESTOS EXPOSURE, MALIGNANT MESOTHELIOMA ADJUSTED FOR AGE AND TIME SINCE FIRST EXPOSURE, AMONG ALL WITTENOOM WOMEN AND AMONG FORMER WORKERS AND RESIDENTS SEPARATELY

Cancer	Odds ratio (95%CI)	*p*-value
Workers		
Malignant mesothelioma 11 cases min 8 max 297 non cases		
Cumulative exposure log(f/ml years)	1.77 (1.11–2.82)	0.017
Cancer of the lung, trachea and bronchus 18 cases, min 3 max 283 non cases		
Cumulative exposure log(f/ml years)	1.25 (0.90–1.72)	0.179
Residents		
Malignant mesothelioma 36 cases, min 68 max 1,632 non cases		
Cumulative exposure log(f/ml years)	2.73 (1.94–3.82)	<0.001
Cancer of the lung, trachea and bronchus 37 cases, min 44 max 1,563 non cases		
Cumulative exposure log(f/ml years)	1.09 (0.83–1.41)	0.543

[1]Women lost to follow up censored at date last known to be alive.

squamous cell, 8 small cell, 3 large cell and 23 of indeterminate histology. Further examination of the adenocarcinomas showed non-significant increases in risk with quantitative measures of the intensity of asbestos exposure (f/ml) (OR = 1.87 95%CI 0.82–4.27), the length of stay at Wittenoom (OR = 1.07 95%CI 0.98–1.16) and cumulative asbestos exposure (f/ml years) (OR = 1.43 95%CI 0.92–2.24).

Discussion

The impact of exposure to blue asbestos on subsequent cancer incidence among the women of Wittenoom has been cruel. Although the time they spent at Wittenoom was short (median 1.3 years), 47 women developed mesothelioma. A further 55 women developed lung cancer. Compared with the Western Australian female population Wittenoom women had a significantly greater risk of all cancers, cancer of the lung, trachea and bronchus and malignant mesothelioma. There was a significant exposure-response relationship between asbestos exposure and malignant mesothelioma for both workers and residents, but not lung cancer.

Our findings are similar to those few studies that have looked at mortality outcomes in women exposed to asbestos in their workplace. World War II gas mask workers subsequently experienced high mortality from mesothelioma SMR = 111.5(95%CI 84.5–146.8), respiratory cancer SMR = 2.5(95%CI 1.7–3.5) and carcinomatosis SMR = 3.2 (95%CI 1.8–5.4) with evidence of increased risk related to duration of exposure.[8] Among a second group of gas mask workers in England rates were also increased for cancer of the lung and pleura SMR = 2.41 (95%CI 1.35–3.97) and cancer of the ovary SMR = 2.75 (95%CI 1.42–4.81) but exposure-response was not examined.[9]

Following up women for decades in cohort studies is difficult given the frequency of name changes due to marriage and divorce and the extent of migration over the period. This may explain why women are often excluded from such studies. We have used various means to reduce our loss to follow up; tracing on the electoral roll (voting is compulsory in Australia and the electoral roll is carefully maintained), searches of the electronic white pages and participation in a cancer prevention program.[16] Italian migrants to Wittenoom who subsequently returned to Italy have been traced in Italy, but this information relates to male ABA workers and not their wives or families.[29] Twenty two percent of the women were defined as lost to follow up most from the time they left Wittenoom. The difficulty maintaining follow-up on this cohort of women may have led to an underestimation of asbestos-related cancers.

We had only limited information on tobacco smoking in this cohort. Applying Axelson's adjustment to our lung cancer SIRs reduced them substantially, although for women workers the risk remains double that of the WA female population, and for all women there remains a 27% increase (SIR1). The high rates of smoking in this cohort probably increased the risk for all cancers reported among this cohort and may have increased cervical cancers among the women workers.[30] There is no association between tobacco smoking and risk of mesothelioma.

The mesothelioma incidence rates reported here (35–256 per 100,000 person-years) are among the highest for any known group of women in the world. The age standardized rate for Western Australian women in 2005 was 0.9 per 100,000.[31] Internationally; among women with environmental exposure in Casale Monferrato Italy, incidence rates of 2.3 to 5.1 per 100,000 person years were reported,[32] whilst Camus *et al.*, report incidence rates among women of 67.5 per million person years and 13.7 per million person years in the Thetford and Asbestos areas respectively of Quebec for the period 1970–1989.[33] For the period 1979–1990 incidence rates of 95.9 per million were reported for women in Manville, NJ, where the largest asbestos manufacturing plant in the United States was located.[34] The women at Wittenoom were exposed exclusively to crocidolite, whereas the women in the other studies were exposed primarily to chrysotile. The mesothelioma mortality rate reported for former gas mask workers exposed mostly to crocidolite for the period 1956–2003 was 138.1 per 100,000 person years,[8] which is between the rates for the Wittenoom residents and the ABA workers.

The duration of residence at Wittenoom was short. Forty five percent of women, cases and non cases, lived at Wittenoom for one year or less. Among those women who subsequently developed mesothelioma the median duration of residence was also short at 2 years for workers and 4.5 years for residents. Other asbestos exposed cohorts with high mortality and cancer incidence report short durations of exposure. Among female British gas mask workers (exposed to Wittenoom crocidolite) the duration of employment was also short with 35% employed for less than 6 months and only 4% employed for longer than 5 years. Those women employed for less than 1 year showed excess mortality from all cancers and lung cancers after 33 years of follow up.[7] Similarly for the largely male ABA miners and millers the median period of employment was brief at 4 months.[2] Possibly a short but intense exposure to asbestos is more harmful than a longer exposure at lower levels.

This study found that ABA workers had a greater risk for mesothelioma and lung cancer than residents. The exposure measurements for the workers and residents were derived using different types of data, which could be one possible explanation for this difference. Workers exposures were derived from one comprehensive dust survey undertaken in 1966 across various workplaces in the mine and mill.[20] Exposures for the residents were derived from this comprehensive survey as well as various other studies using personal monitors over the 1970s to early 1990s.[10] Using results from several surveys may have increased the possibility of measurement error, although it may also have allowed better measurement as more data was available therefore reducing the amount of interpolation between surveys over time. Any measurement error or bias is likely to be non differential because it would not differ with disease status. The effect of nondifferential misclassification on the asbestos mesothelioma association would be to attenuate

the results towards the null and so lessen the association shown for residents. Further, the asbestos exposure measurements are likely to be underestimates for the former worker women. Most women did not work in the mine or mill or even on the site of operations, but in the town. However where women did work onsite they tended to work in the company office which was located downstream of the mill. The fly screens in the office were covered with dust and words could be written on the fibers that settled on the desks. Women workers in the office were not offered the annual chest X-rays given to the miners and millers.[36] Those who worked in the hotel and shop in town were also in contact with workers who would enter in their dusty work clothes.

Examination of differences between women workers and residents with mesothelioma revealed no difference in their age of arrival at Wittenoom or their year of arrival. Residents tended to live at Wittenoom longer than workers. Of the 11 workers who developed mesothelioma only one had worked in the bagging room in the mill (probably the "dirtiest" area in terms of asbestos dust in Wittenoom); three others had worked as Clerks in the office, which was located within 1 km of the mill[36]; one worked in the Canteen (also near the mill), two worked as assistants in the Company shop in the town and two worked as Barmaids in the hotel in the town, and we had missing information for 3 women. Worker women may have also have had domestic exposure (most women were at Wittenoom with their husbands who were employed in the mine or mill) and we know that some of the Wittenoom women laundered other ABA workers' clothes (in an attempt to increase savings so that they could leave Wittenoom sooner).[37] Unfortunately we do not have information on domestic exposure among the female workers. We found that domestic exposure tended to increase the risk of malignant mesothelioma in the residents. Chrysotile samples taken from inside asbestos miners and millers houses in the United States ranged from a minimum of 50–100 ng/m^3 to a maximum between 2,000–5,000 ng/m^3.[38] If these figures are comparable to the levels that Wittenoom women were exposed to in their houses then it is not a large addition to their already high exposure obtained from their workplaces. A study among the wives of asbestos cement factory workers in Casale Monferrato, Italy reported excess mortality from cancer of the pleura SMR = 792 (95% CI 216–2,029) following only domestic exposure to asbestos. These women lived in the same township as the asbestos cement factory (as did the Wittenoom women) so it was not possible to disentangle the environmental and domestic exposure.[39] A meta-analysis examining domestic and neighborhood exposure and risk of pleural mesothelioma reported an RR = 8.1 (95%CI 5.3–12) for domestic exposure and RR = 7.0 (95%CI 4.7–11) for neighborhood exposure.[40]

This study found that the latency period between exposure to blue asbestos at Wittenoom and diagnosis with malignant mesothelioma in ABA workers was significantly shorter than that in residents and consequently the incidence rate in workers appears to have peaked earlier than that of the residents. We have earlier reported a longer latency period in Wittenoom residents compared with the Wittenoom (male) ABA workers.[15] A longer latency period is consistent with the lower risk for mesothelioma experienced by residents compared to workers. Metintas *et al.*, suggested that a higher level of asbestos exposure (as seen in occupational *vs.* environmental exposure) might shorten the latency time.[41]

The pattern of mesothelioma incidence rates in the women workers shows a different pattern to that of the male ABA workers. The first cases of mesothelioma among the male workers developed between 10 and 19 years since first exposure whereas for women this was 20–29 years. On the other hand the mortality rate for the male workers was of a similar magnitude to the women's incidence rate for the periods 20–29 years (115 per 100,000 person years) and 30–39 years (281 per 100,000 person years) since first exposure.[24] The rate among male workers continued to increase in those with 40 or more years since first exposure (364 per 100,000 person years) unlike the women worker's rate that appeared to decline among those with 40 or more years since first exposure. The median estimated cumulative exposure for male workers was 6.0 f/ml years compared to 0.5 f /ml years for women workers.[2] More than 600 women residents came to Wittenoom after the mine and mill closed in December 1966, when exposure levels in the town were substantially lower than during the period of mill operation. To the end of 2005 one of these has subsequently developed mesothelioma.

To date there have been no new cases of mesothelioma among women who were first exposed to asbestos more than 52 years ago. However this may change as the median time since first exposure was 37 years (IQR 27–44 years) as at the end of 2005. Among female gas mask workers exposed to crocidolite no cases of mesothelioma arose more than 51 years after first exposure[8] and among workers at the "Eternit" asbestos cement factor in Casale Monferrato, Italy latency of more than 50 years was associated with a reduced risk of mesothelioma, although with wide confidence intervals.[42] Similarly Musk *et al.*, found that the rate of mesothelioma appeared to level off after 50 years since first exposure in the Wittenoom workers.[43] This suggests that crocidolite fibers are eventually cleared from the mesothelium. Fiber clearance has been observed experiments in rats[44] and baboons.[45] Lung fiber counts at postmortem from female gas mask workers exposed to a high intensity but relatively short duration of crocidolite asbestos suggested a rate of clearance of ~15% per annum.[46] Longer follow up is necessary to determine if the risk of mesothelioma levels off or even decreases after 50 years have passed since first exposed to asbestos.

Conclusion

Forty years after the asbestos mine and mill at Wittenoom were closed, there is a high toll from cancer among the former female residents of the town and company workers. Women from Wittenoom have greater rates of mesothelioma and possibly lung cancer than women in the WA population. There was a significant exposure-response relationship with mesothelioma but not lung cancer. There were fewer cases of mesothelioma, a different pattern of incidence, lower asbestos exposure and no demonstrated exposure-response relationship for lung cancer among the women compared to the largely male ABA workers. These differences emphasize the importance of examining women and men separately, where possible, with regards to disease outcome.

Acknowledgements

The authors acknowledges Ms. Jan Sleith, Dr. Janice Hansen, Mr. Robin Mina, Ms. Nola Olsen, Emeritus Professor Geoffrey Berry, Dr. Tim Threlfall—Western Australian Cancer Registry, Dr. Jim Leigh, Australian Mesothelioma Registry and the reviewers for their comments. They also thank National Health and Medical Research Council, Jem Foundation.

References

1. Hobbs MS, Woodward SD, Murphy B, Musk AW, Elder JE. The incidence of pneumoconiosis, mesothelioma and other respiratory cancer in men engaged in mining and milling crocidolite in Western Australia. IARC Sci Publ 1980;30:615–25.
2. Armstrong BK, de Klerk NH, Musk AW, Hobbs MS. Mortality in miners and millers of crocidolite in Western Australia. Br J Ind Med 1988;45:5–13.
3. de Klerk N, Musk AW, Armstrong BK, Hobbs MST. Diseases in miners and millers of crocidolite from Wittenoom, Western Australia: A Further Follow-up to December 1986. Annl Occup Hyg 1994; 38(Suppl 1):647–655.
4. Blair A, Zahm SH, Silverman DT. Occupational cancer among women: research status and methodologic considerations. Am J Ind Med 1999;36:6–17.

5. Newhouse ML, Wagner JC. Validation of death certificates in asbestos workers. Br J Ind Med 1969;26:302–7.
6. Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933–80. Occup Environ Med 2000;57:782–5.
7. Wignall BK, Fox AJ. Mortality of female gas mask assemblers. Br J Ind Med 1982;39:34–8.
8. McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in 1940. Occup Environ Med 2006;63:852–5.
9. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med 1982;39:344–8.
10. Hansen J, de Klerk N, Musk A, Hobbs M. Individual exposure levels in people environmentally exposed to crocidolite. Appl Occup Environ Hyg 1997;12:485–90.
11. Hansen J, de Klerk NH, Eccles JL, Musk AW, Hobbs MS. Malignant mesothelioma after environmental exposure to blue asbestos. Int J Cancer 1993;54:578–81.
12. Graham L. Report of the select committee appointed to inquire into Wittenoom. Perth: Legislative Assembly of the Parliament of Western Australia, 1994.
13. Hansen J, de Klerk NH, Musk AW, Hobbs MS. Environmental exposure to crocidolite and mesothelioma: exposure-response relationships. Am J Respir Crit Care Med 1998;157:69–75.
14. Hansen J. Mortality and morbidity after environmental exposure to crocidolite (blue asbestos) at Wittenoom, Western Australia. Master of Public Health, University of Western Australia, Perth; 1995.
15. Reid A, Berry G, de Klerk N, Hansen J, Heyworth J, Ambrosini G, Fritschi L, Olsen N, Merler E, Musk AW. Age and sex differences in malignant mesothelioma after residential exposure to blue asbestos (crocidolite). Chest 2007;131:376–82.
16. Musk A, De Klerk NH, Ambrosini G, Eccles J, Hansen J, Olsen N, Watts V. Vitamin A cancer prevention I. Observations in workers previously exposed to asbestos at Wittenoom, Western Australia. Int J Cancer 1998;75:355–361.
17. Threlfall TJ, Thompson JR, Olsen N. Cancer in Western Australia: incidence and mortality 2003 and Mesothelioma 1960–2003. Department of Health, Perth, Western Australia. Report No.: Statistical series number 74, 2005.
18. Leigh J, Driscoll T, Hendrie L. The incidence of mesothelioma in Australia 1996 to 1998. Australian Mesothelioma Register Report 2001. Canberra: National Occupational Health and Safety Commission; 2001. Report No.: ISBN O-642-70989-0, 2001.
19. Percy C, Van Holten V, Muir C, eds. International classification of diseases for oncology, 2nd edn. Geneva: World Health Organization, 1990.
20. Major G. Asbestos dust exposure. In: Major G, ed. First Australian pneumoconiosis conference, 1968. Sydney: Joint Coal Board, 1968; 467–74.
21. de Klerk N, Musk A, Williams V, Filion P, Whitaker D, Shilkin K. Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoom Gorge, W. Australia. Am J Ind Med 1996;30:579–87.
22. de Klerk NH, Musk AW, Eccles JL, Hansen J, Hobbs MS. Exposure to crocidolite and the incidence of different histological types of lung cancer. Occup. Environ Med 1996;53:157–9.
23. de Klerk NH, Armstrong BK, Musk AW, Hobbs MS. Cancer mortality in relation to measures of occupational exposure to crocidolite at Wittenoom Gorge in Western Australia. Br J Ind Med 1989;46:529–36.
24. Berry G. Incidence of mesothelioma in former miners and millers of crocidolite at Wittenoom and in residents of the town. In: 17th International Symposium on Epidemiology in Occupational Health, 2004, Melbourne. Occup Environ Med 2004;e24.
25. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 2000;44:565–601.
26. StataCorp. StataCorp Stata Statistical Software: Release 9. In: college station. TX: StataCorp LP, 2005.
27. Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Ind Med 1988;13:105–18.
28. Checkoway H, Pearce N, Crawford-Brown DJ. Research methods in occupational epidemiology. New York: Oxford University Press, 1989.
29. Merler E, Ercolanelli M, de Klerk N. Identification and mortality of Italian emigrants returning to Italy after having worked in the crocidolite mines at Wittenoon Gorge, Western Australia. Epidemiol Prev 2000;24:255–61.
30. Syrjanen K, Shabalova I, Petrovichev N, Kozachenko V, Zakharova T, Pajanidi J, Podistov J, Chemeris G, Sozaeva L, Lipova E, Tsidaeva I, Ivanchenko O, et al. Smoking is an independent risk factor for oncogenic human papillomavirus (HPV) infections but not for high-grade CIN. Eur J Epidemiol 2007;22:723–35.
31. Threlfall TJ, Thompson JR, Olsen N (2005). Cancer in Western Australia: Incidence and mortality 2003 and Mesothelioma 1960–2003. Department of Health, Western Australia, Perth, Statistical series number 74.
32. Magnani C, Terracini B, Ivaldi C, Botta M, Mancini A, Andrion A. Pleural malignant mesothelioma and non-occupational exposure to asbestos in Casale Monferrato, Italy. Occup Environ Med 1995; 52:362–7.
33. Camus M, Siemiatycki J, Case BW, Desy M, Richardson L, Campbell S. Risk of mesothelioma among women living near chrysotile mines versus US EPA asbestos risk model: preliminary findings. Ann Occup Hyg 2002;46(Suppl 1):95–8.
34. Berry M. Mesothelioma incidence and community asbestos exposure. Environ Res 1997;75:34–40.
35. McCulloch J. Asbestos—its human cost. St. Lucia, Qld. Australia: University of Queensland Press, 1986.
36. Layman L. Work and workers' responses at Wittenoom 1943–1966. Commun Health Stud 1983;7:1–18.
37. Nicholson WJ, Rohl AN, Weisman I, Selikoff IJ. Environmental asbestos concentrations in the United States. IARC Sci Publ 1980;30:823–7.
38. Magnani C, Terracini B, Ivaldi C, Botta M, Budel P, Mancini A, Zanetti R. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. Br J Ind Med 1993;50:779–84.
39. Bourdes V, Boffetta P, Pisani P. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. Eur J Epidemiol 2000;16:411–7.
40. Metintas M, Ozdemir N, Hillerdal G, Ucgun I, Metintas S, Baykul C, Elbek O, Mutlu S, Kolsuz M. Environmental asbestos exposure and malignant pleural mesothelioma. Respir Med 1999;93:349–55.
41. Magnani C, Ferrante D, Barone Adesi F, Bertolotti M, Todesco A, Mirabelli D, Terracini B. Cancer risk after cessation of asbestos exposure. A cohort study of Italian asbestos cement workers. Occup Environ Med. 2007. doi:10.1136/oem.2007.032847.
42. Musk AW, de Klerk N. Epidemiology of malignant mesothelioma in Australia. In: Second Heidelberg Thoracic Oncology Symposium, 2002. Heidelberg, 2002.
43. Wagner JC, Berry G, Skidmore JW, Timbrell V. The effects of the inhalation of asbestos in rats. Br J Cancer 1974;29:252–69.
44. Rendall R, du Toit R. The retention and clearance of glass fibre and different varities of asbestos by the lung. Ann Occup Hyg 1994;38 (Suppl 1):757–61.
45. Berry G. Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. Inhal Toxicol 1999;11:111–30.

