Lung Cancer

NCRI
National
Cancer
Research
Institute

LUNG CANCER
RESEARCH IN THE UK
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LUNG CANCER RESEARCH IN THE UK:

Report of the NCRI Strategic Planning Group on Lung Cancer

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CHAPTER ONE

EXECUTIVE SUMMARY

In its 2002 Strategic Analysis, NCRI identified that lung cancer has received much less funding than research on other cancers, relative to both incidence and mortality. For this report, NCRI Partners have explored possible reasons for the low level of investment and considered how best to encourage more lung cancer research. Wherever possible, this consideration has been informed by objective evidence.

In summary, our findings showed that:

- In 2005, of research targeted to a specific tumour type, only 3.9% was aimed at lung cancer, although this disease accounts for 22% of all cancer deaths.
- Lung cancer has a reputation for being difficult to study and has been associated with a culture of 'nihilism'.
- The UK's publication output for lung cancer as a proportion of total biomedical output runs at only 60% of the world average.
- A workforce survey identified 160 scientists and clinicians engaged in research on lung cancer. However on average they spent less than half their research time studying lung cancer.
- Difficulty in obtaining lung cancer tissue for study is an obstacle to some types of research.
- The poor survival rate from lung cancer means that many patients do not get the opportunity to participate in research, and also patient advocacy for more research is less well developed than for other cancers.

However there were some more encouraging signs:

- The quality of UK lung cancer publications is higher than the world average in terms of the impact factor of the journals in which they were published and numbers of citations they receive.
- Worldwide there is an upward trend in the proportion of lung cancer publications appearing in the Science Citation Index.
- A workforce survey suggested that there is capacity for more lung cancer research if the right incentives can be found.
- There is no evidence that applications for research grants in lung cancer are treated less favourably than those for other cancers. There is evidence of a higher than average success rate at one peer review committee.
- New treatments are becoming available and there is a strong portfolio of clinical trials.

Partners concluded that the poor positioning of lung cancer research is long-standing, with deep-seated origins. There is no single mechanism to increase research activity. Instead, needs and opportunities have been identified across a number of scientific priorities within lung cancer. Some encouraging trends exist and sustained effort is needed by NCRI Partners and others to push forward the agreed actions. At publication, the recommended actions are at varying stages of planning and readiness for implementation. Some will need dedicated funding whilst others will be pursued through existing funding mechanisms. NCRI will actively monitor progress, encourage collaboration across disciplines in lung cancer, and will publish updates as appropriate.

In summary the agreed actions are:
(see Chapter 8 for more detail)

The profile of lung cancer research

1 NCRI will establish a working party among organisations specialising in communication about cancer, to develop actions targeted at raising the profile of lung cancer research – its needs, value, and potential for impact. Groups to be targeted will include professionals, young people considering a career in science and the public. The working party will also consider how to promote patient advocacy. It is likely that targeted resources will be required to take forward the actions of this working party.

Biology of lung cancer

2 onCore UK and the Lung Cancer Clinical Studies Group will create and implement a plan for the collection of lung cancer biospecimens. A framework for this has been drawn up and its implementation will reflect the priorities outlined in this report, covering all major lung cancer types (including mesothelioma).

3 Studies examining how normal cells progress to become lung cancer cells will be promoted. This will require the collection of specimens from volunteers at high risk of developing lung cancer and as such will interact with Action 2 above.

Screening and early diagnosis

4 NCRI will convene a meeting of health economists, clinicians and policy-makers as a first step in constructing a health economic model for spiral CT screening for lung cancer. This model will help to identify and define the interrelationship between the key factors that will determine the feasibility of a national screening programme. This will be with a view to identifying evidence gaps to which research can then be targeted.

5 NCRI Partners should actively develop research on the identification and validation of biomarkers, particularly diagnostic biomarkers. This will need careful planning to dovetail with the evolving biomarker strategies of individual Partners, and will also be dependent on the collection of lung cancer biospecimens. It is likely to require specific incentives in the form of dedicated funding to draw more investigators into lung cancer research, and will also include collaboration with industry.

Provision of care

6 The link between the NCRI Lung Cancer Clinical Studies Group (CSG) and the Primary Care Clinical Studies Development Group will be strengthened, and the latter will be asked explicitly to consider developing more studies in lung cancer. Topics could include issues of care delivery as well as improvements in diagnosis.

7 NCRI will bring together cancer researchers, behavioural scientists, health educators and health policy-makers to agree actions on the development and evaluation of interventions to encourage early help-seeking behaviour among people who are at high risk of having cancer.

Supportive and palliative care

8 The needs of lung cancer patients for supportive and end-of-life care will be specifically targeted with a call for proposals for which dedicated funds have already been pledged. The call will be managed by the existing Management Committee for the NCRI Supportive and Palliative Care Collaboratives.

Mesothelioma

9 The Department of Health for England is developing a framework for mesothelioma services which will also facilitate research. The NCRI Lung Cancer Clinical Studies Group will consider how to increase the number of mesothelioma patients who can be offered clinical trials through the NCRN network, and any tissue banking initiative will include mesothelioma.

CHAPTER TWO

INTRODUCTION

2.1 THE NATIONAL CANCER RESEARCH INSTITUTE

The NCRI is a partnership which brings together government, charity and private sector organisations in order to utilise the resources available for cancer research in the UK in the most effective way, through coordination of effort and joint planning towards an integrated national strategy for cancer research. The primary mission of the NCRI is to maximise the patient benefit from cancer research in the UK and to ensure that research is also targeted towards a reduction in the incidence of cancer in the longer term. Our activities are intended to have additional benefits, for example in increasing the knowledge base for biomedicine more widely, in the commercial exploitation of discoveries and in the dissemination of information relating to cancer research in the UK.

In discharging its role and mission, NCRI:

- Provides strategic oversight for cancer research, identifying gaps in the cancer research portfolio in the UK and highlighting new scientific opportunities;
- Promotes joint initiatives in order to address research gaps and to capitalise on opportunities;
- Coordinates clinical and translational research in cancer through national networks;
- Develops national facilities and resources.

As one of its core activities the NCRI established a database containing information on the cancer research conducted by the Partners (for a full list of the Partners see Appendix I). In October 2002 the NCRI published its report 'Strategic Analysis 2002: An overview of Cancer Research in the UK directly funded by the NCRI Partner Organisations' (www.ncri.org.uk). For the first time this provided an accurate picture of how cancer research funding in the UK is distributed across disease sites and areas of research.

2.2 LUNG CANCER AS A PRIORITY

Lung cancer causes over 33,000 deaths every year in the UK, accounting for 6% of all deaths and 22% of deaths due to cancer. Survival rates from lung cancer are low, with only 7% of patients in England and Wales alive five years after diagnosis compared to a figure of approximately 15% in the US (CR-UK CancerStats Monograph, 2004). There has been little improvement in survival rates since the introduction of platinum based chemotherapy.

Tobacco causes 80-90% of lung cancer cases (CR-UK CancerStats Monograph, 2004). It is often stated that tobacco control measures are likely to be the most important single tool in decreasing lung cancer mortality. Yet, however effective such measures are, we will continue to have large numbers of cases in smokers and ex-smokers for some time to come. Non-tobacco related lung cancer deaths are also significant, killing more people every year in the UK than cervical cancer and melanoma combined. Research is therefore still needed to improve the outcomes for all lung cancer patients.

One of the most striking findings from analysis of the NCRI Cancer Research Database is that the funding received by lung cancer research is much lower than for other cancers, relative to both incidence and mortality (NCRI Strategic Analysis, 2002).

As a result, NCRI decided to undertake a more detailed study of lung cancer research in order to gain a better understanding of why this might be and to consider possible remedies to help redress the balance.

2.3 THE STRATEGIC PLANNING GROUP ON LUNG CANCER

2.3.1 Approach

The NCRI set up its Strategic Planning Group on Lung Cancer in mid-2004.

Strategic Planning Groups (SPGs) are joint planning exercises, aimed at developing a coherent approach among a group of NCRI Partners to funding research in specific areas. The Groups consist of senior representatives of NCRI partner organisations, patient representatives and other interested parties where appropriate. The role of an SPG is to carry out an evidence-based overview of an area to identify gaps and opportunities in research and begin to implement and oversee agreed actions which participating Partners may undertake either individually or collectively.

The method of working is to gather evidence from multiple sources, which generally include analysis from the NCRI's own Cancer Research Database, expert opinion, published data and, where appropriate, specially commissioned reports. The SPG uses this evidence to examine issues such as resources and infrastructure, training and workforce capacity, funding and portfolio balance to identify key priority areas, and any barriers to progress in those areas. This evidence-based approach allows the SPG to devise solutions tailored to the obstacles and opportunities in the area under investigation.

The next three chapters summarise the evidence that has been gathered, and Chapter 6 then analyses the reasons for the low level of funding. Chapter 7 addresses scientific priorities in broad terms and Chapter 8 details the planned actions designed to increase the quality and quantity of lung cancer research in the UK.

2.3.2 Membership

The Lung Cancer SPG was chaired by Peter Cardy, Chief Executive of Macmillan Cancer Support, and consisted of senior representatives from Cancer Research UK, the Medical Research Council, the Department of Health for England, the Scottish Executive Health Department, the Roy Castle Lung Cancer Foundation and the National Cancer Director for England. In addition, there were two patient members and the Chief Executive of Cancerbackup (see Appendix II for full details of membership).

2.3.3 Terms of reference

The remit of the Lung Cancer SPG was:

- To take a strategic overview of UK research in the field;
- To identify opportunities for appropriate action by NCRI member organisations, either collaboratively or individually;
- To maximise impact of research for the benefit of patients and their carers.

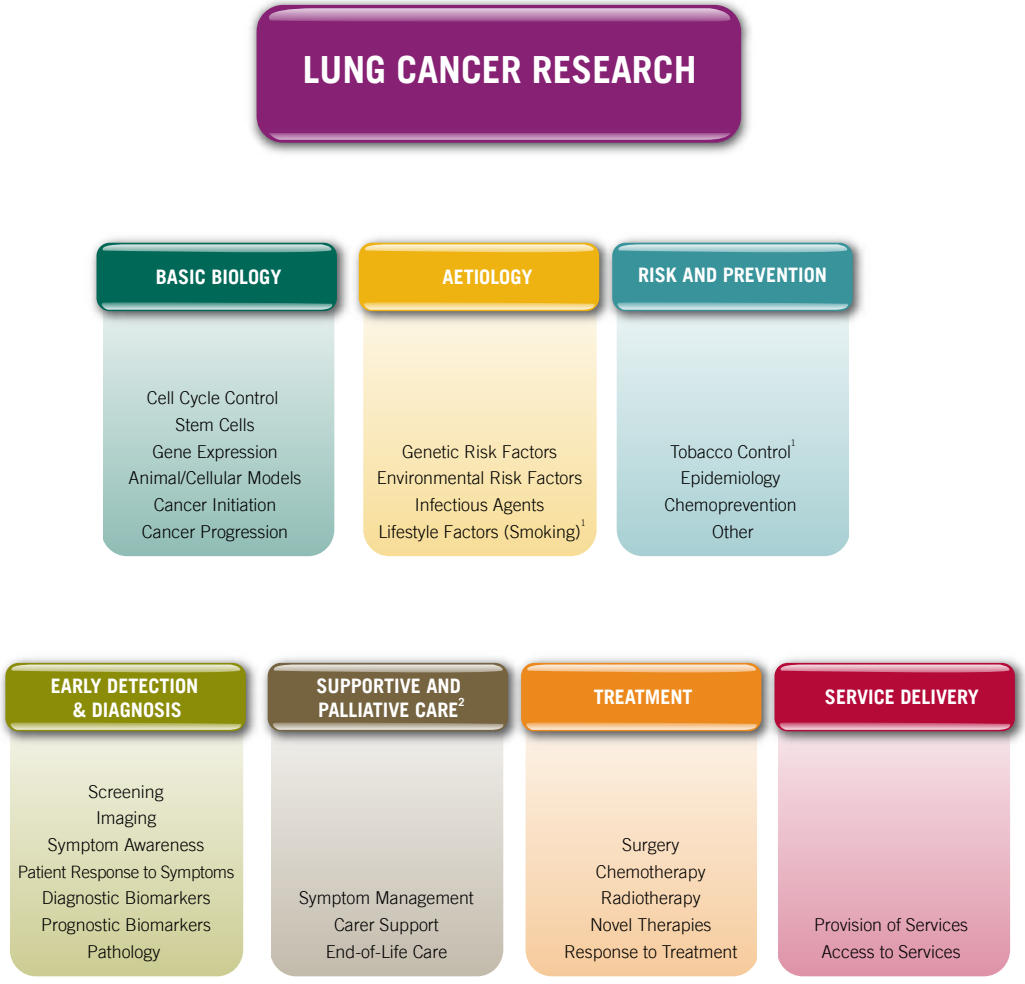
2.3.4 Scope

For the purposes of the SPG, lung cancer was defined to include all primary non-small cell lung cancers, small cell lung cancer, and mesothelioma of the pleura. Cancer of others parts of the respiratory tract or thorax were not considered.