Cancer Epidemiology, Biomarkers & Prevention

Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-analysis

Alison Reid, Nick de Klerk and Arthur W. (Bill) Musk

Cancer Epidemiol Biomarkers Prev 2011;20:1287-1295. Published OnlineFirst May 24, 2011.

Published OnlineFirst May 24, 2011; DOI:10.1158/1055-9965.EPI-10-1302

Cancer Epidemiology, Biomarkers & Prevention

Review

Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-analysis

Alison Reid[1,2], Nick de Klerk[2,3], and Arthur W. (Bill) Musk[2,4]

Abstract

Introduction: The asbestos and ovarian cancer relationship is not well understood because of small numbers of women exposed to asbestos, small numbers of cases, and misclassification of peritoneal mesothelioma as ovarian cancer on death certificates. The aim of this study was to conduct a meta-analysis to quantify the evidence that exposure to asbestos causes ovarian cancer.

Methods: Fourteen cohort and two case-control studies were identified in Medline searches from 1950 to 2008.

Results: Statistically significant excess mortality was reported in four of the cohort studies, all of which determined their outcomes from the death certificate. Peritoneal mesotheliomas were reported in these studies, two of which reexamined pathology specimens and reported disease misclassification. Exposure-response relationships were inconsistent. When all studies were included in a meta-analysis, the effect size was 1.75 (95% CI, 1.45–2.10) attenuating to 1.29 (95% CI, 0.97–1.73) in studies with confirmed ovarian cancers.

Conclusion: Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. This result may have occurred because of disease misclassification. *Cancer Epidemiol Biomarkers Prev; 20(7); 1287–95.* ©*2011 AACR.*

Introduction

In May 2009, a summary of the latest assessment of the carcinogenicity of metals, arsenic, dusts, and fibers, including asbestos, by the International Agency for Research on Cancer (IARC) Monograph Working Group was published in the *Lancet Oncology* (1). For the first time, the evidence was declared sufficient in humans to show that exposure to asbestos causes cancer of the ovary (2). It has long been established that exposure to asbestos causes malignant mesothelioma, lung cancer, and asbestosis, as well as "benign" pleural diseases. Excess mortality and incidence of these diseases have been shown repeatedly in cohorts of occupationally exposed workers and exposure–response relationships have shown a clear causal relationship between asbestos exposure and mesothelioma, lung cancer, and asbestosis (3–6). However, the IARC Monograph that will provide the evidence supporting the sufficient ruling has not yet been published.

The relationship between asbestos exposure and ovarian cancer is not as well understood as that of asbestos-related diseases. Studies that have examined this issue have been limited for 2 major reasons:

1. Small numbers of cases: Much fewer women than men have been exposed to asbestos, particularly in more heavily exposed occupational settings where relative risks are higher. Although many women in epidemiologic studies have had domestic or general environmental exposure, levels have generally been relatively low so that risks and hence numbers of cases have also been few.
2. Difficulties with diagnosis: Many of the studies that have reported excess ovarian cancer following asbestos exposure have examined mortality from ovarian cancer and used the cause of death as listed on the death certificate to identify the cause of death. The accuracy of death certificates has been questioned repeatedly (7, 8), particularly in relation to asbestos-related diseases (9). Pleural mesothelioma has a long history of being misreported on death certificates most often being labeled as lung or pleural cancer (3, 9, 10). It has been particularly difficult to distinguish between peritoneal mesothelioma and ovarian serous carcinoma. Immunohistochemical tests to aid in the identification of mesothelioma cells became available in 1996–1997 with

Authors' Affiliations: [1]Centre for Medical Research, [2]School of Population Health, [3]Centre for Child Health Research, The University of Western Australia, Crawley, Perth; and [4]Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

Corresponding Author: Alison Reid, Centre for Medical Research, M519, The University of Western Australia, 35 Stirling Highway, Crawley, Perth 6009, Western Australia, Australia. Phone: 618-9346-7258; Fax: 618-9346-1818; E-mail: alison.reid@uwa.edu.au

doi: 10.1158/1055-9965.EPI-10-1302

the introduction of calretinin. Since then, many new markers have become available, although none of these are useful in distinguishing between ovarian cancer and peritoneal mesothelioma. A recent review of the value of immunohistochemistry to distinguish between peritoneal mesothelioma and serous carcinoma of the ovary and peritoneum concluded that "positive serous carcinoma markers, by and large, have a higher degree of sensitivity and specificity in assisting in discriminating between these malignancies than the positive mesothelioma markers. From a practical point of view, a combination of MOC-31 (or BER-EP4), estrogen receptors, and calretinin immunostaining should allow a clear distinction to be made between epithelioid peritoneal mesotheliomas and serous carcinomas in most cases (11)."

Accordingly, peritoneal mesothelioma has often been listed on the death certificate as stomach, colon, or ovarian cancer or carcinomatosis (9, 12–14).

However, there are biologically plausible reasons as to why exposure to asbestos may cause ovarian cancer. Asbestos fibers have been found in the ovaries of women who were exposed to asbestos in the Norwegian pulp and paper industry and also among women whose household contacts worked with asbestos (15, 16), although possible sample contamination cannot be ruled out. The mode of distribution of the fibers through the body following inhalation is not well understood. The fibers may migrate across the diaphragm through the peritoneal cavity and penetrate the ovaries. Animal studies have observed asbestos fibers within the cytoplasm of epithelial and interstitial cells within 24 hours after brief inhalation (17). Once fibers have entered the interstitium, they then have access to the vascular and lymphatic systems. Fibers in the lymphatic system can be channeled to the visceral pleura and subsequently to the pleural cavity. Mechanical irritation leading to fibrosis or to cancer, or "frustrated phagocytosis" (where the macrophage is damaged because it is unable to digest the whole asbestos fiber because of its length), thus leading to the production of hydroxyl radicals and reactive oxygen species that induce cell injury (18, 19), are 2 mechanisms by which the fibers may cause cancer once they reach the ovary. Experiments in which 10 g of tremolite mixed with 400 mL of water was injected intraperitoneally into mice, hamsters, guinea pigs, and rabbits showed that in 2 of 10 rabbits and 2 of 16 guinea pigs, the abnormality that developed in the epithelium of the ovary resembled lesions observed in early human ovarian cancers (20). "Overall, the available evidence in favor or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (21).

The aims of this study were (1) to review the epidemiologic studies that have reported effect estimates for ovarian cancer incidence or mortality in women following exposure to asbestos and (2) to conduct a meta-analysis of those studies to quantify whether that exposure to asbestos causes ovarian cancer.

Methods

Studies were identified through a systematic review of the literature available on MEDLINE from 1950 to December 2008. The database was searched using combinations of the search terms "women" or "females" or "girls" and "asbestos" or "fibres" or "dust" or "crocidolite" or "chrysotile" or "amosite" or "occupational exposure" or "environmental exposure" or "household exposure" or "neighbourhood exposure" or "residential exposure" or "locational exposure" or "domestic exposure" or "familial exposure" or "exposure" with one of the following outcomes "cancer" or "mortality" or "death" or "neoplasms" or "ovarian cancer." Any cohort or case–control study that examined women and asbestos exposure and was published in English was included. Studies were also identified from references listed in published articles. Case reports were not included.

Summary effect estimates were examined using the *metan* suite of commands in Stata 10.1 (22, 23). Models that assumed that the study populations were all relatively homogenous (fixed effects) and models that assumed that the true exposure-related risks in each study vary randomly (random effects) were examined and both are reported. All studies described in Table 1 were included in the meta-analysis. Expected deaths [based on the number of observed deaths and the standardized mortality ratios (SMR)] and 95% Confidence Intervals (95% CI) were calculated for the study of Polish women diagnosed with asbestosis, which did not include them in their published article (24). Forest plots were produced automatically as part of the *metan* suite of commands in Stata 10.1.

Results

Fourteen cohort (3, 12, 24–34) and 2 case–control (35, 36) studies of women exposed to asbestos in their jobs or from their general environment and that examined ovarian cancer incidence or mortality as an outcome were identified from the literature (Table 1). Four of the cohort studies had been reported on several times over their years of follow-up: In each case, only the latest report is shown in the table and included in the meta-analysis (3, 12, 26, 28).

Generally, the number of cases of ovarian cancer reported in the cohort studies was small, ranging from 1 case [among Polish women diagnosed with asbestosis (24) and Turin textile workers (29)] to 12 cases reported among Leyland crocidolite gas mask workers (25). However, 5,072 cancer cases were reported among the whole Finnish female working population born between 1906 and 1945 in which exposure to asbestos was determined from a job exposure matrix (33). The case–control studies had more cases than the cohort studies: 69 cases reported

Published OnlineFirst May 24, 2011; DOI:10.1158/1055-9965.EPI-10-1302

Table 1. Cohort and case–control studies of women exposed occupationally or environmentally to asbestos that examine ovarian cancer mortality or incidence as an outcome

Study	Author (ref)	Publication year	Number of women exposed	Type of asbestos exposure	Period of follow-up	Peritoneal mesothelioma cases (*n*)	Pleural mesothelioma cases (*n*)	Ovarian cancer cases (*n*)	SMR (95% CI)	Ovarian cancers confirmed
Cohort studies										
Leyland gas mask workers	Acheson et al. (25)	1982	757	Crocidolite	1951–1980	2	15[a] (5)	12	2.75 (1.42–4.81)	No
Blackburn gas mask workers	Acheson et al. (25)	1982	570	Chrysotile	1951–1980	0	7[a] (1)	5	1.48 (0.48–3.44)	No
Employees on central register, Germany	Rosler et al. (32)	1994	616	Chrysotile and crocidolite	1977–1988	4	9	2	1.09[b] (0.13–3.95)	No
Italian women compensated for asbestosis	Germani et al. (27)	1999	631	Chrysotile and crocidolite	1980–1997	12	14	9	4.77 (2.18–9.06)	No
Population of Finnish female workers	Vasama-Neuvonen et al. (33)	1999	892,591 (born between 1906 and 1945)	Not stated	1971–1995	N/A	N/A	5,072	SIR = 1.3 (0.9–1.8)[e]	Yes
East London asbestos factory workers	Berry et al. (3)	2000	700	Crocidolite and chrysotile	1951–1980	11	14	9	2.53 (1.16–4.80)	Yes—earlier report (13)
Polish women diagnosed with asbestosis	Szeszenia-Dabrowska et al. (24)	2002	490	Not stated	1970–1999	0	3[d]	1	0.79	No
Turin asbestos textile factory workers	Mamo et al. (29)	2004	645	Chrysotile	1981–1995	0	10	1	1.28 (0.02–7.12)	No
Polish asbestos cement products factory workers	Wilczynska et al. (34)	2005	1,470	Not stated	1945–1999	0	3	8	1.76 (0.76–3.47)	No
		6	3.76[f] (1.38–8.18)							
Italian asbestos textile workers	Pira et al. (30)	2005	1,077	Mixed with crocidolite	1946–1996	9[c]	11[d]	5	2.61 (0.85–6.09)	No

(Continued on the following page)

Published OnlineFirst May 24, 2011; DOI:10.1158/1055-9965.EPI-10-1302

Table 1. Cohort and case–control studies of women exposed occupationally or environmentally to asbestos that examine ovarian cancer mortality or incidence as an outcome (Cont'd)

Study	Author (ref)	Publication year	Number of women exposed	Type of asbestos exposure	Period of follow-up	Peritoneal mesothelioma cases (*n*)	Pleural mesothelioma cases (*n*)	Ovarian cancer cases (*n*)	SMR (95% CI)	Ovarian cancers confirmed
Nottingham gas mask workers	McDonald et al. (12)	2006	1,154	Crocidolite	1940–2002	18	47	10	1.8 (0.9–3.3)	Yes–earlier report (14)
Italian asbestos cement factory workers	Magnani et al. (28)	2007	777	Chrysotile and crocidolite	1965–2003	16[c]	39[d]	9	2.27 (1.04–4.32)	Yes
Italian wives of asbestos factory workers	Ferrante et al. (26)	2007	1,780	Chrysotile and crocidolite	1965–2003	3[c]	21[d]	11	1.42 (0.71–2.54)	No
Wittenoom women	Reid et al. (31)	2009	2,968	Crocidolite	1982–2006	1	46	11	SIR = 1.27 (0.52–2.02)	Yes
Case–control studies										
Johns Hopkins Hospital patients[g]	Rosenblatt et al. (36)	1992	77 cases 46 controls	Not stated	1981–1985	N/A	N/A	69 18	1.3 (0.3–3.6) respiratory exposure 2.8 (0.9–8.8) relatives exposed to fibers	Yes
Norwegian pulp and paper workers (nested case–control study)	Langseth et al. (35)	2004	46 cases 184 controls	Not stated	1953–1999	N/A	N/A	6	2.02 (0.72–5.66)	Yes

[a]Lung and pleural cancers combined (number of mesotheliomas listed on death certificates in this cohort).
[b]Standardized proportionate mortality ratio.
[c]Peritoneal cancers.
[d]Pleural cancers.
[e]Medium/high exposure.
[f]Among women who worked in asbestos yarn and cloth production areas (high exposure).
[g]Fibers include asbestos, talc, and fiberglass.

Published OnlineFirst May 24, 2011; DOI:10.1158/1055-9965.EPI-10-1302

some respiratory exposure to asbestos and 18 cases reported relatives with occupational asbestos exposure among participants of the Johns Hopkins study. Among Norwegian pulp and paper mill workers, there were 6 cases who had worked in areas where they were likely to have been exposed to asbestos.

Statistically significant excess mortality or incidence of cancer of the ovary was reported in 4 of the 14 cohort studies. SMRs and their 95% CIs in these 4 studies ranged from 4.77 (95% CI, 2.18–9.06) to 2.27 (95% CI, 1.04–4.32; refs. 3, 25, 27, 28). Of the remaining 10 cohort studies, 5 reported a tendency to excess mortality, although SMR estimates were unstable, ranging from 2.61 (95% CI, 0.85–6.09) to 1.42 (95% CI, 0.71–2.54). Women who worked in asbestos yarn and cloth production in a Polish asbestos cement products factory had a statistically significant excess mortality from ovarian cancer [SMR = 3.76 (95% CI, 1.38–8.18)], although the association was not significant over all the female factory workers (12, 25, 26, 30, 34). Five studies reported ovarian cancer incidence or mortality around the same population as their reference populations (24, 29, 31–33). Both case–control studies reported a nonsignificant excess incidence with asbestos exposure. Women with relatives with occupational asbestos exposure reported a nonsignificant but 3-fold risk of ovarian cancer, although the overall risk for all women in that study was close to unity (35, 36).

The type of asbestos to which the women were exposed was crocidolite (blue asbestos—the most mesotheliogenic of the asbestos fibers; ref.37) only in 3 cohorts (12, 25, 31), chrysotile (white asbestos) only in 2 (25, 29), chrysotile and crocidolite in 5 cohorts (3, 26–28, 32), mixed fibers including crocidolite in 1 cohort (30), and 4 studies (including the 2 case–control studies) did not report the fiber type (24, 34–36). The remaining study of economically active Finnish women born between 1906 and 1945 had their probability of asbestos exposure determined on the basis of their job titles, as reported in the 1970 census and a job exposure matrix (the FINJEM; ref. 38): the types of asbestos were not distinguished, although anthophyllite was mined and widely used throughout Finland (39). Four of the studies that reported a significant excess risk of ovarian cancer reported exposure to crocidolite or chrysotile and crocidolite.

Small numbers of cases or lack of exposure information inhibited the examination of exposure–response relationships and mortality or incidence of ovarian cancer. Nevertheless, 3 studies (3, 14, 28) examined SMRs by category of exposure (low/medium/high), duration of employment (years), or latency (time between first exposure to asbestos and onset of disease), and 1 examined ovarian cancer incidence and quantitative asbestos exposure characteristics by using a nested case–control design and conditional logistic regression (31). Among East London factory workers, there was a significant overall excess of ovarian cancers, but when examined by category and duration of exposure, the trend was not significant ($P = 0.18$). However, the excess was significant among women who had "severe" exposure for more than 2 years (3). A nonstatistically significant exposure trend with duration of exposure was observed among Italian factory workers; 0 cases: <1 year, SMR = 2.4, 1–4 years; 0 cases: 5–9 years, SMR = 2.7, 10–19 years; SMR = 2.8, 20–29 years; and SMR = 2.9, ≥30 years (28). Exposure–response relationships were examined in an earlier report of the Nottingham gas mask workers. Mortality from ovarian cancer was higher among women exposed for more than 1 year [observed/expected (O/E) 3/0.95] than among those exposed for less than 1 year (O/E 2/1.13; ref. 14). Several quantitative measures of asbestos exposure, including intensity (f/mL), duration of employment or residence, and time since first exposure, were not associated with the incidence of ovarian cancer among the Wittenoom women (31).

Twelve of the cohort studies listed in Table 1 examined mortality from ovarian cancer and relied on the cause of death as listed on the death certificate. In addition, cases of peritoneal mesothelioma were observed in 8 of these studies, suggesting that misclassification of peritoneal mesothelioma as ovarian cancer may have occurred.

Cases of peritoneal mesothelioma were reported in 4 of the studies that reported a statistically significant excess mortality from ovarian cancer (3, 25, 27, 28). Two of these studies attempted to confirm the diagnosis of ovarian cancer pathologically. Among East London factory workers, ovarian cancer was confirmed in 2 cases with material available (from a total of 4 ovarian cancers up to 1968; ref.13). Two cases listed as carcinomatosis were confirmed as ovarian cancers, and 1 case listed as ovarian cancer was determined to be a peritoneal mesothelioma (13). The latest follow-up to 1980 reported 9 cases of ovarian cancer, but it is not clear how many of these were confirmed histologically (3). Among Italian asbestos cement workers, 7 of 9 cases were confirmed as ovarian cancers (28). Three cohort studies reported a statistically significant excess rate of ovarian cancer but did not reexamine ovarian cancer pathology specimens. One of these (Italian women compensated for asbestosis; ref. 27) had more cases of peritoneal mesothelioma than ovarian cancer, suggesting that misclassification may have occurred. Among Leyland gas mask workers exposed to crocidolite, there were 2 cases of peritoneal mesothelioma and 12 cases of ovarian cancer. The authors suggested that ovarian cancers might have been peritoneal mesotheliomas misclassified (25). There were no reported cases of peritoneal mesothelioma among Polish asbestos cement products factory workers compared with 8 cases of ovarian cancer (34). Misclassification of disease is important to the internal validity of these studies, as with small numbers of cases of ovarian cancer, any misclassification could overestimate (or underestimate) the reported association with asbestos exposure.

Five studies that did not find a statistically significant excess rate of ovarian cancer reexamined ovarian cancer pathology where available. In an earlier report on the Nottingham crocidolite gas mask workers, of 6 ovarian cancer deaths, 2 were confirmed as ovarian cancers and 1

Published OnlineFirst May 24, 2011; DOI:10.1158/1055-9965.EPI-10-1302

was determined to be a peritoneal mesothelioma. Material was not available on the other 3 cases (14). The latest report of this cohort by McDonald and colleagues could not further review ovarian cancer pathology as only cause of death codes were available (12). Among the Wittenoom women, specimens from 9 cases of ovarian cancer were available for reexamination from a total of 16 cases. All 9 cases were confirmed as ovarian cancers (31). Similarly, all cases of ovarian cancer were confirmed among Finnish women defined as exposed to asbestos from a job exposure matrix as well as the 2 case–control studies (33, 35, 36).

Confounding and independent risk factors for ovarian cancer have not been addressed well in most studies, predominantly because they have been retrospective studies of occupational cohorts and limited data on potential confounders were available. Only 3 of the studies (the 2 case–control studies and the cohort of economically active Finnish women) assessed any of the following variables: age at menarche or menopause, late first pregnancy and age at first delivery, use of oral contraceptives, or tubal ligation, all known to be independent risk factors for ovarian cancer. Although few studies have collected data on these other risk factors, this may not have influenced the findings significantly, as they are unlikely to be associated with asbestos exposure and therefore are not likely to confound any association.

Loss to follow-up was a significant problem for 3 studies; all reporting more than 20% loss to follow-up (3, 31), with the highest reporting 33% (12). In an attempt to overcome this loss, one of the studies stopped accruing person-years at risk for those lost to follow-up from the date they were last known to be alive, thus underestimating person-years at risk and overestimating the SMR (31). Berry and colleagues did not state how they censored those lost to follow-up (3), but in an earlier report, Newhouse and colleagues censored those lost to follow-up on their last date of employment, so underestimating person years at risk and thus overestimating the SMR (13). McDonald and colleagues presented 2 sets of results, 1 for the complete cohort and 1 for a subset with more complete follow-up. SMRs were slightly larger among the more complete subset than those for the whole cohort (12). High loss to follow-up may over- or underestimate the risk of disease following exposure to asbestos, depending on the type of censoring method used to account for the loss to follow-up.

The meta-analysis that examined all studies showed a 75% excess risk of ovarian cancer in women who had been exposed to asbestos (Table 2). The effect size was similar between the models that assumed no heterogeneity between the studies (fixed effects) and those that assumed the exposure-related risks differed randomly between the studies (random effects). Figure 1 shows the corresponding forest plot for both the fixed- and random-effects models for all studies combined. The analyses were repeated for all cohort studies only and case–control studies only and similar effects were observed, although the effect was not statistically significant in the case–control studies (Table 2). When only those studies that confirmed their ovarian cancer pathology were included in a meta-analysis, the effect estimate declined, although remained statistically significant. The effect declined again and was not statistically significant when those studies that examined cancer incidence were included in a meta-analysis. These 4 studies did not rely on cause of death information from the death certificates to classify their cases.

A meta-analysis conducted on 9 of the cohort studies (12, 24, 26–31, 34) that also reported SMRs and 95% CIs (or provided enough information so that they could be calculated) for mesothelioma gave a fixed-effects size of 70.9

Table 2. Summary statistics for asbestos exposure and incidence or mortality from ovarian cancer

	Number of studies	Number of cases	Fixed-effects size (95% CI)	Random-effects size (95% CI)	Heterogeneity, χ^2	Heterogeneity, degrees of freedom	Heterogeneity, *P*
All studies combined	16	5,240	1.75 (1.45–2.10)	1.80 (1.45–2.24)	17.91	15	0.268
Cohort studies only	14	5,165	1.75 (1.45–2.12)	1.83 (1.44–2.33)	17.61	13	0.173
Case–control studies only	2	75	1.69 (0.76–3.73)	1.69 (0.76–3.73)	0.29	1	0.593
All studies that reviewed ovarian pathology	7	5,186	1.54 (1.22–1.95)	1.54 (1.22–1.95)	5.72	6	0.455
Cohort studies that reviewed ovarian pathology	5	5,102	1.53 (1.20–1.95)	1.59 (1.17–2.15)	5.38	4	0.251
Studies that examined cancer incidence	4	5,158	1.29 (0.97–1.73)	1.29 (0.97–1.73)	1.08	3	0.781

Published OnlineFirst May 24, 2011; DOI:10.1158/1055-9965.EPI-10-1302

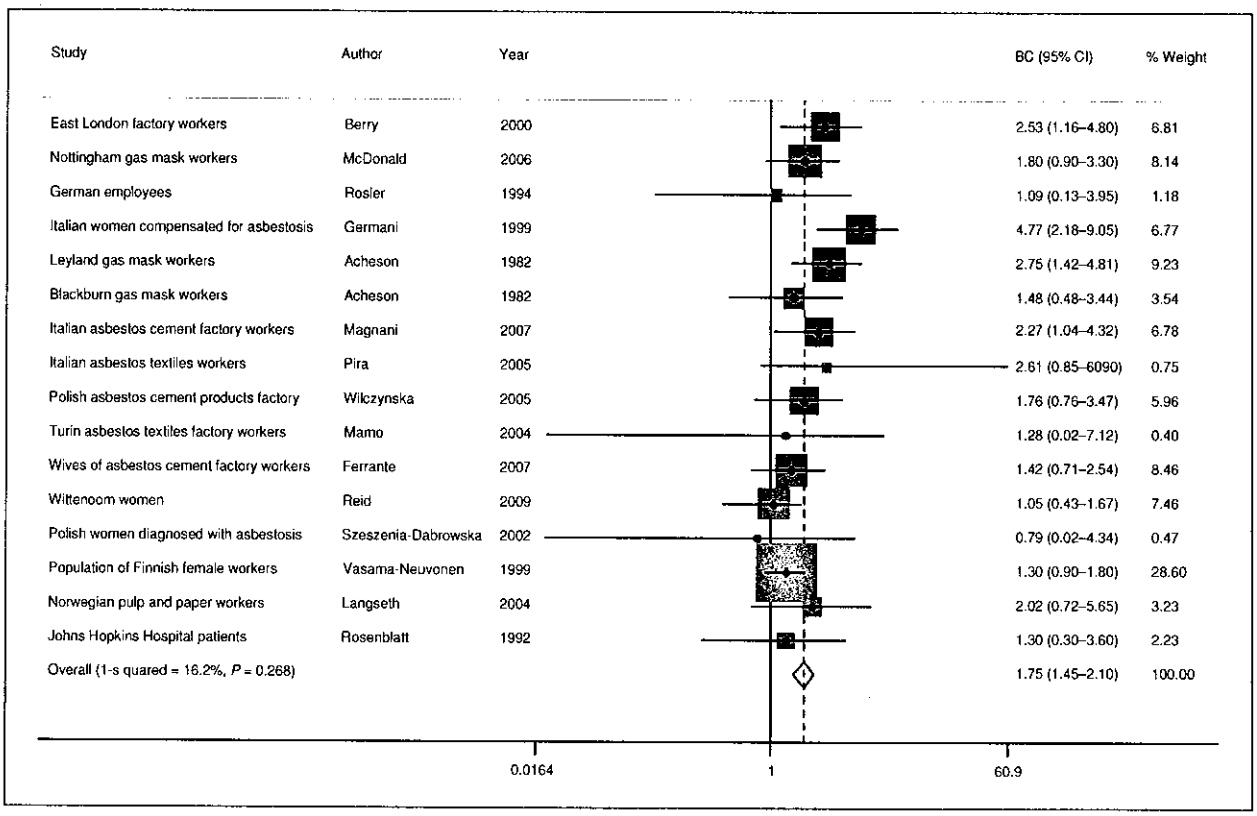

Figure 1. Forest plot of fixed summary effect for ovarian cancer and asbestos exposure.

(95% CI, 61.4–82.0) and random-effects size of 63.2 (95% CI, 41.9–95.3; data not shown). Figure 2 shows the relationship between standardized mortality or incidence ratios for mesothelioma and ovarian cancer for the 9 cohort studies that examined both mesothelioma and ovarian cancer included in the mesothelioma meta-analysis. There is clearly no relationship between the two. When the exposure is sufficient to have caused mesothelioma, there is no corresponding increased risk in ovarian cancer.

Discussion

Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. This result was obtained when all studies were included in the meta-analysis and again when only those studies that had reexamined ovarian cancer pathology were included. Only the meta-analysis of those studies that reported ovarian cancer incidence (i.e., those studies that did not rely on cause of death certification to classify their cases of ovarian cancer) did not observe a significant excess risk.

In the studies that did not examine ovarian cancer pathology, or confirmed cases of mesothelioma from a cancer or mesothelioma registry, misclassification of the cause of death in some cases is likely to have occurred, given that misclassification was reported in those studies that did reexamine cancer pathology specimens. Misclassification may result in an underestimate of peritoneal mesothelioma and an overestimate of ovarian cancer or the converse. Among women, peritoneal mesothelioma may be more likely to be classified as ovarian, colon, or stomach cancer, rather than a rare occupational cancer. The cohort study referred to in the *Lancet* summarizing the IARC reclassification (women gas mask workers) did not reexamine pathology (25). An examination of cancer

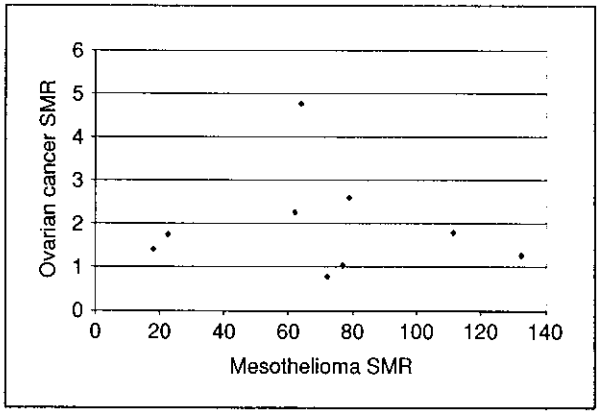

Figure 2. Relationship between mesothelioma and ovarian cancer-standardized mortality ratios for 9 cohort studies presented in Table 1 (3–6, 9, 27, 28, 31, 36)

incidence (and its use of cancer registration rather than death certification for disease outcome data) may have produced different results. Notably, the meta-analysis on the 2 case–control and 2 cohort studies that examined ovarian cancer incidence did not report a statistically significant excess risk of ovarian cancer.

The IARC makes its determinations of cancer causality (if an observed association between an exposure and a disease is causal) by using Bradford Hill's suggested hierarchy of criteria (40, 41). The first of these was the strength of the association. In this review, the greatest risk of ovarian cancer was observed among Italian women compensated for asbestosis. Their risk was almost 5-fold compared with their reference population (SMR = 4.77). However, their SMR for peritoneal mesothelioma was 40.9 and for pleural mesothelioma was 64.0, between 8 and 13 times larger than that observed for ovarian cancer (27). The effect size from the meta-analysis for ovarian cancer ranged from 1.29 among those studies that examined cancer incidence to 1.85 for all cohort studies. The effect size for mesothelioma was 70.9 (95% CI, 61.4–82.0). Clearly, the effect size for mesothelioma, a disease known to be caused by exposure to asbestos, is much larger than that for ovarian cancer. Also, if there was misclassification of mesothelioma and ovarian cancer, then some relationship between the 2 SMRs shown in Figure 2 is likely to have been observed. Similarly, if there was an exposure–response relationship, then some relationship between the SMRs should have been observed. Another explanation for the lack of correlation between mesothelioma and ovarian cancer SMRs is that asbestos exposure does not cause ovarian cancer.

Hill's second criterion for causality was consistency—that the observed association been repeated in different people, places, and times (40). The present study has shown that 4 of 14 cohort studies reported a statistically significant excess rate for ovarian cancer among women exposed to asbestos. Of the remaining 10 studies, 5 reported a tendency to excess but failed to reach statistical significance and 5 reported rates that were similar to those of their reference populations. Strong evidence of consistency was not observed among these studies, although no study reported any protective effect.

Also included in Hill's criteria for causation was biological gradient or demonstration of an exposure–response relationship (40). In the studies presented in this article, examination of exposure–response relationships was limited because of the small numbers of cases of ovarian cancer. Most of the studies were limited by small numbers of women both in terms of the number of women exposed to asbestos and the subsequent small numbers of ovarian cancers. However, where exposure–response relationships were examined, they were inconsistent. No study showed a statistically significant trend of ovarian cancer with degree of asbestos exposure. In addition, there was no evidence of a significant trend across studies as grouped exposure increased (see Fig. 2).

Other Hill's criteria are temporality (which is met because disease follows exposure) and specificity (which Hill largely discounts: It is known that asbestos causes more than one disease). Plausibility, coherence, and analogy are all satisfied, and experiment is not really applicable.

Conclusion

Taken without further analysis, women thought to have ovarian cancer had an increased rate in the meta-analysis if reporting having been exposed to asbestos, compared with reference populations. However, this finding may result from the methods used to identify the ovarian cancer cases. Where disease outcome was identified from the cause of death as listed on the death certificate, given the small numbers of ovarian cancer cases in each study, even misclassification of 1 cancer may exert a large impact on the exposure effect. The meta-analysis of those studies that examined ovarian cancer as determined on the death certificate reported an excess risk. In contrast, no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases were ascertained from a cancer registry. The IARC Monograph that contains the evidence supporting its sufficient ruling that asbestos exposure causes ovarian cancer is not yet in the public domain. However, the authors of this article suggest that the IARC decision to determine asbestos exposure as a cause of ovarian cancer was premature and not wholly supported by the evidence. Meta-analysis techniques cannot account or adjust for the quality of the data contained in the original studies that are used in the meta-analysis. If the original data contain errors of classification, then errors are built into the meta-analysis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank Jan Sleith, Nola Olsen, Robin Mina, National Health and Medical Research Council, and JEM Foundation.

Received December 14, 2010; revised May 4, 2011; accepted May 6, 2011; published OnlineFirst May 24, 2011.

References

1. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens—part C: metals, arsenic, dusts, and fibres. Lancet Oncol 2009;10:453–4.

2. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs. IARC Monographs Supplement 7. Lyon, France: International Agency for Research on Cancer; 1987.

3. Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933–80. Occup Environ Med 2000;57:782–5.
4. de Klerk NH, Musk AW, Eccles JL, Hansen J, Hobbs MS. Exposure to crocidolite and the incidence of different histological types of lung cancer. Occup Environ Med 1996;53:157–9.
5. Dement JM, Brown DP, Okun A. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. Am J Ind Med 1994;26:431–47.
6. Peto J, Seidman H, Selikoff IJ. Mesothelioma mortality in asbestos workers: implications for models of carcinogenesis and risk assessment. Br J Cancer 1982;45:124–35.
7. Sington JD, Cottrell BJ. Analysis of the sensitivity of death certificates in 440 hospital deaths: a comparison with necropsy findings. J Clin Pathol 2002;55:499–502.
8. Maclaine GD, Macarthur EB, Heathcote CR. A comparison of death certificates and autopsies in the Australian Capital Territory. Med J Aust 1992;156:462–3, 6–8.
9. Newhouse ML, Wagner JC. Validation of death certificates in asbestos workers. Br J Ind Med 1969;26:302–7.
10. Reid A, Heyworth J, de Klerk N, Musk AW. The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. Occup Environ Med 2008;65:743–9.
11. Ordonez NG. Value of immunohistochemistry in distinguishing peritoneal mesothelioma from serous carcinoma of the ovary and peritoneum: a review and update. Adv Anat Pathol 2006;13:16–25.
12. McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in 1940. Occup Environ Med 2006;63:852–5.
13. Newhouse ML, Berry G, Wagner JC, Turok ME. A study of the mortality of female asbestos workers. Br J Ind Med 1972;29:134–41.
14. Wignall BK, Fox AJ. Mortality of female gas mask assemblers. Br J Ind Med 1982;39:34–8.
15. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. Am J Ind Med 1996;29:435–9.
16. Langseth H, Johansen BV, Nesland JM, Kjaerheim K. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. Int J Gynecol Cancer 2007;17:44–9.
17. Roggli VL, Brody AR. Experimental models of asbestos-related diseases. In:Roggli VL, Greenberg SD, Pratt PC, editors. Pathology of asbestos-associated diseases. Boston, MA: Little Brown & Company; 1992. p. 257–98.
18. Shukla A, Gulumian M, Hei TK, Kamp D, Rahman Q, Mossman BT. Multiple roles of oxidants in the pathogenesis of asbestos-induced diseases. Free Radic Biol Med 2003;34:1117–29.
19. Manning CB, Vallyathan V, Mossman BT. Diseases caused by asbestos: mechanisms of injury and disease development. Int Immunopharmacol 2002;2:191–200.
20. Graham J, Graham R. Ovarian cancer and asbestos. Environ Res 1967;1:115–28.
21. Kane AB. Mechanisms of mineral fibre carcinogenesis. IARC Sci Publ 1996:11–34.
22. Stata Corp. Stata Statistical Software: Release 10. College Station, TX: Stata Corp LP; 2007.
23. Sterne JAC, Newton HJ, Cox NJ, editors. Meta-analysis in Stata: an updated collection from the Stata Journal. College Station, TX: Stata Press; 2009.
24. Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A. Mortality study of workers compensated for asbestosis in Poland, 1970–1997. Int J Occup Med Environ Health 2002;15:267–78.
25. Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br J Ind Med 1982;39:344–8.
26. Ferrante D, Bertolotti M, Todesco A, Mirabelli D, Terracini B, Magnani C. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. Environ Health Perspect 2007;115:1401–5.
27. Germani D, Belli S, Bruno C, Grignoli M, Nesti M, Pirastu R, et al. Cohort mortality study of women compensated for asbestosis in Italy. Am J Ind Med 1999;36:129–34.
28. Magnani C, Ferrante D, Barone Adesi F, Bertolotti M, Todesco A, Mirabelli D, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. Occup Environ Med 2008;65:164–70.
29. Mamo C, Costa G. Mortality experience in an historical cohort of chrysotile asbestos textile workers. 2004[cited 2008 May 1]. Available from:http://www.livingframemedia.co.uk/cag/gac2004/english/ws_E_03_e.pdf.
30. Pira E, Pelucchi C, Buffoni L, Palmas A, Turbiglio M, Negri E, et al. Cancer mortality in a cohort of asbestos textile workers. Br J Cancer 2005;92:580–6.
31. Reid A, Segal A, Heyworth JS, de Klerk NH, Musk AW. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom.Cancer Epidemiol Biomarkers Prev 2009;18:140–7.
32. Rosler JA, Woitowitz HJ, Lange HJ, Woitowitz RH, Ulm K, Rodelsperger K. Mortality rates in a female cohort following asbestos exposure in Germany. J Occup Med 1994;36:889–93.
33. Vasama-Neuvonen K, Pukkala E, Paakkulainen H, Mutanen P, Weiderpass E, Boffetta P, et al. Ovarian cancer and occupational exposures in Finland. Am J Ind Med 1999;36:83–9.
34. Wilczynska U, Szymczak W, Szeszenia-Dabrowska N. Mortality from malignant neoplasms among workers of an asbestos processing plant in Poland: results of prolonged observation. Int J Occup Med Environ Health 2005;18:313–26.
35. Langseth H, Kjaerheim K. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. Scand J Work Environ Health 2004;30:356–61.
36. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol 1992;45:20–5.
37. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 2000;44:565–601.
38. Kauppinen T, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. Am J Ind Med 1998;33:409–17.
39. Meurman LO, Pukkala E, Hakama M. Incidence of cancer among anthophyllite asbestos miners in Finland. Occup Environ Med 1994;51:421–5.
40. Hill AB. The environment and disease: association or causation?Proc R Soc Med 1965;58:295–300.
41. International Agency for Research on Cancer. Preamble to the IARC Monographs. B. Scientific review and evaluation. 2006[cited 2010 Feb 4]. Available from:http://monographs.iarc.fr/ENG/preamble/currentb2studies/humans0706.php.