Some areas of potential relevance were not considered. Notably, research on prevention has been the subject of an earlier SPG, which led to the National Prevention Research Initiative (NPRI) (www.mrc.ac.uk/index/funding-npri.html). This funds research on health behaviours, including projects aimed at reducing the prevalence of smoking. In the first funding round, 4 tobacco control projects were awarded a total of £0.5m and another funding round is expected by the end of 2006. The UK Clinical Research Collaboration (UKCRC) is also running an SPG on Public Health which, following on from the NPRI, has identified tobacco control as an area of major importance. In addition, both the NCRI Lung Cancer Clinical Studies Group and the Primary Care Clinical Studies Development Group will continue to explore new research proposals in this area.

NCRI has also established two Collaboratives in Supportive and Palliative Care, following recommendations from another SPG. The Lung Cancer SPG has therefore only addressed issues in this area of specific relevance to lung cancer.

The scope of the SPG is summarised in **Figure 1**.



1. Areas covered by other SPGs or outside the remit of the Lung Cancer SPG.
2. Only areas with specific relevance to lung cancer were considered.

FIGURE 1: Scope of the NCRI Lung Cancer SPG

CHAPTER THREE

BREAKDOWN OF NCRI PARTNERS' FUNDING OF LUNG CANCER RESEARCH

3.1 METHOD

The grants contained in the Cancer Research Database are coded by disease site and by the internationally recognised Common Scientific Outline (CSO) (http://www.cancerportfolio.org/cso.jsp). The CSO is organised into seven over-arching categories;

- Biology
- Aetiology
- Prevention
- Early Detection, Diagnosis and Prognosis
- Treatment
- Cancer Control, Survival and Outcomes
- Scientific Model Systems

These categories are then subdivided into 38 specific codes. Used in conjunction with the disease site coding, this system enables comparison of portfolios, and when applied consistently over time, can help to identify trends in research funding.

For the Lung Cancer SPG, an analysis of the 2005 Cancer Research Database (CRD) was conducted by disease type and by CSO code.

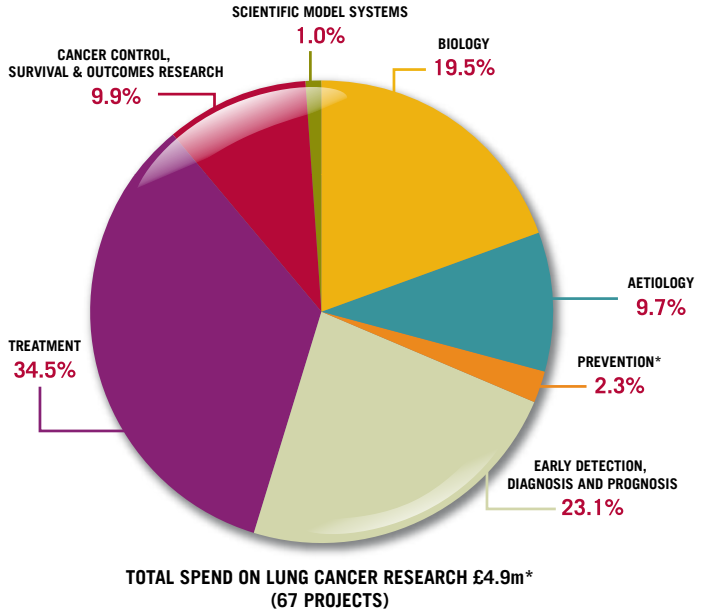


FIGURE 2: Breakdown of spend on lung cancer by Common Scientific Outline, 2005

Approximately 40% of the entire NCRI portfolio can be classified by disease site, with the other 60% being either fundamental research or relevant to all tumour sites. The awards that were identified by this filter were then examined for content, with any awards on tobacco control segregated in the analysis, as they are not included in the scope of the SPG. (Note: In the coding system mesothelioma grants are designated lung cancer.)

3.2 RESULTS

Using data from the 2005 CRD entry, there were 67 lung cancer projects (excluding tobacco control) including one mesothelioma project, accounting for £4.9m pa of research spend (£5.5m pa including tobacco control). This represents 1.4% of the entire cancer research spend, or 3.9% of the research that can be attributed to a specific disease. Lung cancer research has received an additional £2m since 2002, although approximately £0.9m of this is due to inclusion of data from the Roy Castle Lung Cancer Foundation, who joined the NCRI in 2004.

The largest portion of spend on lung cancer research is on treatment (35%), with early detection, diagnosis and prognosis second with 23% (**Figure 2**). However, it should be noted that due to the small size of the lung cancer portfolio, any analysis can be easily skewed by single large awards. For example, in 2004 only 10% of the portfolio was spent on basic biology, while by 2005 this proportion had doubled, largely due to a single award by the MRC.

When research spend is compared to disease mortality, it is clear that there is a large disparity between the burden of lung cancer and the funding devoted to it. Lung cancer accounts for 22% of all cancer deaths, yet attracts only 4.4% of the site specific research spend (includes tobacco control), accounting for a difference of 17% as illustrated in **Figure 3**.

(For further details of the analysis please see Appendix III.)

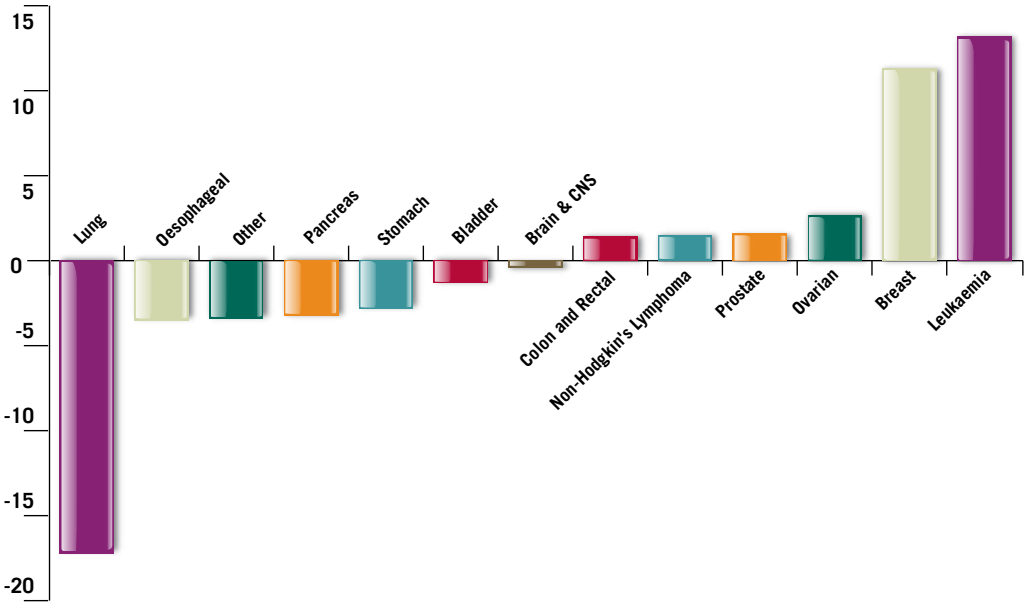


FIGURE 3: Difference between percentage spend on research and percentage of cancer mortalities due to each disease site

CHAPTER FOUR

OUTPUT FROM LUNG CANCER RESEARCH IN THE UK: BIBLIOMETRIC ANALYSIS

4.1 METHOD

Professor Grant Lewison of City University was commissioned to undertake a bibliometric analysis of the UK output of lung cancer research in comparison with other countries. A filter was developed to identify lung cancer publications present in the Science Citation Index (SCI) between 1999 and 2003. This was based on all papers from the journal *"Lung Cancer"*; papers in respiratory journals with "cancer" words in the title; papers in cancer journals with a "respiratory" word in the title; or papers with both "respiratory" and "cancer" title words (for further details of the filter see Appendix IV). The filter has a specificity (precision) of 0.91 and sensitivity of 0.94.

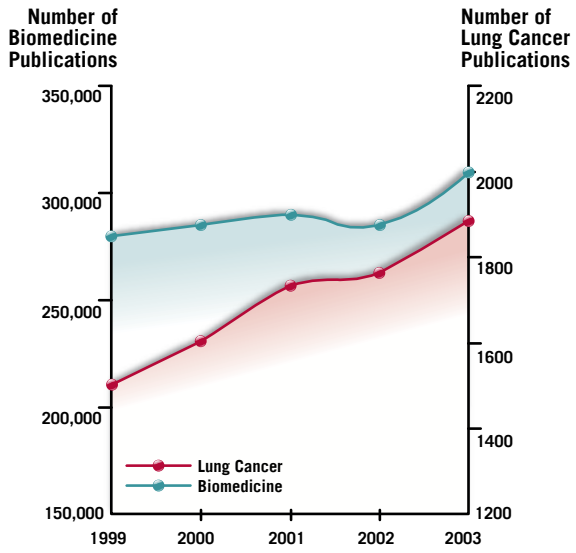


FIGURE 4: Lung cancer publications as a proportion of biomedicine publications as a whole, 1999 - 2003

4.2 RESULTS

In 1999 lung cancer publications accounted for 0.54% of all biomedicine publications included in the Science Citation Index, rising to 0.61% in 2003 (**Figure 4**). When the world output from lung cancer research (measured in numbers of publications) versus biomedicine as a whole is arbitrarily assigned a value of 1.0, the output of individual countries relative to this world average can be assessed. As shown in **Figure 5**, the UK has a relative output of 0.6 for lung cancer research.

Given the small spend on lung cancer research in the UK, this under-representation is not unexpected. A previous publication suggests that this position is not reflected in respiratory medicine as a whole, with the UK performing well in diseases such as asthma and cystic fibrosis (*Thorax* 60(1):63-7, 2005).

A more encouraging trend was that UK papers tended to be published in high quality journals and were highly cited, as shown in **Figure 6**. Impact factors are a measure of the influence of a scientific journal, based on how often the papers published in the journal are cited in other publications. Between 1999-2003, 42% of world-wide lung cancer publications were published in journals in the highest impact factor brackets, whereas 50% of UK publications appeared in these brackets, 8% above the average. Of lung cancer papers published in 1999, the world five year average citation rate is 11.3 citations per paper published. This compares with 13.3 citations per paper for publications from the UK, 15% above the world average.