Ann. Occup. Hyg., pp. 1–9

doi:10.1093/annhyg/meq089

The effect of smoking on the risk of lung cancer mortality for asbestos workers in Great Britain (1971–2005)

GILLIAN FROST[1]*, ANDREW DARNTON[2] and ANNE-HELEN HARDING[1]

[1]*Health and Safety Laboratory, Mathematical Sciences Unit, Harpur Hill, Buxton, Derbyshire SK17 9JN, UK;* [2]*Health and Safety Executive, Redgrave Court, Epidemiology Unit, Bootle, Merseyside L20 7HS, UK*

Received 6 July 2010; in final form 11 October 2010

Objectives: Workers in the asbestos industry tend to have high smoking rates compared to the general population. Both asbestos exposure and cigarette smoking are recognized risk factors for lung cancer mortality, but the exact nature of the interaction between the two remains uncertain. The aim of this study was to examine the effect of smoking and smoking cessation among asbestos workers in Great Britain (GB) and investigate the interaction between asbestos exposure and smoking. Methods: The study population consisted of 98 912 asbestos workers recruited into the GB Asbestos Survey from 1971, followed-up to December 2005. Poisson regression was used to estimate relative risks of lung cancer mortality associated with smoking habits of the asbestos workers and to assess whether these effects differed within various categories of asbestos exposure. The interaction between asbestos exposure and smoking was examined using the Synergy (*S*) and Multiplicativity (*V*) indices, which test the hypotheses of additive and multiplicative interaction, respectively. The proportion of lung cancers among smokers attributable to the interaction of asbestos and smoking was also estimated. Results: During 1 780 233 person-years of follow-up, there were 1878 deaths from lung cancer (12% of all deaths). Risk of lung cancer mortality increased with packs smoked per day, smoking duration, and total smoke exposure (pack-years). Asbestos workers who stopped smoking remained at increased risk of lung cancer mortality up to 40 years after smoking cessation compared to asbestos workers who never smoked. The effects of smoking and stopping smoking did not differ by duration of asbestos exposure, main occupation, age at first asbestos exposure, year of first exposure, or latency period. The interaction between asbestos exposure and smoking for asbestos workers was greater than additive [*S* 1.4, 95% confidence interval (CI) 1.2–1.6], and the multiplicative hypothesis could not be rejected (*V* 0.9, 95% CI 0.3–2.4). For those asbestos workers who smoked, an estimated 26% (95% CI 14–38%) of lung cancer deaths were attributable to the interaction of asbestos and smoking. Conclusions: This study emphasizes the importance of smoking prevention and cessation among those who work in the asbestos industry.

Keywords: Great Britain; lung cancer mortality; occupational asbestos exposure; smoking; smoking cessation

INTRODUCTION

Smoking tobacco is the major determinant of lung cancer and accounts for ~90% of all cases (Quinn *et al.*, 2001). The relationship between smoking and lung cancer is well documented (Doll and Peto, 1978; Doll *et al.*, 2004; IARC, 2004), along with the benefits of smoking cessation (US DHHS, 1990; Peto *et al.*, 2000). Asbestos is also an important lung carcinogen, accounting for an estimated 2–3% of lung cancer deaths in Britain during 1980–2000 (Darnton *et al.*, 2006). However, the combined effect of asbestos exposure and smoking on lung cancer

*Author to whom correspondence should be addressed.
Tel: +44 (0) 1298-218317; fax: +44 (0) 1298-218840;
e-mail: gillian.frost@hsl.gov.uk

risk remains uncertain despite many studies of asbestos exposed groups. Most studies have focused on two hypotheses: whether the combined effect of asbestos and smoking is additive (each factor acts independently) or multiplicative (the effect of asbestos exposure on lung cancer risk is proportional to the effect of smoking) (Doll and Peto, 1985; Hammond *et al.*, 1979; Lee, 2001). However, some recent reviews have suggested that while there is some interaction between the factors (their combined effect is more than additive), its extent is less than multiplicative (Liddell, 2001; Berry and Liddell, 2004). Furthermore, of the many studies of asbestos-exposed cohorts that have now been reported, few have examined the association between lung cancer risk and more specific smoking habits such as intensity and duration (Liddell and Armstrong, 2002) and smoking cessation in combination with asbestos exposure (de Klerk *et al.*, 1991; Reid *et al.*, 2006).

The Great Britain (GB) Asbestos Survey was established in 1971 by the Health and Safety Executive to monitor the long-term health of asbestos workers. The survey comprises a large cohort of asbestos-exposed workers from the former asbestos product manufacturing industry and, more recently, workers in the asbestos removal industry. The objective of this study was to examine lung cancer mortality risk associated with smoking and smoking cessation among asbestos workers and also to examine the interaction between exposure to asbestos and smoking on lung cancer mortality risk.

METHODS

The cohort includes all asbestos workers in GB who have had medical examinations because of regular work with asbestos. The British Medical Association Research Ethics Committee gave approval for the survey. Participants were initially recruited on a voluntary basis into the GB Asbestos Survey, which was established in 1971 to monitor mortality among workers in the asbestos products manufacturing industry. The cohort was expanded to include those working with insulation (application or removal) who were required to undergo statutory medicals under the Asbestos Licensing Regulations 1983 and later to all those exposed to asbestos above the specified 'action limit' as required by the Control of Asbestos at Work Regulations 1987. Medical examinations were carried out at 2-yearly intervals during the period over which they were working with asbestos (Harding *et al.*, 2009).

At each medical examination, workers completed the survey questionnaire, which recorded personal details, date of first occupational exposure to asbestos, current employment details, and smoking history. Details collected about smoking habits included current smoking habit (whether a current, former, or non-smoker), the number of cigarettes smoked per day, and the age started smoking if a current or former smoker, and the age stopped smoking if a former smoker. Data collected at follow-up medical examinations were used to update smoking status and job details.

Survey participants were flagged for death registrations at the National Health Service Central Register (NHSCR) for England and Wales or the General Register Office for Scotland (GROS). Deaths were also identified through the GB mesothelioma register (McElvenny *et al.*, 2005).

Statistical methods

Poisson regression was used to estimate relative risks (RRs) of lung cancer mortality among the asbestos workers. Deaths occurring until December 2005 were included in the analyses. The dependent variable was the number of deaths, with the person-years at risk as offset variable. Person-years were calculated from the date of first medical examination (entry into the study) as the starting date and the date of death, loss to follow-up (for example, emigration from GB), or the end of the study period, whichever occurred first, as the ending date.

RRs were estimated for smoking-related variables with adjustment for age (5-year classes, 40–75+ years), calendar period (5-year periods, 1980–2000+), sex, and proxy measures of asbestos exposure. Main occupation (manufacturing, insulation work, removal work, or 'other' exposed work) and length of occupational exposure to asbestos (three categories: <10, 10–29, 30+ years) were used as proxies for type of asbestos exposure and cumulative exposure, respectively. The covariates of interest were smoking status, age started smoking, smoking intensity (packs smoked per day), smoking duration, total smoke exposure (pack-years), age stopped smoking, and time since smoking cessation. Length of occupational exposure to asbestos, smoking duration, pack-years of exposure, and time since smoking cessation were considered time-dependent covariates.

The number of cigarettes smoked per day was taken as the average recorded over all of the participants' examinations for former smokers. For current smokers, the number of cigarettes smoked per day could vary from one examination to the next, and the number recorded at their final examination was assumed to apply to the end of follow-up. For the purpose of the analyses packs per day were used,

where one pack was equivalent to 20 cigarettes. For current smokers, smoking duration was calculated from the age started smoking to current age, age at death, loss to follow-up, or end of follow-up and for former smokers, age started smoking to current age or age stopped smoking. Total smoke exposure (pack-years) was computed as the product of the number of packs smoked per day and smoking duration. For former smokers, the time since smoking cessation was calculated from the age stopped smoking to current age, age at death, loss to follow-up, or end of follow-up. All variables were entered as a series of indicator variables and used never-smokers as the reference category.

Harding *et al.* (2009) demonstrated that, among the GB asbestos workers, length of asbestos exposure, main occupation, age at first exposure, year of first exposure, and latency (time since first exposure) were statistically significantly associated with lung cancer mortality. These variables were therefore used to assess whether the effects of smoking varied with asbestos exposure. Both duration of exposure and main occupation were categorized as above. Age at first exposure (<20, 20–39, 40+ years), year of first exposure (pre-1950, 1950–1969, post-1969), and latency (<20, 20–39, 40+ years) were also considered categorical variables with latency as a time-dependent covariate. The basic model for the interaction analysis included age, calendar period, sex, main occupation, and duration of exposure as before but also included total smoke exposure (pack-years) in order to adjust for potential differences in smoking exposure. The interaction between each smoking variable and each asbestos exposure variable was entered into the model (including the main effects) one at a time, and the *P*-value of the interaction was assessed using the Wald test. Hommel's procedure (Wright, 1992) was used to adjust *P*-values for the large number of tests performed ($n = 35$). Only interactions that were statistically significant (adjusted $P \leq 0.05$) would be investigated further.

The nature of the joint effect of smoking and asbestos exposure on lung cancer mortality was investigated using two indices for interaction effects: the Synergy (S) and Multiplicativity (V) indices (Rothman, 1976; Lee, 2001). The index S is given by $(R_{AS} - R_0)/(R_A + R_S - 2R_0)$ (Rothman, 1976) and V by R_0R_{AS}/R_AR_S (Lee, 2001), where R_A is the risk of lung cancer mortality for never-smokers exposed to asbestos, R_S is the risk for current smokers not exposed to asbestos, and R_{AS} is the risk for current smokers exposed to asbestos, each relative to the risk for never-smokers not exposed to asbestos ($R_0 = 1$).

A value of S greater than one indicates some degree of interaction between smoking and asbestos exposure on lung cancer mortality (which could include a multiplicative effect), with a value of S equal to one indicating no interaction (i.e. the effect of the two factors on risk is additive). The second index V is the reciprocal of the relative asbestos effect (RAE), a term first used by Berry *et al.* (1985) to describe the ratio of the RR due to asbestos exposure in non-smokers to that in smokers. The index V was used in this study due to its more intuitive interpretation than the RAE: a value of V greater than one corresponds to an interaction that is more than multiplicative, V less than one corresponding to less than multiplicative (including no interaction at all), and equal to one indicates a multiplicative interaction.

A reference group of workers unexposed to asbestos could not be identified within the cohort and so indices were calculated based on comparisons of risks for those classified as having 'low' asbestos exposure versus those with 'high' asbestos exposure for never and current smokers. Workers were assigned to the low or high asbestos exposure categories based on the length of occupational asbestos exposure. Low exposure was classed as <10 years of occupational exposure and high exposure as 30+ years of exposure.

Poisson regression was used to estimate the lung cancer risks R_0, R_A, R_S, and R_{AS} with adjustment made for age, calendar period, sex, and main occupation. The 95% confidence intervals (CIs) for S were obtained using the delta method to form CIs for $\ln(S)$ and exponentiating the limits (Hosmer and Lemeshow, 1992; Rongling and Chambless, 2007). CIs for V were calculated assuming the RR estimate is log-normally distributed (Lee, 2001).

Sensitivity analysis was carried out to investigate whether the results were affected by choice of categories for low and high asbestos exposure. Other categories considered included <3 years for low and 40+ years for high asbestos exposure, <5 years and 35+ years, and <7 years and 30+ years. In order to increase the number of cases in the never-smoker categories, the possibility of including former smokers with never-smokers was also investigated. Also assessed was the use of an alternative definition of low and high asbestos exposure that was not based on the duration of exposure. Harding *et al.* (2009) found that those employed in insulation work had the greatest risk of mesothelioma mortality and those in manufacturing had the lowest. Using this as a marker for asbestos exposure, the synergy and multiplicativity indices were again estimated but using employment in the manufacturing industry

as low asbestos exposure and employment in the insulation industry as high.

The RRs estimated from the above model (R_0, R_A, R_S, and R_{AS}) were also used to estimate the proportion of deaths attributable to asbestos exposure, smoking, and the interaction of the two among asbestos workers who were current or never-smokers, using the methods of Lee (2001). CIs were calculated from the variance of the attributable fraction estimated using the delta method (Hosmer and Lemeshow, 1992; Rongling and Chambless, 2007). All analyses were carried out in Stata 10 (StataCorp, 2007).

RESULTS

Altogether 98 912 asbestos workers were followed-up for a total of 1 780 233 person-years between 1971 and 2005. This differs from what was previously reported (Harding *et al.*, 2009) because the database has since been updated with further survey questionnaires and death notifications relevant to the study period. Ninety-eight per cent of workers were traced for follow-up with the NHSCR and GROS. By the end of 2005, there had been 15 553 deaths in the study population, with lung cancer accounting for 12% (n = 1,878) of all deaths. Ninety-five per cent of participants were males and >50% were smokers at the time of the last medical examination. A majority of workers (56%) reported asbestos removal work as their main occupation during the study, and experienced, on average, 11 years of occupational exposure to asbestos (Table 1). On average, both current and former smokers started to smoke while in their teens and smoked around one packet of cigarettes a day. Participants who were current smokers at the time of their last examination had been smoking for an average of 35 years and former smokers reported smoking for ~17 years. On average, former smokers stopped smoking at 35 years of age and, by the end of follow-up, had ceased smoking for ~25 years (Table 2).

After adjustment for age, calendar period, sex, main occupation, and length of occupational exposure to asbestos, both current and former smokers had statistically significantly elevated risks of lung cancer mortality compared to never-smokers (RR 14.7, 95% CI 10.5–20.6 and RR 4.6, 95% CI 3.3–6.6, respectively; Fig. 1). Starting to smoke at any age statistically significantly increased the risk of lung cancer mortality compared to never-smokers (Fig. 1), with starting to smoke before 16 years of age associated with the greatest risk (RR 13.7, 95% CI 9.7–19.4). The risk of lung cancer mortality initially increased with the number of cigarette packs smoked per day but levelled out at two or more packets a day (Fig. 1). There was a strong dose–response relationship, with the risk of lung cancer mortality increasing with both smoking duration and total smoke exposure (Fig. 1). Among former smokers, the risk of lung cancer mortality was lowest for those who had stopped smoking before 30 years of age (Fig. 1) but remained statistically significantly higher than never-smokers (RR 1.8, 95% CI 1.01–3.2). There was an inverse relationship between time since smoking cessation and lung cancer mortality risk (Fig. 1). The risk for former smokers who had stopped smoking for 40+ years was not statistically significantly different to that of never-smokers (RR 1.5, 95% CI 0.8–2.8). The interaction analysis did not reveal any interactions that were statistically significant at the 5% level (all adjusted $P > 0.70$; results not shown).

Table 3 shows the results of the Poisson regression subdividing the asbestos workers by smoking status

Table 1. Characteristics of the GB asbestos workers (1971–2005)

Characteristic	
Number of individuals	98 912
Person-years at risk	1 780 233
All deaths (lung cancers)	15 553 (1878)
Males	95%
Current smokers at last exam	53%
Main occupation	
Manufacturing	30%
Insulation work	5%
Removal work	56%
Other	9%
Exposure length, mean (SD), years	11 (11)
Age at first exposure, mean (SD), years	30 (11)

SD, standard deviation.

Table 2. Smoking habits of the GB asbestos workers, by smoking status at the last medical examination (1971–2005)

Characteristic	Smoking status	
	Current	Former
Age started smoking, years	17 (4)	18 (4)
Average packs smoked per day	0.9 (0.4)	0.9 (0.6)
Smoking duration, years	35 (15)	17 (12)
Total smoke exposure, pack-years	30 (22)	18 (18)
Age stopped smoking, years	—	35 (12)
Years since smoking cessation	—	25 (12)

Data are means, with standard deviations in parentheses.

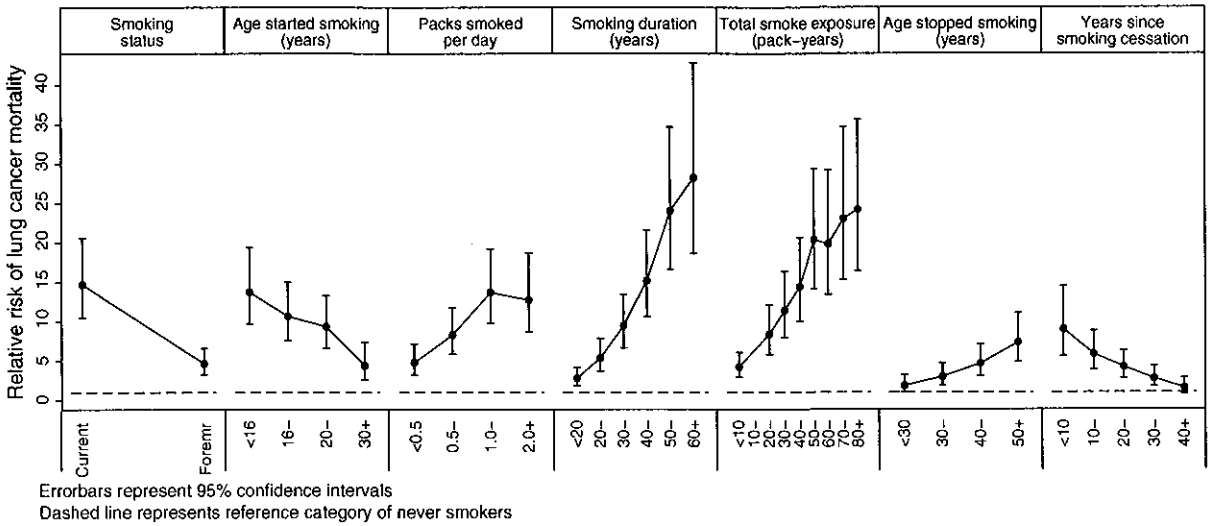

Fig. 1. RR of lung cancer mortality for GB asbestos workers adjusted for age, calendar period, sex, main occupation, and length of occupational exposure to asbestos (1971–2005).

Table 3. Synergy and multiplicativity indices for GB asbestos workers (1971–2005)

Smoking status	Asbestos exposure	Label	Deaths	Person-years	RR	(95% CI)
Never	Low	R_0	8	280 812	1.0	
	Medium	—	19	127 484	1.9	(0.8–4.3)
	High	R_A	8	23 686	1.6	(0.6–4.2)
Former	Low	—	61	156 892	5.6	(2.7–11.7)***
	Medium	—	125	143 494	6.5	(3.2–13.3)***
	High	—	116	48 028	9.7	(4.7–20.0)***
Current	Low	R_S	473	581 497	18.8	(9.4–37.9)***
	Medium	—	636	257 181	22.7	(11.3–45.6)***
	High	R_{AS}	322	50 590	26.2	(13.0–53.1)***
Synergy index (S)					1.4	(1.2–1.6)***
Multiplicativity index (V)					0.9	(0.3–2.4)

RRs adjusted for age, calendar period, sex, and main occupation using Poisson regression; low, <10 years occupational exposure to asbestos; medium, 10–29 years occupational exposure to asbestos; high, ≥30 years occupational exposure to asbestos.
***Significant at $P \leq 0.001$.

and duration of asbestos exposure and the corresponding synergy (S) and multiplicativity (V) indices. Although the risk of mortality from lung cancer for never-smokers with high exposure was greater than never-smokers with low exposure, this was not statistically significant (RR 1.6, 95% CI 0.6–4.2). Index S was statistically significantly >1, providing evidence against the additive hypothesis of no interaction between smoking and asbestos exposure (S 1.4, 95% CI 1.2–1.6). Index V was <1, but this was not a statistically significant difference and so the multiplicative hypothesis could not be rejected (V 0.9, 95% CI 0.3–2.4).

The use of different low and high asbestos exposure categories did not greatly affect results (data not shown). For all categorizations, never-smokers with high asbestos exposure had greater risk of lung cancer mortality compared to never-smokers with low asbestos exposure, but this was never a statistically significant result. For the synergy index, the results led to the same conclusion in all cases, except when using the most extreme categorization of low and high asbestos exposure (<3 years versus 40+ years duration), where S was not statistically significantly different to unity. In all cases, the multiplicativity index was not statistically significantly different to unity. As discussed above, this study found that the risk of lung cancer mortality was not statistically significantly different to never-smokers for those who had stopped smoking for

Table 4. Percentage attributable risks from smoking and asbestos exposure among GB asbestos workers (1971–2005)

Smoking status	Asbestos exposure	Deaths	Person-years	% Attributable to			
				Background	Asbestos only	Smoking only	Both factors
Never	Low	8	280 812	100%[a]	—	—	—
	High	8	23 686	63%[b] (1–125%)	37%[c] (−25 to 99%)	—	—
Current	Low	473	581 497	5%[d] (2–9%)	—	95%[e] (91–98%)	—
	High	322	50 590	4%[f] (1–7%)	2%[g] (−3 to 7%)	68%[h] (57–79%)	26%[i] (14–38%)

Calculated using RRs adjusted for age, calendar period, sex, and main occupation (R_0, R_A, R_S, and R_{AS}, Table 3); Values in parentheses show 95% CIs; low, <10 years occupational exposure to asbestos; high, ≥30 years occupational exposure to asbestos.
[a]Assumed to be 100%.
[b]$1/R_A$.
[c]$(R_A - 1)/R_A$.
[d]$1/R_S$.
[e]$(R_S - 1)/R_S$
[f]$1/R_{AS}$.
[g]$(R_A - 1)/R_{AS}$.
[h]$(R_S - 1)/R_{AS}$.
[i]$(1 - R_A - R_S + R_{AS})/R_{AS}$, formulae from Lee (2001).

≥40 years. Therefore, in order to increase the number of cases in the never-smoker categories, these former smokers were included with the never-smokers and the analysis repeated. The estimates of the two indices were again similar to those presented here (results not shown). When using occupation to define low and high asbestos exposure (manufacturing and insulation industries, respectively), never-smokers with high asbestos exposure had greater risk of lung cancer mortality compared to never-smokers with low asbestos exposure, but again this was not a statistically significant result (RR 2.0, 95% CI 0.8–5.0). Both the synergy and multiplicativity indices were similar to those obtained when duration was used to classify asbestos exposure (*S* 1.7, 95% CI 1.4–2.1; *V* 0.9, 95% CI 0.4–2.3).

Table 4 shows the percentage of lung cancer deaths attributable to asbestos and smoking among asbestos workers who were never and current smokers, which were calculated using the RRs from Table 3. For those exposed to both smoking and asbestos, an estimated 26% (95% CI 14–38%) of lung cancer deaths were attributable to the interaction between asbestos and smoking. Among this group, there were more deaths attributable to smoking only than asbestos exposure only (68% versus 2%). Consequently, the estimated fraction of lung cancer deaths prevented if workers had not smoked (risk attributable to smoking in the presence of asbestos) was 94% (=26% + 68%); the estimated fraction of lung cancer deaths prevented if workers had not been exposed to asbestos (risk attributable to asbestos in the presence of smoking) was 28% (=26% + 2%); and the fraction of lung cancer deaths prevented if neither exposure had occurred (risk attributable to the combined effect of asbestos and smoking) was 96% (=26% + 68% + 2%) among asbestos workers who smoked.

DISCUSSION

The GB Asbestos Survey is an important study set up to monitor the long-term health and mortality of workers occupationally exposed to asbestos. Since 1971, it has been successful in recruiting and following a large number of these workers and continues to do so today. The survey not only collects personal details and information regarding occupational exposure to asbestos but also asks questions about current smoking habits. Few asbestos studies have detailed information on the smoking habits of asbestos workers, but this study enabled a detailed examination into the effect of smoking and smoking cessation on lung cancer mortality risk among asbestos workers in GB and also an investigation into the interaction between exposure to asbestos and smoking on lung cancer mortality risk.

One limitation of the survey is the lack of detailed exposure measurements and information about the type of asbestos fibres. There is evidence that different forms of asbestos pose different health risks. A review published in 2000 (Hodgson and Darnton, 2000) suggested that the risk differential between the carcinogenic potency of chrysotile and amphibole fibres for lung cancer was between 1:10 and 1:50. A recent meta-analysis by Berman and Crump (2008a) investigated differences in carcinogenic potency of chrysotile and amphibole asbestos, incorporating the effect

of fibre size. They estimated that chrysotile was less potent than amphibole asbestos for lung cancer by factors ranging between 6 and 60. There was also an indication that the relative potency of chrysotile to amphibole asbestos varied with fibre size; hypotheses that the two fibre types are equally potent were rejected for the two metrics based on thin fibres (widths <0.4 or <0.2 μm), but not rejected for the metrics based on larger fibres (widths >0.2 μm) (Berman and Crump, 2008a). Workers employed in different sectors of the asbestos industry were likely to come into contact with different forms of asbestos. Variations in risk by occupation are therefore likely to reflect, to some extent, differences in the type of asbestos workers were exposed to. Therefore, this study used main occupation as a proxy for the type of asbestos exposure.

Cumulative exposure is also related to lung cancer risk, displaying an increase in risk with increasing exposure (Boffetta, 1998; Henderson *et al.*, 2004). Although length of occupational exposure was used as a proxy for cumulative exposure in this study, this would not necessarily account for variations in intensity of asbestos exposure.

Lung cancer is the most common cancer (Quinn *et al.*, 2001) and also the most common cause of death from cancer (WHO, 2009), in the world. In England and Wales in 2005, lung cancer was the second and third most common cancer for males and females, respectively (ONS, 2008) and accounted for ~5% of all deaths (ONS, 2006). However, lung cancer accounted for 12% of all deaths among the GB asbestos workers. This difference is, in part, due to the smoking habits of the asbestos workers, with a large proportion (53%) of the participants being current smokers at the time of their final examination. Throughout the study period, the proportion of current smokers among the asbestos workers was greater than that in the national population, where just 45% of persons aged ≥ 16 were current smokers in 1974, dropping to a minimum of ~28% in the 1990s (Walker *et al.*, 2002) and 24% in England in 2005 (Goddard, 2008).

The analysis of the smoking habits of the asbestos workers showed that lung cancer risk was greatest among those who smoked the most cigarettes over the longest period of time and also for those with greatest total smoking exposure. These results mirror those from investigations into smoking without asbestos exposure (Doll and Peto, 1978; Zang and Wynder, 1992; Lubin and Caporaso, 2006). Starting to smoke at an early age also increased the risk of lung cancer mortality for asbestos workers. It has been suggested that young smokers may be more susceptible to smoking-related DNA damage (Wiencke *et al.*, 1999).

Smoking cessation has major and immediate health benefits. Stopping smoking at any age reduces the risk of lung cancer mortality compared with continued smoking (Doll *et al.*, 1994), and the greater the length of time since smoking cessation, the greater the benefit (Rogot and Murray, 1980; Peto *et al.*, 2000). A reduced risk of lung cancer is usually evident within 5 years of cessation, but convergence towards the lung cancer rates of those who have never smoked for former smokers has not been consistently observed (US DHHS, 1990). For workers of the crocidolite mine and mill at Wittenoom, de Klerk *et al.* (1991) and Reid *et al.* (2006) reported a convergence to near never smoking rates of lung cancer incidence among those who had stopped smoking for ≥ 10 years (OR 1.30, 95% CI 0.25–6.90) and ≥ 20 years (OR 1.9, 95% CI 0.5–7.2), respectively. These values are much less than found in this study, where convergence was not seen until ≥ 40 years after smoking cessation (RR 1.6, 95% CI 0.9–2.9), and this rate of decline did not vary by duration of asbestos exposure or occupation type.

From an asbestos workers' perspective, smoking cessation represents the most practical and effective means of promoting good health. Changing occupation may not be a viable option for many workers, but also there is conflicting evidence as to the effect of removal from asbestos exposure. Many studies have reported a decline in the risk of lung cancer after removal from asbestos exposure (Walker, 1984), but some studies continue to find that the risk of lung cancer does not decrease after removal of exposure (Jarvholm and Sanden, 1998) or even that it initially increases after removal (Pira *et al.*, 2005). A recent review of the mathematical models used in the US Environmental Protection Agency health assessment document for asbestos found no convincing evidence against the assumption that the RR of lung cancer remains constant after 10 years from last exposure (Berman and Crump, 2008b). However, it is important to note that even if the risk of lung cancer does not decrease following cessation of asbestos exposure, removal from exposure would prevent an increase in cumulative dosage.

Synergy and multiplicativity indices were used to test for additive and multiplicative interaction (respectively) between asbestos exposure and smoking. There was no control group of workers unexposed to asbestos in this study, and so current and never-smokers were subdivided into low and high exposure according to the length of occupational exposure to asbestos. Using these categories, the synergy index was statistically significantly >1 (S 1.4, 95% CI 1.2–1.6), providing evidence against the additive hypothesis of no interaction. The multiplicativity index

was not statistically significantly different to 1 (*V* 0.9, 95% CI 0.3–2.4), and so the multiplicative hypothesis could not be rejected. These results were consistent when the durations used in defining low and high asbestos exposure were altered and also when the division was made based on occupation.

The results of this study indicated that there was some level of interaction between asbestos exposure and smoking and that the multiplicative hypothesis could not be rejected. This is consistent with a recent meta-analysis by Wraith and Mengersen (2007), which combined separate indices to obtain an overall estimate of 1.70 (95% credible interval 1.09–2.67) for the synergy index and 0.86 (95% credible interval 0.52–1.41) for the multiplicativity index. However, another review using similar literature found evidence that, on average, the interaction between smoking and asbestos exposure was less than multiplicative with a 'best estimate' of the average RAE of 2.04 (95% CI 1.28–3.25), which corresponds to a multiplicativity index of 0.49 (95% CI 0.31–0.78) (Liddell, 2001).

The attributable proportion due to the interaction between smoking and asbestos is very closely related to the value of the synergy index. This study estimated that among asbestos workers who smoked, ~26% (95% CI 14–38%) of lung cancer deaths were attributable to the interaction between asbestos and smoking. This was generally slightly lower than the estimates found in the literature, although it appears to be statistically consistent. The estimate of the attributable proportion corresponding to the synergy index obtained by Wraith and Mengersen (2007) was 41% (95% credible interval 8–63%). Erren *et al.* (1999) calculated a weighted average synergy index across 12 studies of 1.64 (95% CI 1.33–2.03), which corresponded to an estimated attributable proportion of 33% (95% CI 22–45%). Also, Lee (2001) found a mean attributable proportion of 36% (no CI given) for seven cohort studies that did not use external comparisons. The differences between the attributable proportion due to interaction found in this study to those in the literature could be due to the use of low versus high asbestos exposure rather than unexposed versus exposed. This could lead to the estimated attributable proportion of lung cancer due to 'background' risk being greater than perhaps it should be, and therefore reducing the attributable proportion due to asbestos only, smoking only, and the interaction of the two. That is, if a comparison group was used that was truly unexposed, then the attributable proportion due to asbestos among never-smokers would probably have been >37%.

CONCLUSIONS

The GB asbestos workers have a greater proportion of smokers than the national population. This study investigated the effect of smoking and smoking cessation among asbestos workers. Starting to smoke at an early age and high intensity smoking for long periods of time increased the risk of lung cancer mortality. However, the earlier asbestos workers stopped smoking the greater the benefit. Asbestos workers who stopped smoking remained at an increased risk of lung cancer mortality up to 40 years after smoking cessation compared to asbestos workers who had never smoked. The effects of smoking and stopping smoking did not differ by asbestos exposure.

There was evidence of an interaction between asbestos exposure and smoking, and the hypothesis of a multiplicative interaction could not be rejected. For those asbestos workers who smoked, an estimated 2% of lung cancer deaths were attributable to asbestos only, 68% to smoking only, and 26% to the interaction of asbestos and smoking.

Those who both smoke and have been exposed to asbestos have the greatest risk of lung cancer mortality. This study emphasizes the importance of smoking prevention and cessation within this high-risk cohort.

FUNDING

Health and Safety Executive

Acknowledgements—We thank the staff at the Health and Safety Laboratory who work on the Asbestos Survey. We also thank the staff at the NHSCR and the GROS for their support.

REFERENCES

Berman DW, Crump KS. (2008a) A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol; 38: 49–73.

Berman DW, Crump KS. (2008b) Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol; 38 (Suppl 1): 1–47.

Berry G, Liddell FDK. (2004) The interaction of asbestos and smoking in lung cancer: a modified measure of effect. Ann Occup Hyg; 48: 459–62.

Berry G, Newhouse ML, Antonis P. (1985) Combined effect of asbestos and smoking on mortality from lung cancer and mesothelioma in factory workers. Br J Ind Med; 42: 12–8.

Boffetta P. (1998) Health effects of asbestos exposure in humans: a quantitative assessment. Med Lav; 89: 471–80.

Darnton AJ, McElvenny DM, Hodgson JT. (2006) Estimating the number of asbestos-related lung cancer deaths in Great Britain from 1980 to 2000. Ann Occup Hyg; 50: 29–38.

de Klerk NH, Musk AW, Armstrong BK *et al.* (1991) Smoking, exposure to crocidolite, and the incidence of lung cancer and asbestosis. Br J Ind Med; 48: 412–7.

Doll R, Peto J. (1985) Asbestos. Effects on health of exposure to asbestos. London: Health and Safety Commission.

Doll R, Peto R. (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Community Health; 32: 303–13.

Doll R, Peto R, Boreham J *et al.* (2004) Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ; 328: 1519.

Doll R, Peto R, Wheatley K *et al.* (1994) Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ; 309: 901–11.

Erren TC, Jacobsen M, Piekarski C. (1999) Synergy between asbestos and smoking on lung cancer risks. Epidemiology; 10: 405–11.

Goddard E. (2008) General Household Survey 2006: smoking and drinking among adults, 2006. Newport, UK: Office for National Statistics.

Hammond EC, Selikoff IJ, Seidman H. (1979) Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci.; 330: 473–790.

Harding A-H, Darnton A, Wergerdt J *et al.* Mortality among British asbestos workers undergoing regular medical examinations (1971–2005). Occup Environ Med; 66: 487–95.

Henderson DW, Rodelsperger K, Woitowitz H-J *et al.* (2004) After Helsinki: a multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. Pathology; 36: 517–50.

Hodgson JT, Darnton AJ. (2000) The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg; 44: 565–601.

Hosmer DW, Lemeshow S. (1992) Confidence interval estimation of interaction. Epidemiology; 3: 452–6.

IARC. (2004) IARC monographs on the evaluation of carcinogenic risks to humans: tobacco smoke and involuntary smoking. Lyon, France: IARCPress.

Jarvholm B, Sanden A. (1998) Lung cancer and mesothelioma in the pleura and peritoneum among Swedish insulation workers. Occup Environ Med; 55: 766–70.

Lee PN. (2001) Relation between exposure to asbestos and smoking jointly and the risk of lung cancer. Occup Environ Med; 58: 145–53.

Liddell FD, Armstrong BG. (2002) The combination of effects on lung cancer of cigarette smoking and exposure in Quebec chrysotile miners and millers. Ann Occup Hyg; 46: 5–13.

Liddell FDK. (2001) The interaction of asbestos and smoking in lung cancer. Ann Occup Hyg; 45: 341–56.

Lubin JH, Caporaso NE. (2006) Cigarette smoking and lung cancer: modeling total exposure and intensity. Cancer Epidemiol Biomarkers Prev; 15: 519–23.

McElvenny DM, Darnton AJ, Price MJ *et al.* (2005) Mesothelioma mortality in Great Britain from 1968 to 2001. Occup Med (Lond); 55: 79–87.

ONS. (2008) Cancer statistics: registrations 2005 (series MB1 No 36). Available at http://www.statistics.gov.uk/statbase/Product.asp?vlnk=8843. Accessed 4 January 2011.

ONS. (2006) Mortality statistics: cause 2005 (series DH2 No 32). Available at: http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=618. Accessed 4 January 2011.

Peto R, Darby S, Deo H *et al.* (2000) Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ; 321: 323–9.

Pira E, Pelucchi C, Buffoni L *et al.* (2005) Cancer mortality in a cohort of asbestos textile workers. Br J Cancer; 92: 580–6.

Quinn M, Babb P, Brock A *et al.* (2001) Cancer trends in England and Wales 1950–1999. London: The Stationery Office.

Reid A, de Klerk NH, Ambrosini GL *et al.* (2006) The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking. Occup Environ Med; 63: 509–12.

Rogot E, Murray JL. (1980) Smoking and causes of death among US veterans: 16 years of observation. Public Health Rep; 95: 213–22.

Rongling L, Chambless L. (2007) Test for additive interaction in proportional hazards models. Ann Epidemiol; 17: 227–36.