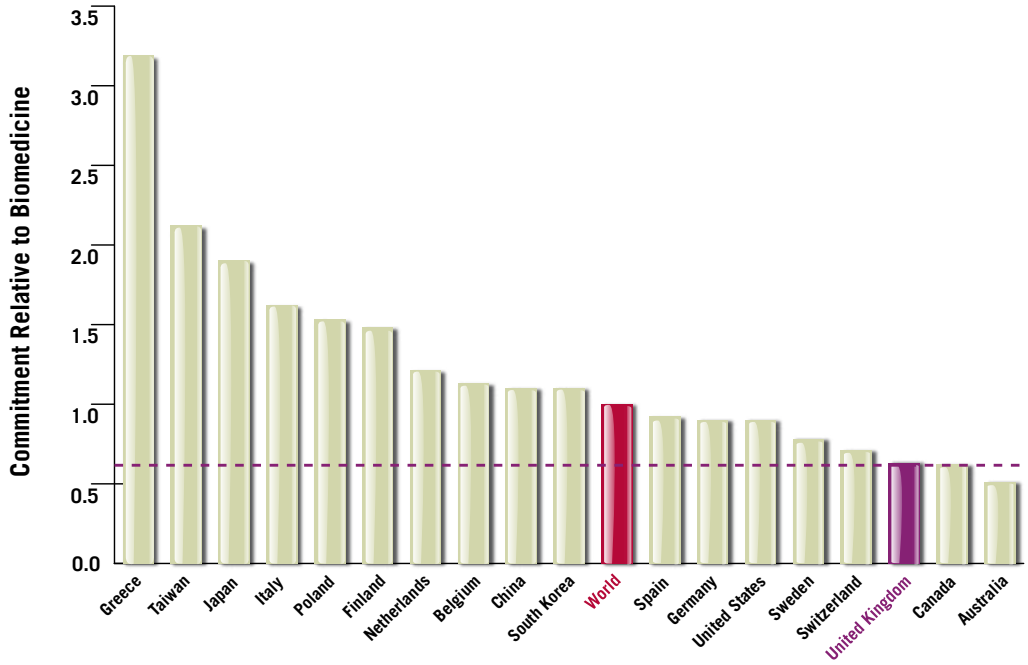


FIGURE 5: Output of lung cancer publications by country relative to biomedicine output as a whole

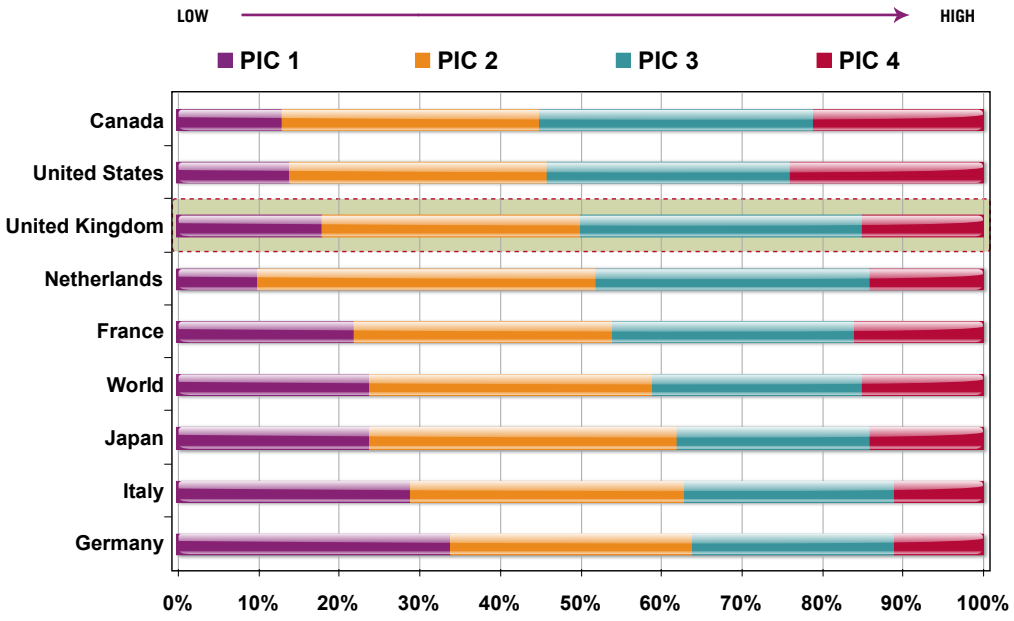


FIGURE 6: Distribution of lung cancer papers by journal impact category (PIC 1 = low, PIC 4 = high) for the eight leading countries and the world, 1999-2003

A postcode analysis was performed to determine what areas were most productive in lung cancer publication. The number of lung cancer publications was compared to the number of publications overall, by different postcodes. This revealed that Liverpool and Leicester have very high numbers of lung cancer publications relative to their overall number of biomedicine publications, as does Oxford (although many publications from the latter concern tobacco control and other areas outside the scope of the SPG). Although London WC is the leading postcode area in terms of biomedical papers overall, it has a relative commitment (RC) to lung cancer research of less than 0.5, while Cambridge has an RC of just 0.25. This suggests that some of the most productive institutions in biomedicine research as a whole have little presence in lung cancer research.

(For further details of the analysis see Appendix IV).

CHAPTER FIVE

WORKFORCE SURVEY

5.1 METHOD

The SPG decided to explore what issues there might be relating to workforce capacity for lung cancer research. To achieve this, a questionnaire was sent out to **principal investigators** active in all areas of the scope covered by the SPG.

The questionnaire was developed in consultation with members of the SPG. The aim was to gather information on the number of researchers active in lung cancer and their areas of current activity (for the complete version of the questionnaire and results please see Appendix V).

Recipients for the questionnaire were identified in several different ways:

- From the Cancer Research Database;
- From contacts provided by members of the SPG;
- From NCRI Clinical Studies Groups;
- From the bibliometric analysis;
- Through referrals by recipients;
- From lists of attendees of lung cancer conferences.

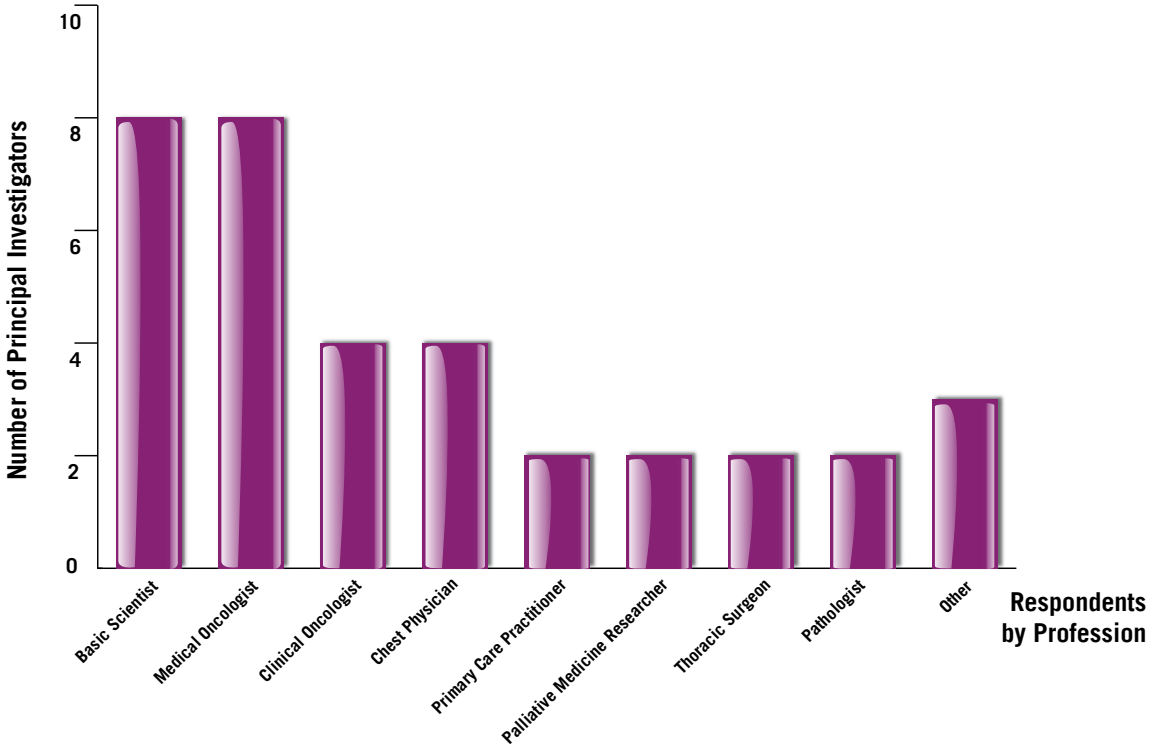


FIGURE 7: Responses to workforce questionnaire by profession of principal investigator

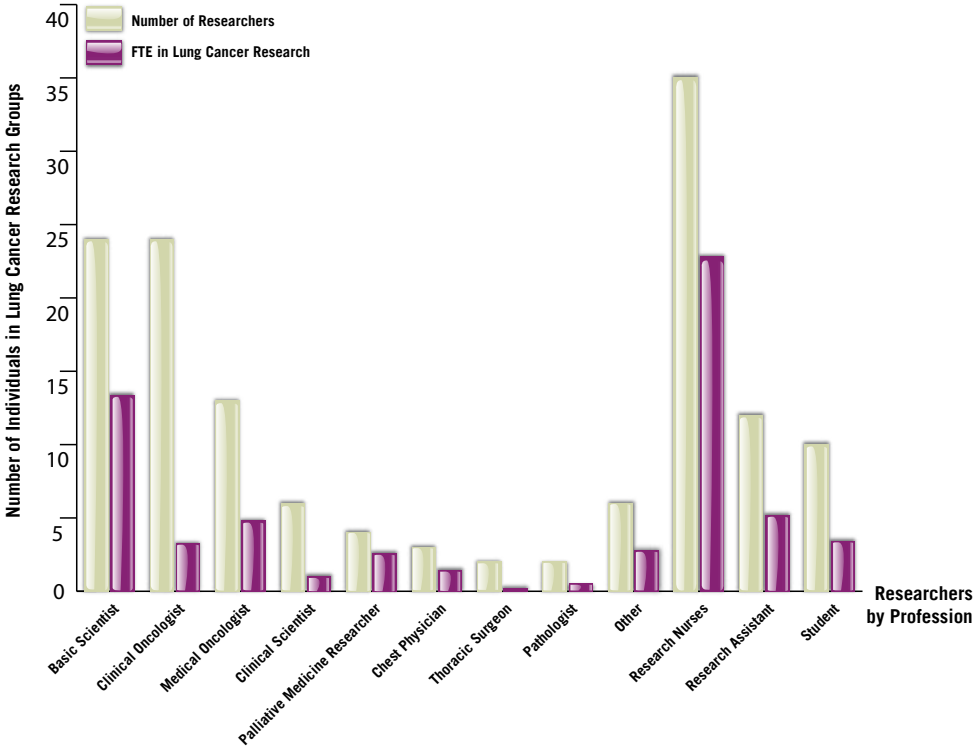


FIGURE 8: Representation of different professions within respondents' research groups

To ensure that a high enough proportion of principal investigators active in lung cancer received the questionnaire the names were cross-referenced against a list of UK researchers who have a lung cancer publication relevant to the SPG in the last five years. From these approaches 110 potentially suitable recipients were identified. Of the 110 questionnaires sent out 58 researchers responded (53%), and of these responses 35 were useable for this analysis. Of the 23 researchers that responded but were not useable, 4 did not fill in the questionnaire satisfactorily, 7 thought that they were not suitable for the survey, 5 had retired from active research and 7 referred us to more suitable colleagues. The number of useable responses was low, but after cross referencing with the lung cancer publication record from 1999-2004, we could only identify one centre with significant interest in lung cancer that did not reply.

5.2 RESULTS

Figure 7 shows the respondents according to the profession with which principal investigators identify themselves. Basic scientists and oncologists accounted for the overall majority (57%) of researchers active in lung cancer, with smaller numbers of chest physicians and other professionals.

Principal investigators (PIs) were asked for the details of their staff working in lung cancer (**Figure 8**). Including the PIs, 160 lung cancer researchers were identified, representing a full time equivalent of 72. There is an average of 4.5 researchers per group (FTE 2.2) with the largest group having 14 members (FTE 5.4). As shown in **Figure 8**, although there are similar numbers of basic scientists and clinical oncologists, the oncologists seem to spend a much smaller portion of their research time on lung cancer, with an FTE of only 3.25 in comparison with 13.33 for the basic scientists. There are also a significant number of research nurses active in this area, but only 10 students were identified, representing a full time equivalent of just 3.4. The SPG thought that this lack of young lung cancer investigators was a concern for the future.

Only 9 out of the 35 groups surveyed replied that they purely or predominantly studied lung cancer, the majority (ie. 20 = 57%) study lung cancer as only one of various disease sites (**Figure 9**). Not only is the number of researchers involved in lung cancer small, but those researchers are,

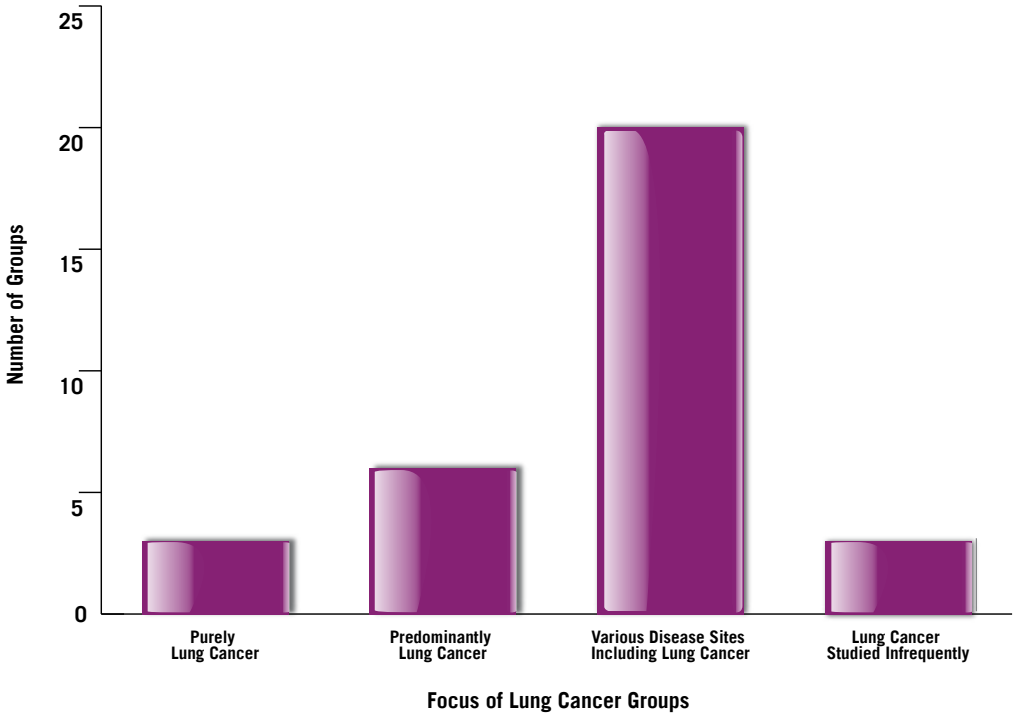


FIGURE 9: Focus of lung cancer research groups

on average, spending just under half of their research time on this disease. This suggests that there is research capacity which could be directed to lung cancer but which currently is not.

The primary research interest of over 18 groups (51% of the respondents) is in treatment of lung cancer, with a smaller number working on early detection and diagnosis, basic biology, aetiology, risk & prevention, and supportive & palliative care (**Figure 10**).

(See Appendix V for further details of the workforce analysis).

Mapping the research publications from the bibliographic analysis onto the groups identified from the questionnaire, gave an overview of the locations in the UK with significant strength and depth in lung cancer research. This approach identified at least four centres with a large number of researchers, a good mix of disciplines amongst the researchers and a good publication record. Four additional centres were identified with strengths in individual areas which, given the opportunity, could develop further.

5.3 CONCLUSIONS

Considered together with the analysis from the Cancer Research Database in Chapter 3 and the results of the bibliometric analysis in Chapter 4, a more complete understanding of the current lung cancer research community can be gained. All the data illustrate, in different ways, the low level of investment in lung cancer, though there are some encouraging signs on quality and an upward trend in the number of publications.

On balance the SPG considered that even though the overall number of researchers is small, there are enough centres with a high enough density of quality lung cancer researchers to constitute critical mass, which could be further developed. Furthermore there is research capacity in these centres which is currently devoted to other diseases which, with the proper incentives, could be re-directed towards lung cancer. There was not therefore, a case for developing 'Collaboratives' as has been done for prostate cancer and in supportive and palliative care.

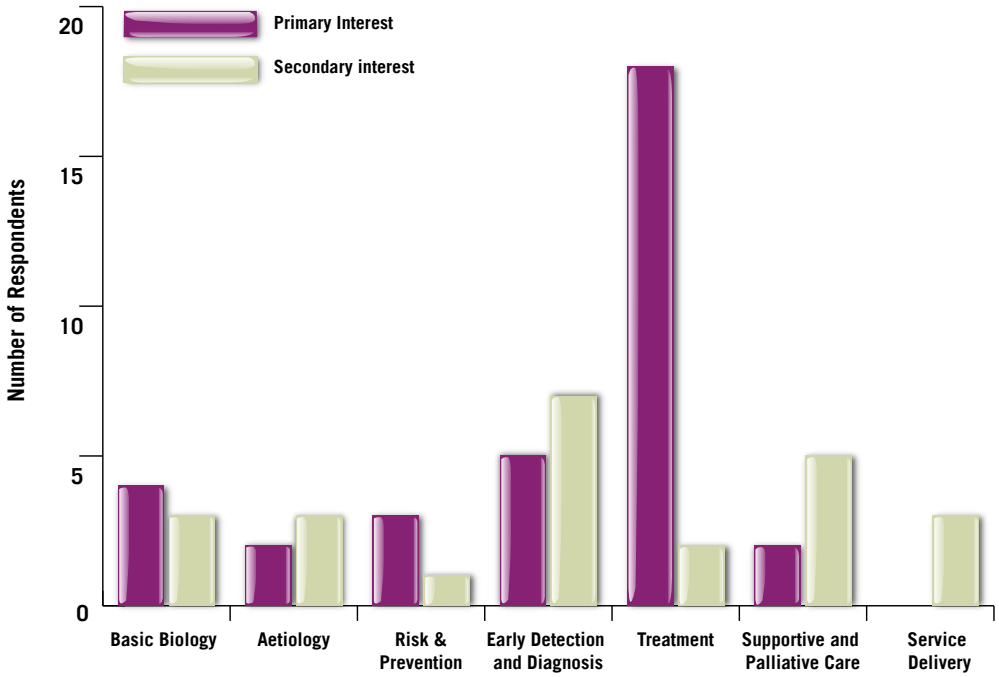


FIGURE 10: Areas of interest for lung cancer research groups

The SPG agreed that measures were needed to encourage researchers to spend more of their time on lung cancer, and to bring talented young people into the field for research training. For these to happen, researchers would need to be convinced that research funding would be forthcoming. These efforts should be concentrated in areas of highest priority, outlined in Chapter 7.

CHAPTER SIX

POSSIBLE REASONS FOR THE LOW LEVEL OF INVESTMENT

6.1 INTRODUCTION

The workforce survey and bibliometric analysis suggested that the relatively low level of funding for lung cancer was not obviously linked to problems in either capacity or quality in the workforce. The SPG therefore looked for other possible reasons.

6.2 ARE PARTNERS UNWILLING TO FUND LUNG CANCER RESEARCH?

The SPG questioned whether lung cancer is disadvantaged in some systematic way by peer review, which is used by all NCRI Partners to allocate their funding.

The success rates of lung cancer grant applications in comparison with other disease sites should indicate if there is an inherent bias against them in the funding process. Few funding streams are amenable to such an analysis, as many grant applications cannot be attributed to a single disease site. Funders with a remit broader than cancer do not usually collect information on success rates in a way that enables detailed breakdowns and often the number of lung cancer applications received is too low for statistical analysis. However, the joint Cancer Research UK/Medical Research Council Clinical Trials Advisory & Awards Committee (CTAAC) has a specific remit for phase II and III clinical trials in cancer. The majority of these trials concentrate on a single disease site, making an analysis of the success rates of lung cancer applications in comparison with other disease sites possible.

Data were collected on full applications to CTAAC from October 2002 to November 2004 (n= 77). Of these 77, 35 were funded (45%). Eight of the 77 applications were in lung cancer, of which 5 were funded, a success rate of 63%, which is well above average (although absolute numbers are small). CTAAC also operates a system of considering outline proposals as a first stage filter, and lung cancer also has a higher than average success rate at this preliminary stage. Because of the time lag between an application being submitted and it being funded, it is not easy to provide an overall combined success rate for the two stages. However the data suggest that for lung cancer it could be around 40% while the average is around 30%. The figures may not be statistically significant but they suggest that any systematic bias against lung cancer trials is very unlikely.

The higher proportion of fundable trials concurs with evidence from the bibliometric analysis that although underrepresented in the UK portfolio, lung cancer research is of higher than average quality. There is thus no evidence for bias against lung cancer in the peer review system. Nevertheless, it remains possible that there are perceptions amongst researchers that such a bias exists, which may help to explain the low number of applications received (see 6.3 below).

6.3 IS THERE A 'NIHILISTIC' ATTITUDE AMONGST LUNG CANCER CLINICIANS AND RESEARCHERS?

Some experts speak of the 'nihilism' surrounding lung cancer, in particular in the treatment of lung cancer patients. A search of the scientific literature yields several articles over the last two decades, from both the UK and elsewhere (eg. *Thorax* 52(11):1018 (1997), *Clin Can Res* 11(13 Pt2):5030s-5032s (2005)). Specifically, they cite evidence that lung cancer patients are not always referred for treatment even where there is clear evidence of benefit in the relevant patient group. Recent clinical guidelines from

the National Institute for Health and Clinical Excellence (NICE) may help to overcome this.

In similar vein, it can sometimes be thought that lung cancer research is unrewarding because it is considered unlikely to have a major impact on patient outcomes. This may sometimes be coupled with an attitude exemplified by some press reports suggesting that lung cancer is an invariably fatal disease, which patients bring on themselves through smoking, thus fostering a culture of 'blame'. Investigators may also feel that it is more difficult to obtain funding for lung cancer research (though we found no evidence to suggest this is true – see 6.2 above). Since lung cancer survival is poor, there are fewer patients able to take on an advocacy role than there are for other common cancers. Such advocacy can be immensely influential in changing attitudes amongst professionals and the public.