Rothman KJ. (1976) The estimation of synergy or antagonism. Am J Epidemiol; 103: 506–11.

StataCorp. (2007) Stata Statistical Software: Release 10. College Station, TX: StataCorp LP.

US DHHS. (1990) The health benefits of smoking cessation. A report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

Walker A, O'Brien M, Traynor J *et al.* (2002) Living in Britain: results from the 2001 General Household Survey. London: The Stationery Office.

Walker AM. (1984) Declining relative risks for lung cancer after cessation of asbestos exposure. J Occup Med; 26: 422–4.

WHO. (2009) Cancer fact sheet No 297. Available at: http://www.who.int/mediacentre/factsheets/fs297/en/index.html. Accessed 4 January 2011.

Wiencke JK, Thurston SW, Kelsey KT *et al.* (1999) Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. J Natl Cancer Inst; 91: 614–9.

Wraith D, Mengersen K. (2007) Assessing the combined effect of asbestos exposure and smoking on lung cancer: a Bayesian approach. Stat Med; 26: 1150–69.

Wright SP. (1992) Adjusted *P*-values for simultaneous inference. Biometrics; 48: 1005–13.

Zang EA, Wynder EL. (1992) A new index for estimating lung cancer risk among cigarette smokers. Cancer; 70: 69–76.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

ABSTRACT

BACKGROUND

The aggressive and heterogeneous nature of lung cancer has thwarted efforts to reduce mortality from this cancer through the use of screening. The advent of low-dose helical computed tomography (CT) altered the landscape of lung-cancer screening, with studies indicating that low-dose CT detects many tumors at early stages. The National Lung Screening Trial (NLST) was conducted to determine whether screening with low-dose CT could reduce mortality from lung cancer.

METHODS

From August 2002 through April 2004, we enrolled 53,454 persons at high risk for lung cancer at 33 U.S. medical centers. Participants were randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009.

RESULTS

The rate of adherence to screening was more than 90%. The rate of positive screening tests was 24.2% with low-dose CT and 6.9% with radiography over all three rounds. A total of 96.4% of the positive screening results in the low-dose CT group and 94.5% in the radiography group were false positive results. The incidence of lung cancer was 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group, as compared with 572 cases per 100,000 person-years (941 cancers) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). There were 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group and 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; P=0.004). The rate of death from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2 to 13.6; P=0.02).

CONCLUSIONS

Screening with the use of low-dose CT reduces mortality from lung cancer. (Funded by the National Cancer Institute; National Lung Screening Trial ClinicalTrials.gov number, NCT00047385.)

The members of the writing team (who are listed in the Appendix) assume responsibility for the integrity of the article. Address reprint requests to Dr. Christine D. Berg at the Early Detection Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd., Suite 3112, Bethesda, MD 20892-7346, or at bergc@mail.nih.gov.

*A complete list of members of the National Lung Screening Trial research team is provided in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1102873) was published on June 29, 2011, at NEJM.org.

N Engl J Med 2011;365:395-409.

LUNG CANCER IS AN AGGRESSIVE AND HETerogeneous disease.[1,2] Advances in surgical, radiotherapeutic, and chemotherapeutic approaches have been made, but the long-term survival rate remains low.[3] After the Surgeon General's 1964 report on smoking and health, mortality from lung cancer among men peaked and then fell; among women, the peak occurred later and a slight decline has occurred more recently.[4] Even though the rate of heavy smoking continues to decline in the United States,[5] 94 million current or former smokers remain at elevated risk for the disease,[6] and lung cancer remains the leading cause of death from cancer in this country.[3] The prevalence of smoking is substantially higher in developing countries than in the United States, and the worldwide burden of lung cancer is projected to rise considerably during the coming years.[7]

Although effective mass screening of high-risk groups could potentially be of benefit, randomized trials of screening with the use of chest radiography with or without cytologic analysis of sputum specimens have shown no reduction in lung-cancer mortality.[8] Molecular markers in blood, sputum, and bronchial brushings have been studied but are currently unsuitable for clinical application.[8] Advances in multidetector computed tomography (CT), however, have made high-resolution volumetric imaging possible in a single breath hold at acceptable levels of radiation exposure,[9] allowing its use for certain lung-specific applications. Several observational studies have shown that low-dose helical CT of the lung detects more nodules and lung cancers, including early-stage cancers, than does chest radiography.[8] Therefore, the National Cancer Institute (NCI) funded the National Lung Screening Trial (NLST), a randomized trial, to determine whether screening with low-dose CT, as compared with chest radiography, would reduce mortality from lung cancer among high-risk persons. The NLST was initiated in 2002.[10] In October 2010, the available data showed that there was a significant reduction with low-dose CT screening in the rates of both death from lung cancer and death from any cause. We report here the findings of the NLST, including the performance characteristics of the screening techniques, the approaches used for and the results of diagnostic evaluation of positive screening results, the characteristics of the lung-cancer cases, and mortality. A comprehensive description of the design and operations of the trial, including the collection of the data and the acquisition variables of the screening techniques, has been published previously.[10]

METHODS

TRIAL OVERSIGHT

The NLST, a randomized trial of screening with the use of low-dose CT as compared with screening with the use of chest radiography, was a collaborative effort of the Lung Screening Study (LSS), administered by the NCI Division of Cancer Prevention, and the American College of Radiology Imaging Network (ACRIN), sponsored by the NCI Division of Cancer Treatment and Diagnosis, Cancer Imaging Program. Chest radiography was chosen as the screening method for the control group because radiographic screening was being compared with community care (care that a participant usually receives) in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (ClinicalTrials.gov number, NCT00002540).[11] The NLST was approved by the institutional review board at each of the 33 participating medical institutions. The study was conducted in accordance with the protocol; both the protocol and the statistical analysis plan are available with the full text of this article at NEJM.org.

PARTICIPANTS

We enrolled participants from August 2002 through April 2004; screening took place from August 2002 through September 2007. Participants were followed for events that occurred through December 31, 2009 (Fig. 1 in the Supplementary Appendix, available at NEJM.org).

Eligible participants were between 55 and 74 years of age at the time of randomization, had a history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years. Persons who had previously received a diagnosis of lung cancer, had undergone chest CT within 18 months before enrollment, had hemoptysis, or had an unexplained weight loss of more than 6.8 kg (15 lb) in the preceding year were excluded. A total of 53,454 persons were enrolled; 26,722 were randomly assigned to screening with low-dose CT and 26,732 to screening with chest radiography. Previously published articles describing the NLST[10,12] reported an enroll-

ment of 53,456 participants (26,723 in the low-dose CT group and 26,733 in the radiography group). The number of enrolled persons is now reduced by 2 owing to the discovery of the duplicate randomization of 2 participants.

Participants were enrolled at 1 of the 10 LSS or 23 ACRIN centers. Before randomization, each participant provided written informed consent. After the participants underwent randomization, they completed a questionnaire that covered many topics, including demographic characteristics and smoking behavior. The ACRIN centers collected additional data for planned analyses of cost-effectiveness, quality of life, and smoking cessation. Participants at 15 ACRIN centers were also asked to provide serial blood, sputum, and urine specimens. Lung-cancer and other tissue specimens were obtained at both the ACRIN and LSS centers and were used to construct tissue microarrays. All biospecimens are available to researchers through a peer-review process.

SCREENING

Participants were invited to undergo three screenings (T0, T1, and T2) at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. Participants in whom lung cancer was diagnosed were not offered subsequent screening tests. The number of lung-cancer screening tests that were performed outside the NLST was estimated through self-administered questionnaires that were mailed to a random subgroup of approximately 500 participants from LSS centers annually. Sample sizes were selected to yield a standard error of 0.025 for the estimate of the proportion of participants undergoing lung-cancer screening tests outside the NLST in each group. For participants from ACRIN centers, information on CT examinations or chest radiography performed outside the trial was obtained, but no data were gathered on whether the examinations were performed as screening tests.

All screening examinations were performed in accordance with a standard protocol, developed by medical physicists associated with the trial, that specified acceptable characteristics of the machine and acquisition variables.[10,13,14] All low-dose CT scans were acquired with the use of multidetector scanners with a minimum of four channels. The acquisition variables were chosen to reduce exposure to an average effective dose of 1.5 mSv. The average effective dose with diagnostic chest CT varies widely but is approximately 8 mSv.[10,13,14] Chest radiographs were obtained with the use of either screen-film radiography or digital equipment. All the machines used for screening met the technical standards of the American College of Radiology.[10] The use of new equipment was allowed after certification by medical physicists.

NLST radiologists and radiologic technologists were certified by appropriate agencies or boards and completed training in image acquisition; radiologists also completed training in image quality and standardized image interpretation. Images were interpreted first in isolation and then in comparison with available historical images and images from prior NLST screening examinations. The comparative interpretations were used to determine the outcome of the examination. Low-dose CT scans that revealed any noncalcified nodule measuring at least 4 mm in any diameter and radiographic images that revealed any noncalcified nodule or mass were classified as positive, "suspicious for" lung cancer. Other abnormalities such as adenopathy or effusion could be classified as a positive result as well. Abnormalities suggesting clinically significant conditions other than lung cancer also were noted, as were minor abnormalities. At the third round of screening (T2), abnormalities suspicious for lung cancer that were stable across the three rounds could, according to the protocol, be classified as minor abnormalities rather than positive results.

Results and recommendations from the interpreting radiologist were reported in writing to the participant and his or her health care provider within 4 weeks after the examination. Since there was no standardized, scientifically validated approach to the evaluation of nodules, trial radiologists developed guidelines for diagnostic follow-up, but no specific evaluation approach was mandated.

MEDICAL-RECORD ABSTRACTION

Medical records documenting diagnostic evaluation procedures and any associated complications were obtained for participants who had positive screening tests and for participants in whom lung cancer was diagnosed. Pathology and tumor-staging reports and records of operative procedures and initial treatment were also obtained for participants with lung cancer. Pathology reports were obtained for other reported cancers to exclude

the possibility that such tumors represented lung metastases. Histologic features of the lung cancer were coded according to the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3),[15] and the disease stage was determined according to the sixth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.[16] At ACRIN sites, additional medical records were also obtained for a number of substudies, including studies of health care utilization and cost-effectiveness.[10]

VITAL STATUS

Participants completed a questionnaire regarding vital status either annually (LSS participants) or semiannually (ACRIN participants). The names and Social Security numbers of participants who were lost to follow-up were submitted to the National Death Index to ascertain probable vital status. Death certificates were obtained for participants who were known to have died. An end-point verification team determined whether the cause of death was lung cancer. Although a distinction was made between a death caused by lung cancer and a death that resulted from the diagnostic evaluation for or treatment of lung cancer, the deaths from the latter causes were counted as lung-cancer deaths in the primary end-point analysis. The members of the team were not aware of the group assignments (see Section 2 in the Supplementary Appendix).

STATISTICAL ANALYSIS

The primary analysis was a comparison of lung-cancer mortality between the two screening groups, according to the intention-to-screen principle. We estimated that the study would have 90% power to detect a 21% decrease in mortality from lung cancer in the low-dose CT group, as compared with the radiography group. Secondary analyses compared the rate of death from any cause and the incidence of lung cancer in the two groups.

Event rates were defined as the ratio of the number of events to the person-years at risk for the event. For the incidence of lung cancer, person-years were measured from the time of randomization to the date of diagnosis of lung cancer, death, or censoring of data (whichever came first); for the rates of death, person-years were measured from the time of randomization to the date of death or censoring of data (whichever came first). The latest date for the censoring of data on incidence of lung cancer and on death from any cause was December 31, 2009; the latest date for the censoring of data on death from lung cancer for the purpose of the primary end-point analysis was January 15, 2009. The earlier censoring date for death from lung cancer was established to allow adequate time for the review process for deaths to be performed to the same, thorough extent in each group. We calculated the confidence intervals for incidence ratios assuming a Poisson distribution for the number of events and a normal distribution of the logarithm of the ratio, using asymptotic methods. We calculated the confidence intervals for mortality ratios with the weighted method that was used to monitor the primary end point of the trial,[17] which allows for a varying rate ratio and is adjusted for the design. The number needed to screen to prevent one death from lung cancer was estimated as the reciprocal of the reduction in the absolute risk of death from lung cancer in one group as compared with the other, among participants who had at least one screening test. The analyses were performed with the use of SAS/STAT[18] and R[19] statistical packages.

Interim analyses were performed to monitor the primary end point for efficacy and futility. The analyses involved the use of a weighted log-rank statistic, with weights increasing linearly from no weight at randomization to full weight at 4 years and thereafter. Efficacy and futility boundaries were built on the Lan–DeMets approach with an O'Brien–Fleming spending function.[20] Interim analyses were performed annually from 2006 through 2009 and semiannually in 2010.

An independent data and safety monitoring board met every 6 months and reviewed the accumulating data. On October 20, 2010, the board determined that a definitive result had been reached for the primary end point of the trial and recommended that the results be reported.[21] The board's decision took into consideration that the efficacy boundary for the primary end point had been crossed and that there was no evidence of unforeseen screening effects that warranted acting contrary to the trial's prespecified monitoring plan. The NCI director accepted the recommendation of the data and safety monitoring board, and the trial results were announced on November 4, 2010.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

The demographic characteristics and smoking history of the participants were virtually identical in the two groups (Table 1). As compared with respondents to a 2002–2004 U.S. Census survey of tobacco use[22] who met the NLST eligibility criteria for age and smoking history, NLST participants were younger, had a higher level of education, and were more likely to be former smokers.[12] As of December 31, 2009, vital status was known for 97% of the participants in the low-dose CT group and 96% of those in the radiography group. The median duration of follow-up was 6.5 years, with a maximum duration of 7.4 years in each group.

ADHERENCE TO SCREENING

The rate of adherence to the screening protocol across the three rounds was high: 95% in the low-dose CT group and 93% in the radiography group. Among LSS participants in the radiography group, the average annual rate of helical CT screening outside the NLST during the screening phase of the trial was 4.3%, which was well below the 10.0% rate estimated in the trial power calculations.

RESULTS OF SCREENING

In all three rounds, there was a substantially higher rate of positive screening tests in the low-dose CT group than in the radiography group (T0, 27.3% vs. 9.2%; T1, 27.9% vs. 6.2%; and T2, 16.8% vs. 5.0%) (Table 2). The rate of positive tests in both groups was noticeably lower at T2 than at T0 or T1 because the NLST protocol allowed tests showing abnormalities at T2 that were suspicious for cancer but were stable across all three rounds to be categorized as negative with minor abnormalities. During the screening phase of the trial, 39.1% of the participants in the low-dose CT group and 16.0% of those in the radiography group had at least one positive screening result. The percentage of all screening tests that identified a clinically significant abnormality other than an abnormality suspicious for lung cancer was more than three times as high in the low-dose CT group as in the radiography group (7.5% vs. 2.1%).

FOLLOW-UP OF POSITIVE RESULTS

More than 90% of the positive screening tests in the first round of screening (T0) led to a diagnostic evaluation (Table 3). Lower rates of follow-up were seen at later rounds. The diagnostic evaluation most often consisted of further imaging, and invasive procedures were performed infrequently. Across the three rounds, 96.4% of the positive results in the low-dose CT group and 94.5% of those in the radiography group were false positive results. These percentages varied little by round. Of the total number of low-dose CT screening tests in the three rounds, 24.2% were classified as pos-

Table 1. Selected Baseline Characteristics of the Study Participants.*

Characteristic	Low-Dose CT Group (N=26,722)	Radiography Group (N=26,732)
	number (percent)	
Age at randomization		
<55 yr†	2 (<0.1)	4 (<0.1)
55–59 yr	11,440 (42.8)	11,420 (42.7)
60–64 yr	8,170 (30.6)	8,198 (30.7)
65–69 yr	4,756 (17.8)	4,762 (17.8)
70–74 yr	2,353 (8.8)	2,345 (8.8)
≥75 yr†	1 (<0.1)	3 (<0.1)
Sex		
Male	15,770 (59.0)	15,762 (59.0)
Female	10,952 (41.0)	10,970 (41.0)
Race or ethnic group‡		
White	24,289 (90.9)	24,260 (90.8)
Black	1,195 (4.5)	1,181 (4.4)
Asian	559 (2.1)	536 (2.0)
American Indian or Alaska Native	92 (0.3)	98 (0.4)
Native Hawaiian or other Pacific Islander	91 (0.3)	102 (0.4)
More than one race or ethnic group	333 (1.2)	346 (1.3)
Data missing	163 (0.6)	209 (0.8)
Hispanic ethnic group‡		
Hispanic or Latino	479 (1.8)	456 (1.7)
Neither Hispanic nor Latino	26,079 (97.6)	26,039 (97.4)
Data missing	164 (0.6)	237 (0.9)
Smoking status		
Current	12,862 (48.1)	12,900 (48.3)
Former	13,860 (51.9)	13,832 (51.7)

* CT denotes computed tomography.
† Patients in this age range were ineligible for inclusion in the screening trial but were enrolled and were included in all analyses.
‡ Race or ethnic group was self-reported.

Table 2. Results of Three Rounds of Screening.*

Screening Round	Low-Dose CT				Chest Radiography			
	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality	Total No. Screened	Positive Result	Clinically Significant Abnormality Not Suspicious for Lung Cancer	No or Minor Abnormality
			no. (% of screened)				*no. (% of screened)*	
T0	26,309	7191 (27.3)	2695 (10.2)	16,423 (62.4)	26,035	2387 (9.2)	785 (3.0)	22,863 (87.8)
T1	24,715	6901 (27.9)	1519 (6.1)	16,295 (65.9)	24,089	1482 (6.2)	429 (1.8)	22,178 (92.1)
T2	24,102	4054 (16.8)	1408 (5.8)	18,640 (77.3)	23,346	1174 (5.0)	361 (1.5)	21,811 (93.4)

* The screenings were performed at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. Results of screening tests that were technically inadequate (7 in the low-dose CT group and 26 in the radiography group, across the three screening rounds) are not included in this table. A screening test with low-dose CT was considered to be positive if it revealed a nodule at least 4 mm in any diameter or other abnormalities that were suspicious for lung cancer. A screening test with chest radiography was considered to be positive if it revealed a nodule or mass of any size or other abnormalities suspicious for lung cancer.

itive and 23.3% had false positive results; of the total number of radiographic screening tests in the three rounds, 6.9% were classified as positive and 6.5% had false positive results.

ADVERSE EVENTS

Adverse events from the actual screening examinations were few and minor. The rates of complications after a diagnostic evaluation procedure for a positive screening test (listed by category in Table 1 in the Supplementary Appendix) were low; the rate of at least one complication was 1.4% in the low-dose CT group and 1.6% in the radiography group (Table 4). A total of 0.06% of the positive screening tests in the low-dose CT group that did not result in a diagnosis of lung cancer and 11.2% of those that did result in a diagnosis of lung cancer were associated with a major complication after an invasive procedure; the corresponding percentages in the radiography group were 0.02% and 8.2%. The frequency of major complications varied according to the type of invasive procedure. A total of 16 participants in the low-dose CT group (10 of whom had lung cancer) and 10 in the radiography group (all of whom had lung cancer) died within 60 days after an invasive diagnostic procedure. Although it is not known whether the complications from the diagnostic procedure caused the deaths, the low frequency of death within 60 days after the procedure suggests that death as a result of the diagnostic evaluation of positive screening tests is a rare occurrence.