Another symptom of nihilism is that, with the notable exception of the Roy Castle Lung Cancer Foundation, there are no major national charities devoted to lung cancer, unlike some other common cancers such as those of breast or prostate. There is thus less dedicated fund-raising for lung cancer and less charity money available to spend.

These factors taken together may have quite a powerful deterrent effect, but there are signs that these attitudes can change. The introduction of multi-disciplinary teams has significantly improved the treatment of patients and there has been a large increase in the number of trials on offer giving patients a greater choice of treatment options. Recent advances in the development of novel therapies such as erlotinib, have injected some optimism into the field. The UK Lung Cancer Coalition was launched in November 2005 (www.uklcc.org.uk). The Coalition is a partnership of clinicians, charities and healthcare companies which has been formed to increase the profile of lung cancer, particularly amongst MPs. The long-term aim of the Coalition is to help co-ordinate efforts to improve lung cancer survival rates. The forward momentum generated by these advances must be harnessed to help generate increased interest in lung cancer amongst the research community.

The SPG hope that by highlighting lung cancer as a priority and making funding available to boost the research spend, this will go some way to counteracting the negative attitudes surrounding this disease. This may not be enough, however, and NCRI Partners who have expertise in public relations, information-giving and patient advocacy may wish to consider a more pro-active approach.

ACTION:
Several NCRI members have a wealth of experience in designing and organising public and other campaigns. As a first step, NCRI will establish a working party amongst these organisations to develop actions targeted at raising the profile of lung cancer research – its needs, value, and potential for impact. This will complement the activities of the UK Lung Cancer Coalition. Groups targeted will include professionals, young people considering a career in science and the public. The working party will also consider how to promote patient advocacy. It is likely that targeted resources will be required to take forward the actions of this working party.

6.4 IS THERE A LACK OF RESEARCH TOOLS?

It is possible that researchers stay away from lung cancer research due to difficulties gaining access to necessary materials such as tissue samples or animal models. An increasing focus on research on genes and other biomarkers associated with disease susceptibility, tumour susceptibility to drugs, and drug toxicity carries an increasing dependency on the availability of such materials.

As part of a questionnaire survey (see Chapter 5 for full results), researchers were asked if access to lung cancer tissue was a significant barrier to progress in the field. Of the researchers who are currently or have previously used tissue samples, 94% agreed or strongly agreed with the statement. The difficulty in getting access to high quality lung cancer samples was also highlighted in an internal audit of tissue resources recently funded by CR-UK. This revealed that only three CR-UK funded centres held lung cancer samples, and that these were accessible only to researchers within the institutes in which they were held.

It appears that this may reflect a genuine obstacle to research in lung cancer biology. The SPG discussed this with Dr Brian Clark, Chief Executive of onCore UK, a charitable company

set up by three NCRI Partners to serve as a national biospecimen and information resource for cancer research (www.oncoreuk.org). Dr Clark's market research has shown a shortfall in the supply of many tumour types, especially the more common cancers. He acknowledged the particular difficulties for lung cancer including the fact that lung tumours are physically less accessible than some others and that availability from surgery was relatively limited. The operational framework which onCore UK plans to establish will collect samples of tumours and blood donated by patients participating in clinical trials within the National Cancer Research Network (NCRN). This is expected to begin on a pilot basis in 2006. Bearing in mind that lung cancer trials are well-represented in the NCRN portfolio (see 7.4) this approach provides some encouragement, though it will be some years before it can have a major impact.

Initial discussions between onCore UK and the Lung Cancer Clinical Studies Group have highlighted several areas of opportunity and need. With lung cancer acknowledged as a priority by the NCRI Partners, there may be an opportunity for a specific effort in the collection of lung cancer samples by onCore UK. The Lung Cancer Clinical Studies Group is well placed to understand the specific needs of the research community and they have been asked in conjunction with onCore UK to develop a plan for the collection and storage of lung cancer biospecimens *(see Appendix VI).*

Access to tissue is only one potential barrier to progress. A number of clinical and basic researchers were asked informally for their views on any additional practical barriers. It was reported that there were a number of relatively useful lung and lung cancer cell lines but that there could be improvements in this area. Development of panels of cell lines taken from patients at different disease stages would be particularly valuable, although difficult to obtain. Cell lines from patients who have developed resistance to therapy before and after treatment were particularly scarce.

There was a mixed response to the need for better/more animal models, with some researchers doubting the impact that such models would have. It remains unclear how valid some animal models of lung cancer are. In recent years the majority of work has been done using human tumours orthotopically grafted into rodents.

More recently genetically engineered models of lung cancer have become available in mice and it is hoped that they may be useful in helping to describe the progression of the disease.

ACTION:
onCore UK and the Lung Cancer Clinical Studies Group have been asked to work together to create and implement a plan specifically for the collection of lung cancer biospecimens. A framework for this has been drawn up (see Appendix VI) and its implementation will reflect the priorities outlined in this report, covering all major lung cancer types (including mesothelioma).

6.5 IS LUNG CANCER TOO DIFFICULT TO STUDY?

In the 2002 Strategic Analysis it was stated that "lung cancer is not a particularly researchable or tractable disease", and there is some basis for this. Conducting trials and other studies on patients with lung cancer can be difficult. Frequently patients deteriorate rapidly, and many do not survive for the duration of a study. Doctors, nurses and family caring for patients can sometimes be protective to the extent of shielding patients from the additional complication of study participation at what is a very difficult time. A greater public awareness about the potential benefits of lung cancer research, as advocated in the last chapter, should help to overcome this.

Conducting studies with lung cancer patients is also very stressful for investigators. Researchers sometimes spend extended periods of time with patients and their families, and have to cope with the high mortality rates in patients they have come to know. The 'burn-out' rate amongst lung cancer investigators is quite high and there is limited support available to them (*Eur J Cancer Care*: 11(3):193-9, 2002).

The natural histories of the different types of lung cancers need further exploration and are difficult to study in a rapidly progressing patient group. Understanding of how a normal lung cell becomes cancerous is incomplete, and there are, as yet, no confirmed inherited genetic risk factors for the majority of cases. There are, however, opportunities to study lung

dysplasia – a precursor of lung cancer – in patients at high risk of developing cancer.

ACTION:
Studies examining how normal cells progress to become lung cancer cells will be promoted. This will require the collection of specimens from volunteers at high risk of developing lung cancer and as such will interact with the previous recommendation on tissue resources (see Chapter 6.4).

6.6 THE OBSTACLES CAN BE OVERCOME

In conclusion, the SPG believes that current obstacles to progress can be surmounted. Encouraging signs from the evidence that has been collected include:

- The slight upward trend in the amount of lung cancer research published from the UK during the period 1999-2003;
- The high quality of UK research relative to other countries;
- The considerable success of the Lung Cancer Clinical Studies Group in the last few years in building a healthy portfolio of clinical trials, achieving high success rate at Clinical Trials Advisory and Awards Committee, and substantially increasing the number of lung cancer patients in clinical trials (see Chapter 7.4);
- Some advances in therapy, with potentially more in the pipeline;
- Some reduction in negative attitudes which should be enhanced by the UK Lung Cancer Coalition.

The research funders are determined to tackle the remaining challenges which include:

- How to provide incentives to the existing biomedical community to turn their talents to lung cancer;
- How to attract new graduates into the field;
- Availability of tissue and other research tools;
- How to provide better public information and improve patient advocacy so as to further reduce negative attitudes;
- The full gamut of research that is needed, that must involve patients near the end-of-life – tumour biology, natural history, genetics, therapeutic trials etc;
- How best to support researchers who work with lung cancer patients.

How this can be done is addressed further in Chapter 8.

CHAPTER SEVEN

SCIENTIFIC PRIORITIES

7.1 OVERVIEW

Given the large number of people suffering from and affected by lung cancer, the SPG were keen to target areas where any increase in investment would have the maximum benefit to patients in the medium to long term.

In parallel with conducting the analysis previously presented, the SPG took evidence from experts on the needs and opportunities for research across the disciplines included within the scope shown in **Figure 1**. The categories within scope are not mutually exclusive and the SPG also considered cross-cutting issues, in particular the opportunities for research based in primary care. Mesothelioma is also considered as a separate topic with different needs and issues. A list of the experts and the topics on which they presented to the SPG is in Appendix VII.

7.2 BASIC BIOLOGY, AETIOLOGY AND EPIDEMIOLOGY

With causation through smoking outwith the scope, the SPG agreed that the main topic to target in aetiology was genetic risk factors, an area which overlaps with basic biology and the study of biomarkers (see also 7.3 below). It has already been noted that because of the rapid trajectory of disease, there is poor understanding of natural history, both in terms of epidemiology and descriptive studies. This lack of understanding of disease mechanisms is problematic for the identification and validation of new therapeutic targets.

The Lung Cancer Clinical Studies Group has identified the need for tissue and other samples from patients with dysplasia of the epithelial cells in the lung. Dysplastic cells show changes and are at a higher risk of becoming cancerous. As these cells can be detected using a bronchoscope there is the potential in the longer term to develop an intervention that prevents the cells from becoming cancerous. However, the behaviour of these cells is not well understood and could be much enhanced by the acquisition and analysis of longitudinal samples taken from patients at risk of developing lung cancer.

There is a need to better understand the natural history of the different lung cancer types. The Lung Cancer Clinical Studies Group is already taking the lead on developing some studies in this area and will work with onCore UK on the generation of tissue resources. For all new clinical studies in lung cancer there will be consideration of the possibility of collecting natural history data and storing samples for translational and genetic studies at a later date.

(See Actions 2 and 3 in Chapter 1).

7.3 SCREENING AND EARLY DIAGNOSIS

7.3.1 Overview

Many lung cancer patients are diagnosed at a stage when it is too late for treatment to be curative. If lung cancer could be detected sooner, then survival could improve without any advances in the therapeutic armoury. Experts who gave evidence to the SPG, and consumer representatives, were unanimous in highlighting this as a major priority for research. The SPG considered three areas where research is, or may be, needed:

- The possibility of population-based screening for lung cancer;
- The development of novel diagnostic tools;

- How to encourage people with symptoms to seek medical advice sooner rather than later.

7.3.2 Screening

For breast and cervical cancer, screening has proven to be a valuable tool in helping to decrease mortality. As lung cancer has an easy to identify, high-risk population (ie. smokers), the possibility of screening for the disease has been pursued for many years. Although several methods have been tested, including X-ray and sputum analysis, none has so far been shown to decrease mortality from the disease. The most promising technique under investigation is spiral computed tomography (CT). This allows detailed images to be taken of the lung and can identify potentially cancerous lesions smaller than 5mm in diameter. This method is currently under investigation in several trials in the US and Europe.

Although screening can identify lung cancers at early stages, it cannot be assumed that this decreases mortality. Screening may identify slow growing, non-aggressive tumours that would otherwise not come to clinical attention, resulting in unnecessary and potentially harmful treatment of some patients. Also, screening detects a large number of lesions which must be either followed over time, or biopsied. Some of these eventually turn out not to be cancer, causing distress to patients and resulting in a number of potentially hazardous procedures. The detrimental effects of these screening artefacts, along with the radiation risk, must be weighed against any potential benefit of detecting the cancer earlier in other individuals.

The UK must now decide if it wishes to fund a trial to contribute to the growing body of international evidence. This is a highly complex decision. The first results from large randomised controlled trials will not be available until 2010, and these will come from the US, a country with a health system very different from that in the UK. European trials will not provide data on mortality until 2015.

Given the complexities of the issues associated with lung cancer screening, the SPG called a workshop with appropriate experts to explore these issues and help formulate advice. Screening experts from the US, UK and Europe were invited to present at a meeting that was co-Chaired by Professor Mike Richards (National Cancer Director for England) and Peter Cardy, as Chair of the SPG.

Dr James Mulshine, Vice President and Associate Provost for Research at Rush University Medical Centre, Chicago, is an internationally recognised expert in lung cancer research, particularly the management of early disease. Whilst acknowledging the contribution of the US National Lung Cancer Screening Trial (NLST), Dr Mulshine emphasised the wisdom of having multiple trials to inform screening policy. Pointing to the example of breast cancer, several large trials were necessary to satisfy policy makers that screening was both effective and cost-effective. As with any study, there is a risk of the NLST providing marginal or inconclusive results highlighting the need for multiple studies. He thought that the UK now had a great opportunity to participate in lung cancer screening research, using up to date technology and procedures to provide the UK-specific knowledge necessary to help inform implementation should trial results prove positive. In addition, the need for UK specific data is strengthened by a difference in the epidemiology of pulmonary nodules between the US and UK. This could have a significant impact on the rate of false positive screens.

The workshop also heard from Dr Robertus van Klaveren, from the University Hospital Rotterdam, principal investigator of the NELSON lung cancer screening trial, a collaboration between the Netherlands, Belgium and Denmark. This study of over 20,000 patients is expected to report in 2015. Dr van Klaveren welcomed any contribution the UK might choose to make, as an increase in the numbers screened in trials could hasten the time to results and strengthen their statistical power, allowing more detailed analysis of sub-groups. The Group were impressed by the NELSON trial, and were clear that any UK trial should follow a similar design both because it would be appropriate to the epidemiology and health service structures in the UK, and also to enable a meta-analysis to be conducted in due course. Indeed, the investigators present were praised for planning on this basis with agreements on data sharing and standards already in place, as illustrated in the recently published Liverpool Lung Statement (*J.Thoracic.Oncol*, June 2006).

Professor John Field, Director of the Roy Castle Lung Cancer Foundation Research Programme, University of Liverpool Cancer Research Centre, and Stephen Duffy, CR-UK Professor of Cancer Screening at the Wolfson Institute of

Preventative Medicine, presented outline plans for a UK study. They suggested a UK lung cancer screening trial of 14,000 people which would have a similar protocol to the NELSON study. This would enable an integrated analysis, which they believed could provide an answer in seven years, bringing forward the overall result by five years in a trans-European pooled analysis.

After discussing this proposal at some length members agreed firstly that it was unlikely that a trial could be mobilised as rapidly as was being proposed, even considering the apparent state of readiness of the research community. As a result they thought that the reduction in time would be more marginal than the five years suggested. Secondly, they agreed that a trial which simply supplemented the NELSON data and potentially brought forward its result would not answer all the necessary questions relating to whether and how a screening programme should be introduced in the UK.

In 2005, the UK National Screening Committee (NSC) commissioned a report to determine the level of evidence required for the introduction of lung cancer screening (report available from the HTA website http://www.hta.nhsweb.nhs.uk/). Of the 22 criteria considered by the NSC only one is satisfied completely with the relevant remainder either not satisfied or only partially satisfied. While current trials would provide the data to address more of these criteria, the SPG noted that these results alone may not provide all the information necessary for policy-makers, for example the information required to help determine the optimal time interval between screens.

In addition, members were concerned about the lack of information available on the economics of introducing and running a lung cancer screening programme in the UK health system. Current trials are based on annual screening which may prove too resource intensive to implement. It is acknowledged that as with any screening programme, there will be a number of false positive scans, and the effect of this both in terms of distress to patients and cost to the NHS needs to be determined. Before any trial is mounted in the UK, there is a need to consider how costs and benefits will be assessed to ensure the trial provides all the necessary information on which to base a decision about screening policy. One issue for consideration will be that if smoking cessation policies are successful over the next few years, the "at risk" population that may benefit from screening will become smaller, and the impact of screening on overall mortality would be less.

ACTION:
NCRI will convene a meeting of health economists, clinicians and policy-makers as a first step in constructing a health economic model for spiral CT screening for lung cancer. The purpose of the model will be to identify and define the interrelationship between the key factors that will determine the feasibility of a national screening programme. This will be with a view to identifying evidence gaps to which research can then be targeted.

7.3.3 Novel diagnostic tools

The ultimate goal of cancer detection is the development of tests that are easy to administer, low risk, can detect pre-cancerous as well as cancerous lesions, can provide information on the aggressiveness of the tumour, and point the way to the best course of treatment. Depending on circumstances, tests might be used for population-based screening or for diagnosis (or exclusion) in patients with symptoms. The search for such tests is being made more feasible by rapid developments in genomics and proteomics. Biomarkers identified using these techniques are also being developed as measures of prognosis and response to treatment.

Currently there is a real danger that the poor profile of lung cancer will be perpetuated in the biomarker field just as in other aspects of cancer research. The comments made in the last chapter about providing incentives to draw both established and new investigators into the field are particularly apposite here. At the same time, the number of potentially useful biomarkers being identified is huge. Techniques must be developed to allow rapid identification of the most promising markers, followed by the development and validation of tests in large-scale clinical trials.

ACTION:
NCRI Partners should actively develop research on the identification and validation of biomarkers, particularly diagnostic biomarkers. This will require careful and long-term planning to dovetail with the evolving biomarker strategies of individual Partners, and will also depend on the collection of lung cancer biospecimens. This research is likely to require specific incentives in the form of dedicated funding to draw more investigators into lung cancer research, and will also include collaboration with industry.

Without such tools, diagnosis of lung cancer can be difficult. For example heavy smokers can present with one or more co-morbidities, such as bronchitis or emphysema. Detecting the signature of lung cancer symptoms against this background is not easy and can lead to delays in diagnosis, and hence treatment. Research is needed to determine whether it is possible to define a set of symptoms and risk factors specific to lung cancer which could be used to raise awareness among doctors, especially those at general practitioner level who see cases much less frequently than do specialists.

Cancer research based in the community or in primary care is not particularly strong in the UK. At present the number of researchers is small and there are few incentives. There is little experience of multi-centre, randomised trials and the current clinical research infrastructure is based predominantly in secondary care settings. There is little research on patients as they move through the different components of the care system.

A Primary Care Clinical Studies Development Group (PCCSDG) was established by NCRI in 2003 as a first step in trying to unite the primary care research community and develop proposals to strengthen the cancer research portfolio. Their initial survey showed very little lung cancer research based in primary care and what there was focussed on tobacco control. They have made good progress in developing the portfolio across a number of cancers and, at the time of writing, there is one study in preparation on early presentation in lung cancer, and another in development on around early diagnosis being designed in collaboration with the Lung Cancer Clinical Studies Group.

A Primary Care Research Network (PCRN) is also being set up in England, which is expected to consist initially of 8 local networks. It is too early to say how this will develop, though it is likely that it will concern itself with generic, rather than disease-specific issues of health care delivery. In addition a School of Primary Care Research is being set up as part of the Department of Health's Research and Development strategy. These are encouraging signs that infrastructure is being developed. Action will then be required to ensure that high quality research proposals will be generated.

ACTION:
The link between the NCRI Lung Cancer Clinical Studies Group (CSG) and the Primary Care Clinical Studies Development Group will be strengthened, and the latter will be asked explicitly to consider developing more studies in lung cancer. Topics could include issues of care delivery as well as improvements in diagnosis.

7.3.4 The need for earlier presentation

Another reason for late diagnosis of lung cancer is that patients do not always seek help at an early stage, when symptoms first become apparent.

The EUROCARE 3 study (www.eurocare.it) relating to patients diagnosed between 1990 and 1994 showed that lung cancer patients in the UK have worse survival rates than those in other comparable Western European countries. In large part, this is due to patients being diagnosed at a later stage of disease. This in turn is likely to be due to delays in patients seeking medical advice, delays in onward referral by GPs and delays in the hospital system. Other studies have shown that some people diagnosed with lung cancer can, when prompted, describe a long history of symptoms for which they did not seek medical attention (*Soc Sci Med*. 2005: Sep 14). Studies in the general public have also shown that awareness about cancer, its risk factors and symptoms is poor.

Delayed presentation is not a problem confined to lung cancer. A number of surveys have shown that for common cancers, including breast and bowel, public awareness of the risk factors and early signs is poor. Delays have also been documented at later stages in the care pathway, for example in the referral by a GP to hospital. As part of a wider consideration of the needs and opportunities for Health Services Research in Cancer, NCRI should include a focus on research aimed at understanding the reasons for delayed treatment and care across all cancers and at all stages of the patient pathway.

ACTION:
There is a great need to develop and evaluate interventions to encourage early help-seeking behaviour among people who are at high risk of having cancer. New tools may also be needed for the robust measurement of public awareness and attitudes in respect of the causes, risks and symptoms of cancer. NCRI will bring together cancer researchers, behavioural scientists, health educators and health policy-makers to agree actions on the development and evaluation of interventions to encourage early help-seeking behaviour among people who are at high risk of having cancer.

7.4 TREATMENT

The Lung Cancer Clinical Studies Group, currently chaired by Dr Tim Eisen, has been particularly successful in increasing the number of trials available for lung cancer and mesothelioma patients. At present there are 21 lung cancer and mesothelioma trials in the portfolio of the National Cancer Research Network (NCRN) which are either open for patients or in the process of being set up. From April to October 2004 nearly 3,800 lung cancer patients were entered into clinical studies. This is a rapid improvement from 2001/02, when only just over 1000 patients participated for the entire year (NCRN figures).

The Clinical Studies Group has been central to this increase and is currently working on improving the balance of the lung cancer portfolio, with the eventual aim that all lung cancer and mesothelioma patients will be suitable for at least one study in the portfolio.

Current trials cover a number of different areas including chemotherapy, radiotherapy and novel agents. Whilst the CSG have been largely successful in increasing the number of trials in the portfolio, there remain areas that could be developed further, for example surgical trials, mesothelioma and small cell lung cancer.

The pipeline of pharmaceutical agents for lung cancer is also healthier than it has been for some years. New molecular agents targeting receptor tyrosine kinases are providing hopes of the first improvements in survival since platinum agents were introduced some thirty years ago. It is hoped that trials of combinations of these agents will show even more benefits in terms of survival and perhaps even mortality. The Clinical Studies Group is well-placed to continue its role in helping to evaluate and pull through new agents into clinical practice.

7.5 SUPPORTIVE AND PALLIATIVE CARE

In NCRI's 2002 Strategic Analysis, supportive and palliative care research was identified as an area requiring additional resources and infrastructure. Following publication of a report from an SPG in this area, two 'Collaboratives' have been established to provide infrastructure to help consolidate and enhance inter-disciplinary research in this field. The Lung Cancer SPG invited Jessica Corner to speak to them about her research. Jessica is Professor of Palliative Care at the University of Southampton, and is Director for Improving Cancer Services with Macmillan Cancer Support. She has dedicated a large portion of her time to researching the needs of lung cancer patients, and she is a member of one of the Collaboratives.

Professor Corner described some of the complexities surrounding research involving lung cancer patients:

- It is a patient group in crisis;
- Patients often have poor prognosis, and many will be undergoing active treatment;
- Staff have difficulty in dealing with a patient group with such a high mortality rate;
- Only very small numbers of patients participate in studies;

- There is a high attrition rate in studies, due to the mortality rate and, as a result, outcomes of research in this area are determined only by those who survive;
- There are only a few dedicated research teams;
- Sustaining dedicated work is difficult in this emotionally demanding research context.