INCIDENCE, CHARACTERISTICS, AND TREATMENT OF LUNG CANCERS

A total of 1060 lung cancers (645 per 100,000 person-years) were diagnosed in the low-dose CT group, as compared with 941 (572 per 100,000 person-years) in the radiography group (rate ratio, 1.13; 95% confidence interval [CI], 1.03 to 1.23). In the low-dose CT group, 649 cancers were diagnosed after a positive screening test, 44 after a negative screening test, and 367 among participants who either missed the screening or received the diagnosis after their trial screening phase was over (Table 5). In the radiography group, 279 cancers were diagnosed after a positive screening test, 137 after a negative screening test, and 525 among participants who either missed the screening or received the diagnosis after their trial screening phase was over. Figure 1A shows the cumulative number of lung cancers through December 31, 2009, according to the screening group. Detailed calculations of sensitivity, specificity, positive predictive value, and negative predictive value are not reported here.

In each group, the percentage of stage IA and stage IB lung cancers was highest among cancers that were diagnosed after a positive screening test (Table 5). Fewer stage IV cancers were seen in the low-dose CT group than in the radiography group at the second and third screening rounds (Table 2 in the Supplementary Appendix). Low-dose CT screening identified a preponderance of adenocarcinomas, including bronchioloalveolar

Table 3. **Diagnostic Follow-up of Positive Screening Results in the Three Screening Rounds.***

Variable	Low-Dose CT				Chest Radiography			
	T0	T1	T2	Total	T0	T1	T2	Total
	number (percent)							
Total positive tests	7191 (100.0)	6901 (100.0)	4054 (100.0)	18,146 (100.0)	2387 (100.0)	1482 (100.0)	1174 (100.0)	5043 (100.0)
Lung cancer confirmed	270 (3.8)	168 (2.4)	211 (5.2)	649 (3.6)	136 (5.7)	65 (4.4)	78 (6.6)	279 (5.5)
Lung cancer not confirmed†	6921 (96.2)	6733 (97.6)	3843 (94.8)	17,497 (96.4)	2251 (94.3)	1417 (95.6)	1096 (93.4)	4764 (94.5)
Positive screening results with complete diagnostic follow-up information	7049 (100.0)	6740 (100.0)	3913 (100.0)	17,702 (100.0)	2348 (100.0)	1456 (100.0)	1149 (100.0)	4953 (100.0)
Any diagnostic follow-up	6369 (90.4)	3866 (57.4)	2522 (64.5)	12,757 (72.1)	2176 (92.7)	1078 (74.0)	957 (83.3)	4211 (85.0)
Clinical procedure	5089 (72.2)	3190 (47.3)	2151 (55.0)	10,430 (58.9)	1414 (60.2)	723 (49.7)	658 (57.3)	2795 (56.4)
Imaging examination	5717 (81.1)	2520 (37.4)	2009 (51.3)	10,246 (57.9)	2010 (85.6)	968 (66.5)	906 (78.9)	3884 (78.4)
Chest radiography	1284 (18.2)	613 (9.1)	650 (16.6)	2,547 (14.4)	867 (36.9)	381 (26.2)	365 (31.8)	1613 (32.6)
Chest CT	5153 (73.1)	2046 (30.4)	1608 (41.1)	8,807 (49.8)	1546 (65.8)	745 (51.2)	712 (62.0)	3003 (60.6)
FDG PET or FDG PET–CT	728 (10.3)	350 (5.2)	393 (10.0)	1,471 (8.3)	179 (7.6)	105 (7.2)	113 (9.8)	397 (8.0)
Percutaneous cytologic examination or biopsy	155 (2.2)	74 (1.1)	93 (2.4)	322 (1.8)	83 (3.5)	37 (2.5)	52 (4.5)	172 (3.5)
Transthoracic	120 (1.7)	60 (0.9)	74 (1.9)	254 (1.4)	67 (2.9)	31 (2.1)	43 (3.7)	141 (2.8)
Extrathoracic	39 (0.6)	17 (0.3)	24 (0.6)	80 (0.5)	20 (0.9)	6 (0.4)	13 (1.1)	39 (0.8)
Bronchoscopy	306 (4.3)	178 (2.6)	187 (4.8)	671 (3.8)	107 (4.6)	56 (3.8)	62 (5.4)	225 (4.5)
With neither biopsy nor cytologic testing	126 (1.8)	95 (1.4)	99 (2.5)	320 (1.8)	45 (1.9)	19 (1.3)	32 (2.8)	96 (1.9)
With biopsy or cytologic testing	194 (2.8)	95 (1.4)	102 (2.6)	391 (2.2)	74 (3.2)	40 (2.7)	36 (3.1)	150 (3.0)
Surgical procedure	297 (4.2)	197 (2.9)	219 (5.6)	713 (4.0)	121 (5.2)	51 (3.5)	67 (5.8)	239 (4.8)
Mediastinoscopy or mediastinotomy	60 (0.9)	32 (0.5)	25 (0.6)	117 (0.7)	22 (0.9)	12 (0.8)	21 (1.8)	55 (1.1)
Thoracoscopy	82 (1.2)	56 (0.8)	96 (2.5)	234 (1.3)	22 (0.9)	11 (0.8)	20 (1.7)	53 (1.1)
Thoracotomy	197 (2.8)	148 (2.2)	164 (4.2)	509 (2.9)	96 (4.1)	44 (3.0)	44 (3.8)	184 (3.7)
Other procedures	168 (2.4)	96 (1.4)	63 (1.6)	327 (1.8)	55 (2.3)	33 (2.3)	34 (3.0)	122 (2.5)

* The screenings were performed at 1-year intervals, with the first screening (T0) performed soon after the time of randomization. FDG PET denotes ^{18}F-fluorodeoxyglucose positron-emission tomography.

† Positive tests with incomplete information on diagnostic follow-up are included in this category (142 at T0, 161 at T1, and 141 at T2 in the low-dose CT group and 39 at T0, 26 at T1, and 25 at T2 in the radiography group).

Table 4. Complications after the Most Invasive Screening-Related Diagnostic Evaluation Procedure, According to Lung-Cancer Status.*

Complication	Lung Cancer Confirmed				
	Thoracotomy, Thoracoscopy, or Mediastinoscopy	Bronchoscopy	Needle Biopsy	No Invasive Procedure	Total
	number (percent)				
Low-dose CT group					
Positive screening results for which diagnostic information was complete	509 (100.0)	76 (100.0)	33 (100.0)	31 (100.0)	649 (100.0)
No complication	344 (67.6)	69 (90.8)	26 (78.8)	26 (83.9)	465 (71.6)
At least one complication	165 (32.4)	7 (9.2)	7 (21.2)	5 (16.1)	184 (28.4)
Most severe complication classified as major	71 (13.9)	2 (2.6)	0	2 (6.5)	75 (11.6)
Most severe complication classified as intermediate	81 (15.9)	5 (6.6)	7 (21.2)	2 (6.5)	95 (14.6)
Most severe complication classified as minor	13 (2.6)	0	0	1 (3.2)	14 (2.2)
Death within 60 days after most invasive diagnostic procedure†	5 (1.0)	4 (5.3)	1 (3.0)	0	10 (1.5)
Radiography group					
Positive screening results for which diagnostic information was complete	189 (100.0)	46 (100.0)	29 (100.0)	15 (100.0)	279 (100.0)
No complication	130 (68.8)	42 (91.3)	28 (96.6)	14 (93.3)	214 (76.7)
At least one complication	59 (31.2)	4 (8.7)	1 (3.4)	1 (6.7)	65 (23.3)
Most severe complication classified as major	22 (11.6)	1 (2.2)	0	1 (6.7)	24 (8.6)
Most severe complication classified as intermediate	32 (16.9)	2 (4.3)	1 (3.4)	0	35 (12.5)
Most severe complication classified as minor	5 (2.6)	1 (2.2)	0	0	6 (2.2)
Death within 60 days after most invasive diagnostic procedure†	4 (2.1)	5 (10.9)	1 (3.4)	1 (6.7)	11 (3.9)

* In the case of multiple evaluation procedures of the same type, the earliest is included. Complications that occurred before the most invasive procedure are not included. Participants could have up to three positive screening tests and therefore may be included up to three times in any row. Columns of procedures are arranged in decreasing order of invasiveness. In the case of the first procedure column, thoracotomy was considered to be more invasive than thoracoscopy, which was considered to be more invasive than mediastinoscopy.

† For patients who did not undergo an invasive procedure, deaths were included if they occurred within 60 days after the positive screening result.

carcinomas. Although the use of the term bronchioloalveolar carcinoma is no longer recommended,[23] while the NLST was ongoing, the term was used to denote in situ, minimally invasive, or invasive adenocarcinoma, lepidic predominant (i.e., neoplastic cell growth restricted to preexisting alveolar structure). In both groups, many adenocarcinomas and squamous-cell carcinomas were detected at either stage I or stage II, although the stage distribution was more favorable in the low-dose CT group than in the radiography group (Table 6). Small-cell lung cancers were, in general, not detected at early stages by either low-dose CT or radiography. A total of 92.5% of stage IA and stage IB cancers in the low-dose CT group and 87.5% of those in the radiography group were treated with surgery alone or surgery combined with chemotherapy, radiation therapy, or both (Table 3 in the Supplementary Appendix).

LUNG-CANCER–SPECIFIC MORTALITY

After the accrual of 144,103 person-years in the low-dose CT group and 143,368 person-years in the radiography group, 356 and 443 deaths from lung cancer in the two groups, respectively, had occurred, corresponding to rates of death from lung cancer of 247 and 309 deaths per 100,000 person-years, respectively, and a relative reduction in the rate of death from lung cancer with low-dose CT screening of 20.0% (95% CI, 6.8 to 26.7; $P=0.004$). Figure 1B shows the cumulative number of deaths from lung cancer in the two screening groups through January 15, 2009. When only participants who underwent at least one screen-

Lung Cancer Not Confirmed				
Thoracotomy, Thoracoscopy, or Mediastinoscopy	Bronchoscopy	Needle Biopsy	No Invasive Procedure	Total
		number (percent)		
164 (100.0)	227 (100.0)	66 (100.0)	16,596 (100.0)	17,053 (100.0)
138 (84.1)	216 (95.2)	59 (89.4)	16,579 (99.9)	16,992 (99.6)
26 (15.9)	11 (4.8)	7 (10.6)	17 (0.1)	61 (0.4)
9 (5.5)	2 (0.9)	0	1 (<0.1)	12 (0.1)
13 (7.9)	9 (4.0)	6 (9.1)	16 (0.1)	44 (0.3)
4 (2.4)	0	1 (1.5)	0	5 (<0.1)
2 (1.2)	4 (1.8)	0	5 (<0.1)	11 (0.1)
45 (100.0)	46 (100.0)	24 (100.0)	4,559 (100.0)	4,674 (100.0)
38 (84.4)	46 (100.0)	23 (95.8)	4,551 (99.8)	4,658 (99.7)
7 (15.6)	0	1 (4.2)	8 (0.2)	16 (0.3)
1 (2.2)	0	0	3 (0.1)	4 (0.1)
6 (13.3)	0	1 (4.2)	2 (<0.1)	9 (0.2)
0	0	0	3 (0.1)	3 (0.1)
0	0	0	3 (0.1)	3 (0.1)

ing test were included, there were 346 deaths from lung cancer among 26,455 participants in the low-dose CT group and 425 deaths among 26,232 participants in the radiography group. The number needed to screen with low-dose CT to prevent one death from lung cancer was 320.

OVERALL MORTALITY

There were 1877 deaths in the low-dose CT group, as compared with 2000 deaths in the radiography group, representing a significant reduction with low-dose CT screening of 6.7% (95% CI, 1.2 to 13.6) in the rate of death from any cause (P=0.02). We were unable to obtain the death certificates for two of the participants in the radiography group who died, but the occurrence of death was confirmed through a review by the end-point verification team. Although lung cancer accounted for 24.1% of all the deaths in the trial, 60.3% of the excess deaths in the radiography group were due to lung cancer (Table 7). When deaths from lung cancer were excluded from the comparison, the reduction in overall mortality with the use of low-dose CT dropped to 3.2% and was not significant (P=0.28).

DISCUSSION

In the NLST, a 20.0% decrease in mortality from lung cancer was observed in the low-dose CT group as compared with the radiography group. The rate of positive results was higher with low-dose CT screening than with radiographic screening by a factor of more than 3, and low-dose CT screening was associated with a high rate of false positive results; however, the vast majority of false positive results were probably due to the presence of benign intrapulmonary lymph nodes or noncalcified granulomas, as confirmed noninvasively by the stability of the findings on follow-up CT scans. Complications from invasive diagnostic evaluation procedures were uncommon, with death or severe complications occurring only rarely, particularly among participants who did not have

Table 5. Stage and Histologic Type of Lung Cancers in the Two Screening Groups, According to the Result of Screening.*

Stage and Histologic Type	Low-Dose CT				Chest Radiography			
	Positive Screening Test (N=649)	Negative Screening Test (N=44)†	No Screening Test (N=367)‡	Total (N=1060)	Positive Screening Test (N=279)	Negative Screening Test (N=137)†	No Screening Test (N=525)‡	Total (N=941)
	number/total number (percent)							
Stage								
IA	329/635 (51.8)	5/44 (11.4)	82/361 (22.7)	416/1040 (40.0)	90/275 (32.7)	16/135 (11.9)	90/519 (17.3)	196/929 (21.1)
IB	71/635 (11.2)	2/44 (4.5)	31/361 (8.6)	104/1040 (10.0)	41/275 (14.9)	6/135 (4.4)	46/519 (8.9)	93/929 (10.0)
IIA	26/635 (4.1)	2/44 (4.5)	7/361 (1.9)	35/1040 (3.4)	14/275 (5.1)	2/135 (1.5)	16/519 (3.1)	32/929 (3.4)
IIB	20/635 (3.1)	3/44 (6.8)	15/361 (4.2)	38/1040 (3.7)	11/275 (4.0)	6/135 (4.4)	25/519 (4.8)	42/929 (4.5)
IIIA	59/635 (9.3)	3/44 (6.8)	37/361 (10.2)	99/1040 (9.5)	35/275 (12.7)	21/135 (15.6)	53/519 (10.2)	109/929 (11.7)
IIIB	49/635 (7.7)	15/44 (34.1)	58/361 (16.1)	122/1040 (11.7)	27/275 (9.8)	24/135 (17.8)	71/519 (13.7)	122/929 (13.1)
IV	81/635 (12.8)	14/44 (31.8)	131/361 (36.3)	226/1040 (21.7)	57/275 (20.7)	60/135 (44.4)	218/519 (42.0)	335/929 (36.1)
Histologic type								
Bronchioloalveolar carcinoma	95/646 (14.7)	1/44 (2.3)	14/358 (3.9)	110/1048 (10.5)	13/276 (4.7)	1/135 (0.7)	21/520 (4.0)	35/931 (3.8)
Adenocarcinoma	258/646 (39.9)	8/44 (18.2)	114/358 (31.8)	380/1048 (36.3)	112/276 (40.6)	37/135 (27.4)	179/520 (34.4)	328/931 (35.2)
Squamous-cell carcinoma	136/646 (21.1)	13/44 (29.5)	94/358 (26.3)	243/1048 (23.2)	70/276 (25.4)	24/135 (17.8)	112/520 (21.5)	206/931 (22.1)
Large-cell carcinoma	28/646 (4.3)	3/44 (6.8)	10/358 (2.8)	41/1048 (3.9)	12/276 (4.3)	10/135 (7.4)	21/520 (4.0)	43/931 (4.6)
Non–small-cell carcinoma or other§	75/646 (11.6)	4/44 (9.1)	52/358 (14.5)	131/1048 (12.5)	40/276 (14.5)	30/135 (22.2)	88/520 (16.9)	158/931 (17.0)
Small-cell carcinoma	49/646 (7.6)	15/44 (34.1)	73/358 (20.4)	137/1048 (13.1)	28/276 (10.1)	32/135 (23.7)	99/520 (19.0)	159/931 (17.1)
Carcinoid	5/646 (0.8)	0	1/358 (0.3)	6/1048 (0.6)	1/276 (0.4)	1/135 (0.7)	0	2/931 (0.2)

* The denominators represent only cancers with a known stage or known histologic type. The stage was not known in the case of 14 cancers after a positive screening test and 6 after no screening in the low-dose CT group and in the case of 4 cancers after a positive screening test, 2 after a negative screening test, and 6 after no screening in the radiography group. The histologic type was not known for 3 cancers after a positive screening test and 9 after no screening in the low-dose CT group and for 3 cancers after a positive screening test, 2 after a negative screening test, and 5 after no screening in the radiography group.

† Negative screening tests included tests that revealed either minor or clinically significant abnormalities that were not suspicious for lung cancer.

‡ The 892 lung cancers in participants with no screening test included 35 in participants who were never screened, 802 that were diagnosed during the post-screening period, and 55 in participants who were due for a screening test.

§ The 289 lung cancers in this category (in the two groups combined) included 28 adenosquamous carcinomas, 6 sarcomatoid carcinomas, 55 unclassified carcinomas, 1 anaplastic-type carcinoma, 1 carcinosarcoma, and 198 coded only as "non–small-cell carcinoma."

lung cancer. The decrease in the rate of death from any cause with the use of low-dose CT screening suggests that such screening is not, on the whole, deleterious.

A high rate of adherence to the screening, low rates of lung-cancer screening outside the NLST, and thorough ascertainment of lung cancers and deaths contributed to the success of the NLST. Moreover, because there was no mandated diagnostic evaluation algorithm, the follow-up of positive screening tests reflected the practice patterns at the participating medical centers. A multidisciplinary team ensured that all aspects of the NLST were conducted rigorously.

There are several limitations of the NLST. First, as is possible in any clinical study, the findings may be affected by the "healthy-volunteer" effect, which can bias results such that they are more favorable than those that will be observed when the intervention is implemented in the community.[24] The role of this bias in our results cannot be ascertained at this time. Second, the scanners that are currently used are technologically more advanced than those that were used in the trial. This difference may mean that screening with today's scanners will result in a larger reduction in the rate of death from lung cancer than was observed in the NLST; however, the ability to detect more abnormalities may result only in higher rates of false positive results.[25] Third, the NLST was conducted at a variety of medical institutions, many of which are recognized for their expertise in radiology and in the diagnosis and treatment of cancer. It is possible that community facilities will be less prepared to undertake screening programs and the medical care that must be associated with them. For example, one of the most important factors determining the success of screening will be the mortality associated with surgical resection, which was much lower in the NLST than has been reported previously in the general U.S. population (1% vs. 4%).[26] Finally, the reduction in the rate of death from lung cancer associated with an ongoing low-dose CT screening program was not estimated in the NLST and may be larger than the 20% reduction observed with only three rounds of screening.