Due to these difficulties, lung cancer patients are largely absent from studies in supportive and palliative care and, as a result, the evidence base for their provision of care and support is weak, and often derives from the experience of patients with other types of cancer. One recent systematic review of outcomes research in lung cancer revealed 199 studies, only 11 of those dealt with quality of care issues. In another review covering a 20-year period, only 9 studies were identified that dealt with non-invasive interventions for enhancing well-being in lung cancer patients. There is also a lack of research examining the impact of the standard of supportive care on disease free intervals or survival.

The SPG recognised that given the rapid trajectory of the illness and the culture of blame surrounding the disease, lung cancer patients face a particularly difficult journey. Their needs can change rapidly as their condition worsens, but there is little research to determine how best to deal with this.

Professor Corner outlined some more specific areas of priority for research, with particular relevance to lung cancer patients and their families:

- Equity of access and quality of treatment and care in lung cancer;
- Stigma and the social predicament of lung cancer and interface of this with disease outcome;
- Social and financial impact of lung cancer;
- Economic issues relating to lung cancer and different care delivery models;
- Specific support needs of diverse patient groups;
- Needs of women with lung cancer;
- Families and carers.

To compound the difficulties cited above, the SPG learned that the NCRN network is currently not optimally configured to facilitate recruitment into social science trials. Research nurses are more focused on treatment based clinical trials and there are fewer incentives for recruiting to social science studies. Networks typically prioritise deploying their staff to settings where they have several active trials or a relatively high potential for recruitment. The NCRN have recognised this, and are currently developing a plan to help manage and balance the trials portfolio, to ensure that more specialist trials can be accommodated within the networks.

The SPG wished to capitalise on the initiative already under way among NCRI Partners in supportive and palliative care (SuPaC) and thought that any additional funding might appropriately be channelled through the SuPaC Management Committee (www.mariecurie.org.uk).

ACTION:
The needs of lung cancer patients for supportive and end-of-life care will be specifically targeted with a call for proposals for which dedicated funds have already been pledged. The call will be managed by the existing Management Committee for the NCRI Supportive and Palliative Care Collaboratives[1]. This next stage in the development of the SuPaC initiative may focus in particular on models of care for disease with a rapid trajectory, symptom management and psychosocial issues for patients, carers and families. Interested investigators are encouraged to contact the SuPaC Management Committee at Marie Curie Cancer Care to register their interest which may help to shape the formal call for proposals planned for 2007.

[1] currently comprising representatives from Cancer Research UK, Department of Health, Economic and Social Research Council, Medical Research Council, Macmillian Cancer Support, Marie Curie Cancer Care.

7.6 MESOTHELIOMA

Mesothelioma is a cancer that principally affects the external lining of the lungs (pleura) and the lower digestive tract (peritoneum). The majority of cases are caused by exposure to asbestos fibres. Numbers of cases of mesothelioma in the UK have been steadily rising, following the profile of workforce exposure to asbestos, with a time lag of 40-50 years. Approximately 1800 people died of mesothelioma in the UK in 2001 (HSE statistics), with the epidemic predicted to peak between 2011 and 2015, resulting in between 2000 and 2500 deaths per year (*Br J Cancer*, 14:92(3):587-93, 2005).

The Group recognised that although mesothelioma is sometimes classified as lung cancer, the differences in the aetiology, epidemiology and treatment options may result in different priorities for research. To explore this further the SPG invited Dr Jeremy Steele to speak to the SPG. Dr Steele is a Consultant Oncologist at the Mesothelioma Research Fund in St Bartholomew's Hospital, London and is actively engaged in mesothelioma research.

For other lung cancers, early detection and diagnosis were identified as priorities by the SPG. These are less of a priority here as there is no treatment or preventative measure that can be offered to patients caught in the early stages of mesothelioma. Indeed, the availability of early diagnosis without treatment options would raise ethical issues. A major priority is therefore clinical trials of treatment regimens involving different combinations of surgery and drug treatment, and in particular to ensure that as many patients as possible are enrolled in clinical trials. There are currently five mesothelioma trials on offer in the UK, and there may be the potential to increase the number of patients recruited into trials.

There is also a need to better understand the biology of mesothelioma, for which tissue specimens are needed. Most mesothelioma patients have tissue samples taken to confirm the histology, but this tissue is rarely used for research. Tumour resections can yield large quantities of tissue, but again samples from resections are rarely made available for research.

There are also infrastructural barriers to research. Mesothelioma is a relatively rare cancer, and many patients do not see a consultant with specific expertise in the disease. Research is difficult to conduct in this small and fragmented patient population, as patients are often very ill and unable to travel the distances required for trial participation. Dr Steele highlighted the need for specialist treatment centres which would primarily be aimed at improving treatment for patients, and would also serve as nuclei to increase the quality and quantity of research in the UK by improving access for patients. The Department of Health in England has recognised this need and is developing a framework for mesothelioma services. Once this is in place it will facilitate research, including the collection of tissue samples and identification of patients for clinical trials.

ACTION:
The Department of Health for England is developing a framework for mesothelioma services which will also facilitate research. The NCRI Lung Cancer Clinical Studies Group will consider how to increase the number of mesothelioma patients who can be offered clinical trials through the NCRN network, and any tissue banking initiative in lung cancer will include collection of mesothelioma tissue.

CHAPTER EIGHT

SUMMARY OF ACTIONS

This report reflects the intention of the SPG to undertake a thorough and reflective review of the current UK lung cancer research landscape. We conclude that the poor positioning of lung cancer research in the portfolio is long-standing and has deep-seated origins. For this reason there is no single solution to the need for more research. Instead, needs and opportunities have been identified across a number of scientific priorities within lung cancer. Some encouraging trends can be fostered, and sustained effort is needed by NCRI Partners. The SPG has recommended that in certain areas more detailed plans for progress are required. NCRI have commissioned various appropriate bodies to produce these plans.

At the time of writing, plans and actions are at varying stages of readiness, and some will need dedicated funding whilst others will be pursued through existing funding mechanisms. NCRI will actively monitor their progress, encourage collaboration across disciplines in lung cancer, and will publish updates from time to time.

PROFILE OF LUNG CANCER RESEARCH

One very significant but intangible barrier to all areas of lung cancer research and treatment is the attitude of nihilism that can sometimes be associated with the disease. This affects not only the general public, but patients, their families and even the care providers and researchers. There are signs that this attitude is beginning to change and members were keen to encourage this, perhaps through some form of public campaign.

Action 1: NCRI will establish a working party among organisations specialising in communication about cancer, to develop actions targeted at raising the profile of lung cancer research – its needs, value, and potential for impact. This will complement the activities of the UK Lung Cancer Coalition. Groups to be targeted will include professionals, young people considering a career in science and the public. The working party will also consider how to promote patient advocacy. It is likely that targeted resources will be required to take forward the actions of this working party (Chapter 6.3).

BIOLOGY OF LUNG CANCER

Basic and translational science underpins many medical advances in the treatment of cancer. Progress in these areas depends on having access to some basic tools, such as animal models, cell lines, tissue specimens and other biosamples. The mechanisms underlying the progression of a normal lung cancer cell to a cancerous one are not well understood. Developing this understanding is vital in helping to develop new drugs to treat cancer, new methods to diagnose cancer, and potentially new interventions to prevent cancer from forming.

Action 2: onCore UK and the Lung Cancer Clinical Studies Group have been asked to work together to create and implement a plan specifically for the collection of lung cancer biospecimens. A framework for this has been drawn up (see Appendix VI) and its implementation will reflect the priorities outlined in this report, covering all major lung cancer types (including mesothelioma) (Chapter 6.4).

Action 3: Studies examining how normal cells progress to become lung cancer cells will be promoted. The Lung Cancer Clinical Studies Group is already taking a lead on this but it will require further collection of specimens from volunteers at high risk of developing lung cancer and as such will interact with the previous recommendation

on tissue resources (Action 2). For all new clinical studies in lung cancer there will be consideration of the possibility of collecting natural history data and storing samples for translational and genetic studies at a later date (Chapter 6.5).

SCREENING AND EARLY DIAGNOSIS

For some other cancers the introduction of a screening programme has reduced mortality from the disease. The effectiveness of screening high risk individuals for lung cancer with spiral CT is as yet unproven, as is the feasibility and affordability of implementing a screening programme.

Action 4: NCRI will convene a meeting of health economists, clinicians and policy-makers to construct a health economic model for spiral CT screening for lung cancer. The purpose of the model will be to identify and define the interrelationship between the key factors that will determine the feasibility of a national screening programme. This will be with a view to identifying evidence gaps to which research can then be targeted (Chapter 7.3.2).

Spiral CT is an expensive and resource intensive method of screening. In the longer term the largest improvements in lung cancer mortality and survival are likely to come from innovations currently at a very early stage of development. Biomarkers are one such tool that have the potential to aid in the diagnosis, prognosis and identification of the most appropriate treatments for lung cancer and other illnesses.

Action 5: NCRI Partners should actively develop research on the identification and validation of biomarkers, particularly diagnostic biomarkers. This will require careful and long-term planning to dovetail with the evolving biomarker strategies of individual Partners, and will also depend on the collection of lung cancer biospecimens. This research is likely to require specific incentives in the form of dedicated funding to draw more investigators into lung cancer research, and will also include collaboration with industry. The magnitude of this issue necessitates a longer term approach, which will take some time to design and implement (Chapter 7.3.3).

PROVISION OF CARE

Earlier detection and diagnosis of lung cancer has emerged as a major area of priority in which progress could result in improvements in mortality in the medium to long term.

Action 6: The link between the NCRI Lung Cancer Clinical Studies Group (CSG) and the Primary Care Clinical Studies Development Group will be strengthened, and the latter will be asked explicitly to consider developing more studies in lung cancer. Topics could include issues of care delivery as well as improvements in diagnosis (Chapter 7.3.3).

Action 7: There is a great need to develop and evaluate interventions to encourage early help-seeking behaviour among people who are at high risk of having cancer. New tools may also be needed for the robust measurement of public awareness and attitudes in respect of the causes, risks and symptoms of cancer. NCRI will bring together cancer researchers, behavioural scientists, health educators and health policy-makers to agree actions on the development and evaluation of interventions to encourage early help-seeking behaviour among people who are at high risk of having cancer (Chapter 7.3.4).

SUPPORTIVE AND PALLIATIVE CARE

Lung cancer patients have specific needs, yet there is little evidence to help understand how best to fulfil these needs. Due to the rapid trajectory and high mortality of the disease, lung cancer patients are often under-represented in large scale studies of this type.

Action 8: The needs of lung cancer patients for supportive and end-of-life care will be specifically targeted with a call for proposals for which dedicated funds have already been pledged. The call will be managed by the existing Management Committee for the NCRI Supportive and Palliative Care Collaboratives (SuPaC). This next stage in the development of the SuPaC initiative may focus in particular on models of care for disease with a rapid trajectory, symptom management and psychosocial issues for patients, carers and families. Interested investigators are encouraged to contact the SuPaC Management Committee at Marie Curie Cancer Care to register their interest which may help to shape the formal call for proposals planned for 2007 (Chapter 7.5).

MESOTHELIOMA

As a relatively rare cancer, with a significantly different epidemiology from other lung cancers the SPG recognised that the priorities for mesothelioma research were likely to be different, with less emphasis on early detection and diagnosis and more on improved treatment options. Progress in this area will be difficult unless the infrastructure is put in place to enable it.