Radiographic screening rather than community care (care that a participant usually receives) was chosen as the comparator in the NLST because radiographic screening was being evaluated in the PLCO trial at the time the NLST was designed.[11]

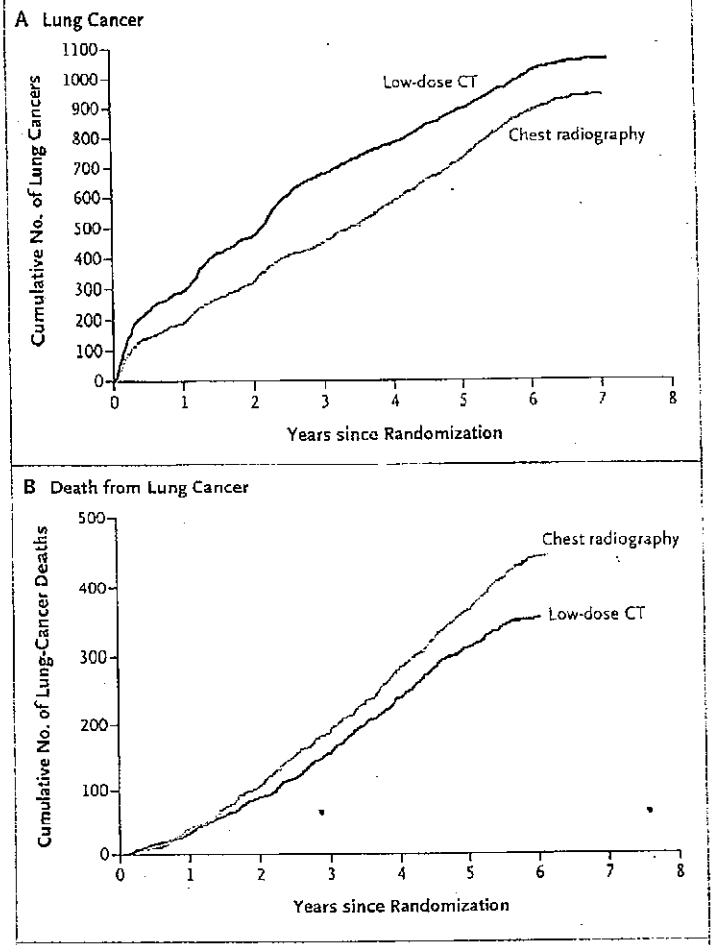

Figure 1. **Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.**

The number of lung cancers (Panel A) includes lung cancers that were diagnosed from the date of randomization through December 31, 2009. The number of deaths from lung cancer (Panel B) includes deaths that occurred from the date of randomization through January 15, 2009.

The designers of the NLST reasoned that if the PLCO trial were to show a reduction in lung-cancer mortality with radiographic screening, a trial of low-dose CT screening in which a community-care group was the control would be of less value, since the standard of care would have become screening with chest radiography. Nevertheless, the choice of radiography precludes a direct comparison of low-dose CT with community care. Analysis of the subgroup of PLCO participants who met the NLST criteria for age and smoking history indicated that radiography, as compared with community care, does not reduce mortality from lung cancer.[27] Therefore, a similar reduction

Table 6. Histologic Type of Lung Cancers in the Two Screening Groups, According to Tumor Stage.*

Histologic Type	Total No. of Cancers	Stage of Cancer						
		IA	IB	IIA	IIB	IIIA	IIIB	IV
		number/total number (percent)						
Low-dose CT group								
Bronchioloalveolar carcinoma	110	83/110 (75.5)	6/110 (5.5)	3/110 (2.7)	1/110 (0.9)	1/110 (0.9)	8/110 (7.3)	8/110 (7.3)
Adenocarcinoma	380	173/376 (46.0)	48/376 (12.8)	17/376 (4.5)	10/376 (2.7)	31/376 (8.2)	33/376 (8.8)	64/376 (17.0)
Squamous-cell carcinoma	243	90/239 (37.7)	35/239 (14.6)	9/239 (3.8)	16/239 (6.7)	26/239 (10.9)	32/239 (13.4)	31/239 (13.0)
Large-cell carcinoma	41	17/41 (41.5)	4/41 (9.8)	0/41	3/41 (7.3)	7/41 (17.1)	5/41 (12.2)	5/41 (12.2)
Non–small-cell carcinoma, other†	131	38/127 (29.9)	10/127 (7.9)	1/127 (0.8)	5/127 (3.9)	16/127 (12.6)	17/127 (13.4)	40/127 (31.5)
Small-cell carcinoma	137	8/133 (6.0)	1/133 (0.8)	5/133 (3.8)	3/133 (2.3)	17/133 (12.8)	27/133 (20.3)	72/133 (54.1)
Carcinoid	6	2/2 (100.0)	0/2	0/2	0/2	0/2	0/2	0/2
Unknown	12	5/12 (41.7)	0/12	0/12	0/12	1/12 (8.3)	0/12	6/12 (50.0)
Total	1060	416/1040 (40.0)	104/1040 (10.0)	35/1040 (3.4)	38/1040 (3.7)	99/1040 (9.5)	122/1040 (11.7)	226/1040 (21.7)
Radiography group								
Bronchioloalveolar carcinoma	35	17/35 (48.6)	1/35 (2.9)	1/35 (2.9)	2/35 (5.7)	3/35 (8.6)	5/35 (14.3)	6/35 (17.1)
Adenocarcinoma	328	83/326 (25.5)	42/326 (12.9)	17/326 (5.2)	12/326 (3.7)	29/326 (8.9)	29/326 (8.9)	114/326 (35.0)
Squamous-cell carcinoma	206	51/205 (24.9)	29/205 (14.1)	6/205 (2.9)	17/205 (8.3)	24/205 (11.7)	28/205 (13.7)	50/205 (24.4)
Large-cell carcinoma	43	9/42 (21.4)	5/42 (11.9)	1/42 (2.4)	1/42 (2.4)	10/42 (23.8)	7/42 (16.7)	9/42 (21.4)
Non–small-cell carcinoma or other†	158	20/155 (12.9)	9/155 (5.8)	3/155 (1.9)	5/155 (3.2)	24/155 (15.5)	24/155 (15.5)	70/155 (45.2)
Small-cell carcinoma	159	11/157 (7.0)	6/157 (3.8)	4/157 (2.5)	5/157 (3.2)	18/157 (11.5)	28/157 (17.8)	85/157 (54.1)
Carcinoid	2	2/2 (100.0)	0/2	0/2	0/2	0/2	0/2	0/2
Unknown	10	3/7 (42.9)	1/7 (14.3)	0/7	0/7	1/7 (14.3)	1/7 (14.3)	1/7 (14.3)
Total	941	196/929 (21.1)	93/929 (10.0)	32/929 (3.4)	42/929 (4.5)	109/929 (11.7)	122/929 (13.1)	335/929 (36.1)

* The denominators represent only cancers for which the stage was known.

† The 289 lung cancers in this category (in the two groups combined) included 28 adenosquamous carcinomas, 6 sarcomatoid carcinomas, 55 unclassified carcinomas, 1 anaplastic-type carcinoma, 1 carcinosarcoma, and 198 coded only as "non–small-cell carcinoma."

Table 7. Cause of Death on the Death Certificate, According to Screening Group.*

Cause of Death	Low-Dose CT Group	Radiography Group	Total
		number/total number (percent)	
Neoplasm of bronchus and lung†	427/1865 (22.9)	503/1991 (25.3)	930/3856 (24.1)
Other neoplasm	416/1865 (22.3)	442/1991 (22.2)	858/3856 (22.3)
Cardiovascular illness	486/1865 (26.1)	470/1991 (23.6)	956/3856 (24.8)
Respiratory illness	175/1865 (9.4)	226/1991 (11.4)	401/3856 (10.4)
Complications of medical or surgical care	12/1865 (0.6)	7/1991 (0.4)	19/3856 (0.5)
Other	349/1865 (18.7)	343/1991 (17.2)	692/3856 (17.9)

* A total of 3875 death certificates were received (1877 for participants in the low-dose CT group and 1998 for those in the radiography group), but the cause of death was unknown for 12 participants in the low-dose CT group and 7 in the radiography group. The denominators represent only the deaths for which the cause was known. Causes of death were categorized according to the following codes in the *International Classification of Diseases, 10th Revision* (ICD-10): neoplasms of bronchus and lung, C33-C34; neoplasms other than bronchus and lung, C00-D48 (excluding C33 and C34); cardiovascular illness, I00-I99; respiratory illness, J00-J99; complications of medical or surgical care, S00-T17.8, T18-T99, and Y40-Y84; unknown, R96-R99 and death certificates without a coded cause of death; and other, all remaining codes.

† The number of deaths from neoplasm of the bronchus and lung in this table is not equal to the number of lung-cancer deaths in the lung-cancer mortality analysis. The lung-cancer deaths included here are those that were determined from information on the death certificate only (without review by the end-point verification team) and include deaths that occurred through December 31, 2009.

in lung-cancer mortality would probably have been observed in the NLST if community care had been chosen instead for the control group.

In addition to the high rate of false positive results, two other potentially harmful effects of low-dose CT screening must be mentioned. Overdiagnosis, a major source of controversy surrounding low-dose CT lung-cancer screening, results from the detection of cancers that never would have become symptomatic.[28] Although additional follow-up would be necessary to measure the magnitude of overdiagnosis in the NLST, a comparison of the number of cancers diagnosed in the two trial groups suggests that the magnitude of overdiagnosis with low-dose CT as compared with radiographic screening is not large. The other harmful effect, the association of low-dose CT with the development of radiation-induced cancers, could not be measured directly, is a long-term phenomenon, and must be assessed in future analyses.[29]

A number of smaller, randomized trials of low-dose CT screening are under way in Europe.[30-36] Because none of these trials have sufficient statistical power to detect a reduction in lung-cancer mortality of the magnitude seen in the NLST, it is expected that meta-analyses of the findings from these trials will be performed. The European studies are gathering types of data that were not collected by the NLST and will be able to address additional questions about low-dose CT screening, including the best strategies for the management of nodules observed with screening.[37]

The observation that low-dose CT screening can reduce the rate of death from lung cancer has generated many questions. Will populations with risk profiles that are different from those of the NLST participants benefit? Are less frequent screening regimens equally effective? For how long should screening continue? Would the use of different criteria for a positive screening result, such as a larger nodule diameter, still result in a benefit? It is unlikely that large, definitive, randomized trials will be undertaken to answer these questions, but modeling and microsimulation can be used to address them. Although some agencies and organizations are contemplating the establishment of lung-cancer screening recommendations on the basis of the findings of the NLST, the current NLST data alone are, in our opinion, insufficient to fully inform such important decisions.

Before public policy recommendations are crafted, the cost-effectiveness of low-dose CT screening must be rigorously analyzed. The reduction in lung-cancer mortality must be weighed against the harms from positive screening results and

overdiagnosis, as well as the costs. The cost component of low-dose CT screening includes not only the screening examination itself but also the diagnostic follow-up and treatment. The benefits, harms, and costs of screening will all depend on the way in which low-dose CT screening is implemented, specifically in regard to the eligibility criteria, screening frequency, interpretation threshold, diagnostic follow-up, and treatment. For example, although there are currently only about 7 million persons in the United States who would meet the eligibility criteria for the NLST, there are 94 million current or former smokers[6] and many more with secondhand exposure to smoke or other risk factors. The cost-effectiveness of low-dose CT screening must also be considered in the context of competing interventions, particularly smoking cessation. NLST investigators are currently analyzing the quality-of-life effects, costs, and cost-effectiveness of screening in the NLST and are planning collaborations with the Cancer Intervention and Surveillance Modeling Network to investigate the potential effect of low-dose CT screening in a wide range of scenarios.

Other strategies for early detection of lung cancer — in particular, molecular markers in blood, sputum, and urine, which can be studied in specimens that were obtained as part of ACRIN's NLST activities and are available to the research community — may one day help select persons who are best suited for low-dose CT screening or identify persons with positive low-dose CT screening tests who should undergo more rigorous diagnostic evaluation.

The American College of Radiology Imaging Network component of the National Lung Screening Trial (NLST) was funded through grants (U01-CA-80098 and U01-CA-79778) under a cooperative agreement with the Cancer Imaging Program, Division of Cancer Treatment and Diagnosis. The Lung Screening Study sites of the NLST were funded through contracts with the Early Detection Research Group and Biometry Research Group, Division of Cancer Prevention: University of Colorado Denver (N01-CN-25514), Georgetown University (N01-CN-25522), Pacific Health Research and Education Institute (N01-CN-25515), Henry Ford Health System (N01-CN-25512), University of Minnesota (N01-CN-25513), Washington University in St. Louis (N01-CN-25516), University of Pittsburgh (N01-CN-25511), University of Utah (N01-CN-25524), Marshfield Clinic Research Foundation (N01-CN-25518), University of Alabama at Birmingham (N01-CN-75022), Westat (N01-CN-25476), and Information Management Services (N02-CN-63300).

Mr. Clapp reports holding a financial interest in Human Genome Sciences; and Dr. Gatsonis, receiving consulting fees from Wilex, MELA Sciences, and Endocyte, lecture fees from Bayer HealthCare, and support from the Radiological Society of North America for developing educational presentations. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the trial participants for their contributions in making this trial possible.

APPENDIX

The members of the writing team of the National Lung Screening Trial Research Team are as follows: Denise R. Aberle, M.D., University of California at Los Angeles, Los Angeles; Amanda M. Adams, M.P.H., American College of Radiology Imaging Network (ACRIN) Biostatistics Center, Brown University, Providence, RI; Christine D. Berg, M.D., Division of Cancer Prevention, National Cancer Institute, Bethesda, MD; William C. Black, M.D., Dartmouth–Hitchcock Medical Center, Lebanon, NH; Jonathan D. Clapp, B.S., Information Management Services, Rockville, MD; Richard M. Fagerstrom, Ph.D., Division of Cancer Prevention, National Cancer Institute, Bethesda, MD; Ilana F. Gareen, Ph.D., ACRIN Biostatistics Center, Brown University, Providence, RI; Constantine Gatsonis, Ph.D., ACRIN Biostatistics Center, Brown University, Providence, RI; Pamela M. Marcus, Ph.D., Division of Cancer Prevention, National Cancer Institute, Bethesda, MD; and JoRean D. Sicks, M.S., ACRIN Biostatistics Center, Brown University, Providence, RI.

REFERENCES

1. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature 2008;455:1069-75.
2. Sanders HR, Albitar M. Somatic mutations of signaling genes in non-small-cell lung cancer. Cancer Genet Cytogenet 2010;203:7-15.
3. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300. [Erratum, CA Cancer J Clin 2011;61:133-4.]
4. Cancer of the lung and bronchus (invasive): trends in SEER incidence and U.S. mortality using the Joinpoint Regression Program, 1975-2007 with up to four Joinpoints, 1992-2007 with up to two Joinpoints, both sexes by race/ethnicity. (http://seer.cancer.gov/csr/1975_2007/results_merged/sect_15_lung_bronchus.pdf.)
5. Pierce JP, Messer K, White MM, Cowling DW, Thomas DP. Prevalence of heavy smoking in California and the United States, 1965-2007. JAMA 2011;305:1106-12.
6. Cigarette smoking among adults and trends in smoking cessation — United States, 2008. MMWR Morb Mortal Wkly Rep 2009;58:1227-32.
7. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 2010;19:1893-907.
8. Doria-Rose VP, Szabo E. Screening and prevention of lung cancer. In: Kernstine KH, Reckamp KL, eds. Lung cancer: a multidisciplinary approach to diagnosis and management. New York: Demos Medical Publishing, 2010:53-72.
9. Naidich DP, Marshall CH, Gribbin C, Arams RS, McCauley DI. Low-dose CT of the lungs: preliminary observations. Radiology 1990;175:729-31.
10. The National Lung Screening Trial Research Team. The National Lung Screening Trial: overview and study design. Radiology 2011;258:243-53.
11. Church TR, National Lung Screening Trial Executive Committee. Chest radiography as the comparison for spiral CT in the National Lung Screening Trial. Acad Radiol 2003;10:713-5.
12. The National Lung Screening Trial Research Team. Baseline characteristics of participants in the randomized National Lung Screening Trial. J Natl Cancer Inst 2010;102:1771-9.
13. Cagnon CH, Cody DD, McNitt-Gray MF, Seibert JA, Judy PF, Aberle DR. Description and implementation of a quality

control program in an imaging-based clinical trial. Acad Radiol 2006;13:1431-41.
14. Gierada DS, Garg K, Nath H, Strollo DC, Fagerstrom RM, Ford MB. CT quality assurance in the lung screening study component of the National Lung Screening Trial: implications for multicenter imaging trials. AJR Am J Roentgenol 2009;193:419-24.
15. Fritz A, Percy C, Jack A, et al., eds. International classification of diseases for oncology. 3rd ed. Geneva: World Health Organization, 2000.
16. Greene FL, Page DL, Fleming ID, et al. AJCC cancer staging manual. 6th ed. New York: Springer-Verlag, 2002.
17. Izmirlian G. Estimation of the relative risk following group sequential procedure based upon the weighted log-rank statistic. arXiv, Cornell University Library, 2011. (http://arxiv.org/abs/1102.5088.)
18. SAS/STAT, version 9.2. Cary, NC: SAS Institute, 2004.
19. R Development Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2009.
20. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Boca Raton, FL: Chapman & Hall/CRC, 2000.
21. Statement concerning the National Lung Screening Trial. October 28, 2010. (http://www.cancer.gov/images/DSMB-NLST.pdf.)
22. Department of Commerce, Census Bureau. National Cancer Institute and Centers for Disease Control and Prevention co-sponsored tobacco use special cessation supplement to the current population survey. 2003. (http://riskfactor.cancer.gov/studies/tus-cps.)
23. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
24. Pinsky PF, Miller A, Kramer BS, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. Am J Epidemiol 2007;165:874-81.
25. Mahesh M, Hevezi JM. Slice wars vs dose wars in multiple-row detector CT. J Am Coll Radiol 2009;6:201-2.
26. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 2001;345:181-8.
27. NCI NLST press conference. NCI radio broadcasts. November 4, 2010. (http://www.cancer.gov/newscenter/radio-broadcasts.)
28. Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst 2010;102:605-13.
29. Berrington de González A, Kim KP, Berg CD. Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk. J Med Screen 2008;15:153-8.
30. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2007;120:868-74.
31. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish Randomized lung cancer ct screening trial — overall design and results of the prevalence round. J Thorac Oncol 2009;4:608-14.
32. Lopes Pegna A, Picozzi G, Mascalchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. Lung Cancer 2009;64:34-40.
33. Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med 2009;180:445-53.
34. Marchianò A, Calabrò E, Civelli E, et al. Pulmonary nodules: volume repeatability at multidetector CT lung cancer screening. Radiology 2009;251:919-25.
35. Becker N, Delorme S, Kauczor H-U. LUSI: the German component of the European trial on the efficacy of multi-slice CT for the early detection of lung cancer. Onkologie 2008;31:Suppl 1:PO320. abstract.
36. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. Thorax 2011;66:308-13.
37. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-9.