Action 9: The Department of Health for England is developing a framework for mesothelioma services which will also facilitate research. The NCRI Lung Cancer Clinical Studies Group will consider how to increase the number of mesothelioma patients who can be offered clinical trials through the NCRN network, and any tissue banking initiative in lung cancer will include collection of mesothelioma tissue (Chapter 7.6).

ACTION		DELIVERY
1	Working Party among organisations specialising in communication about cancer to develop actions targeted at raising the profile of lung cancer research.	Roy Castle Lung Cancer Foundation to be the lead Partner. First meeting Autumn 2006. Agreed Plan and first actions Spring 2007.
2	onCore UK and the Lung Cancer Clinical Studies Group will create and implement a plan for the collection of lung cancer biospecimens.	Plan and timetable for implementation to be published Winter 2006.
3	Studies examining how normal cells progress to become lung cancer cells will be promoted by pursuing opportunities for sample collection from people at high risk of developing cancer.	Study under way in high-risk patient group. When complete, the Lung Cancer Clinical Studies Group will facilitate development and submission of proposals for a larger scale study.
4	NCRI will convene a meeting of health economists, clinicians and policy-makers to decide how construct a health economic model for spiral CT screening for lung cancer to identify and define the interrelationship between the key factors that will determine the feasibility of a national screening programme.	Meeting Late Summer/Autumn 2006. Develop model early 2007.
5	Partners to actively develop research on the identification and validation of biomarkers, particularly diagnostic biomarkers. This will be dependent on collection of lung cancer biospecimens and may require dedicated funding. This will include collaboration with industry.	NCRI to facilitate stakeholder discussions during 2007.
6	The link between the NCRI Lung Cancer Clinical Studies Group (CSG) and the Primary Care Clinical Studies Development Group will be strengthened, and the latter will be asked explicitly to consider developing more studies in lung cancer.	The NCRN portfolio already contains one study of time to diagnosis in lung cancer. Two further studies of lung cancer in primary care are in preparation and expected to come forward for funding in 2007/08.
7	NCRI will also bring together cancer researchers, behavioural scientists, health educators and health policy-makers to agree actions on the development and evaluation of interventions to encourage early help-seeking behaviour among people who are at high risk of having cancer.	Meeting planned for 2007.
8	The needs of lung cancer patients for supportive and end-of-life care will be specifically targeted with a call for proposals for which dedicated funds have already been pledged. The call will be managed by the existing Management Committee for the NCRI Supportive and Palliative Care Collaboratives.	Funds have already been pledged and the call for proposals will be issued early in 2007, with awards made later in the same year.
9	The Department of Health for England is developing a framework for mesothelioma services which will also facilitate research. The NCRI Lung Cancer Clinical Studies Group will consider how to increase the number of mesothelioma patients who can be offered clinical trials through the NCRN network.	Action already in hand.

APPENDIX I

PARTNERS IN THE NATIONAL CANCER RESEARCH INSTITUTE

Association of the British Pharmaceutical Industry

Economic and Social Research Council

The Roy Castle Lung Cancer Foundation

Association for International Cancer Research

Leukaemia Research Fund

Chief Scientist Office – Scottish Executive Health Department

Biotechnology and Biological Sciences Research Council

Ludwig Institute for Cancer Research

Tenovus The Cancer Charity

Breakthrough Breast Cancer

Macmillan Cancer Support

Wales Office of Research & Development

Breast Cancer Campaign

Marie Curie Cancer Care

The Wellcome Trust

Cancer Research UK

Medical Research Council

Yorkshire Cancer Research

Department of Health

Research & Development Office for the Northern Ireland Health and Personal Social Services

APPENDIX II

MEMBERS OF THE LUNG CANCER STRATEGIC PLANNING GROUP

Chair – Mr Peter Cardy, Chief Executive, Macmillan Cancer Support
Dr Helen Campbell, Portfolio Manager for Cancer Research, Department of Health
Dr Jane Cope, Administrative Director, National Cancer Research Institute
Dr Michael Cornbleet, Senior Medical Officer, Scottish Executive
Dr Mike Davies, Board Programme Manager, Medical Research Council
Mr Tom Haswell, Patient
Dr Aoife Regan, Programme Manager, National Cancer Research Institute
Professor Mike Richards, National Cancer Director, Department of Health
Mrs Joanne Rule, Chief Executive, Cancerbackup
Mr Ray Strachan, Patient
Dr Richard Sullivan, Director of Clinical Programmes, Centres and Infrastructure, Cancer Research UK
Mr Mike Unger, Chief Executive, Roy Castle Lung Cancer Foundation

APPENDIX III

NCRI CANCER RESEARCH DATABASE PORTFOLIO ANALYSIS

The Cancer Research Database (CRD) is a comprehensive database containing the cancer research directly funded by the NCRI Partners. Information included on the CRD is submitted by member organisations in the form of a common data-set that includes the details of the Principal Investigator(s), an abstract of the research conducted and details of funding awarded. The awards are then reliably and consistently classified according to the information contained in the research abstracts.

In order to be able to interrogate the database in an accurate and reproducible way, every research project entered on the CRD has been classified using the internationally recognised Common Scientific Outline (CSO) and by disease site. For more details on the Common Scientific Outline please see the International Cancer Research Partners website (http://www.cancerportfolio.org/).

The portfolio of all projects active on 1st April 2005 was analysed to determine the spend on lung cancer. The entire portfolio represented £343m, and 37% (£126m) of this could be attributed to a disease site, the remainder being either fundamental biology or relevant to all sites.

The total spend on lung cancer (including mesothelioma) was £5.5m. Excluding tobacco control, which was not in the remit of the SPG, the spend was £4.9m, representing 67 lung cancer grants including one for mesothelioma.

When spend is analysed by CSO category, the area attracting the largest amount of funding is treatment, followed by early detection, prognosis and diagnosis.

Eight NCRI Partners funded lung cancer research in 2005. Of these, CR-UK is the largest contributor, followed by the Roy Castle Lung Cancer Foundation. The majority of funding (78%) for lung cancer research is long-term (>= 36 months), similar to the figure for the entire portfolio (76% long term funding).

Figure A1 shows the distribution, with Liverpool and London being the largest recipients of funding. This would be expected given the large number of institutes in London and the Roy Castle Lung Cancer Research Centre in Liverpool. It is interesting that some centres, such as Leicester, manage to produce a relatively high number of good quality publications (see Chapter 4.2), yet they receive a relatively low proportion of NCRI funds. It is possible that the research being conducted in these centres is largely funded from outside the NCRI partnership. The workforce questionnaire cites the North West Cancer Research Fund as a major donor in Leicester.

FIGURE A1: Distribution of NCRI Partners' spend on lung cancer research in the UK

APPENDIX IV

BIBLIOMETRIC ANALYSIS OF LUNG CANCER PUBLICATIONS

In order to obtain a measure of the productivity of the lung cancer research community in the UK a bibliometric analysis was commissioned from Professor Grant Lewison of City University.

The study was intended to examine the output of the UK in lung cancer research within the world-wide production of papers in the Science Citation Index © (SCI) Thomson Scientific for the five years, 1999-2003. This was to include the following analyses:

- Outputs of papers, year by year (limited to articles and reviews);
- Relative output of leading countries to lung cancer research;
- Proportion of published lung cancer papers, on a scale from clinical to basic;
- Citation Impact Factors of the journals in which the papers were published;
- Actual citation scores of papers published in 1999 and 2000 and cited through 2003.

Within the UK, a geographical analysis was to be conducted showing the outputs from each of the leading postcode areas (ie. cities). In addition, the country of origin of all investigators named on a paper was analysed to identify the countries with whom the UK collaborates.

Papers are retrieved from the SCI by use of a filter, designed to catch all relevant papers. The filter consisted of five parts:

- Papers in a specialist lung cancer journal (Lung Cancer) or with (asbestos + (apoptosis or lung)) or mesothelioma or NSCLC[1] or SCLC[1] in their titles (A);
- Papers in cancer journals (B);
- Papers with "cancer" title words (C);
- Papers in respiratory journals (D);
- Papers with "respiratory" title words (E).

Papers were then selected if they were in the following combination of groups: A or ((B or C) + (D or E)). The final values of specificity or precision, p, and sensitivity or recall, r, were 0.91 and 0.94, and the calibration factor, p/r, was 0.97. This is the estimated ratio of the true number of lung cancer-relevant papers to the number actually retrieved.

An analysis of the addresses of all contributing authors on the papers retrieved revealed a high degree of collaboration between European countries in the field of lung cancer. The UK has particularly strong associations with Greece, but has a lesser degree of collaboration than might be expected with large players such as the USA and Japan, given their contribution to biomedical publication as a whole. Greece also has a much higher than expected relative commitment to lung cancer research. At present it is unknown how and why this high degree of collaboration between the UK and Greece has developed. It appears that several groups have built up traditions of employing scientists from Greece, which has then led to collaborations between the countries.

[1] *NSCLC = Non small cell lung cancer; SCLC = small cell lung cancer.*

This analysis also compared the output of the postcodes with the distribution of the Research Outputs Database (ROD) for 1999-2001. This allowed the number of lung cancer publications for individual areas to be compared to the overall number of biomedical publications. This revealed that Liverpool and Leicester have very high number of lung cancer publications relative to their overall biomedicine publications, as does Oxford, but many of these publications concern areas outside the scope of the SPG. By contrast, there is relatively little lung cancer research in London except for SW (mainly the National Heart and Lung Institute, part of Imperial College) and EC (St Bartholomew's Hospital). London WC, which is the leading postcode area in terms of biomedical papers overall but has a relative commitment to lung cancer research of less than 0.5, and Cambridge has an RC of just 0.25. This suggests that some of the most productive institutes in biomedicine research as a whole have little presence in lung cancer research.

Papers were classified according to how "basic" or "clinical" they appeared to be. This was done by first classifying the journals in which the papers appear, and then by scoring the presence of selected "clinical" or "basic" words in the titles of the papers. An overall score is then calculated, with RL1 being the most clinical and RL4 being the most basic. For the lung cancer portfolio, 74% of papers could be classified in this way. UK output is slightly but not significantly more clinical than the world average, and this suggests, in view of its relatively low output, that rather little basic research in lung cancer is taking place in the UK.

The NCRI and Professor Lewison are currently exploring the possibility of publishing the full bibliometric analysis. Please see the NCRI website for further details (www.ncri.org.uk).

APPENDIX V

WORKFORCE SURVEY

This is a copy of the survey sent to lung cancer researchers. It was designed to be filled in by principal investigators.

1. CONTACT DETAILS

Name of Research Unit/Centre/ lab:	
Your Discipline:	
Name of research leader (if not you):	
Your Name:	
Your Address: Your Tel: Your Email:	

2. STAFF

a) Research active staff including students

We are interested in the overall number and nature of researchers currently active in lung cancer research (including mesothelioma) across the UK. There may be problems with critical mass; missing cohorts; lack of specific specialties etc. Please use the table below to give details of the researchers involved in lung cancer at your Unit/Centre.

Researcher's name (optional)*	Approx age	Profession/ discipline	Grade	Full time or part time? (1.0 FTE or xFTE)	What proportion of this time is devoted to lung research?	Duration of contract	Degree sought (e.g.Ph.D, MD. Please State)	Degree obtained (Please state)	Source of funding
Dr D M Bloggs	27	Medical oncologist		0.5FTE	50%	2 years		MD	MRC

* If names are supplied this will enable us to approach a sample of researchers ask for their views and will prevent duplication

b) Research support staff

Please give details of research support staff (e.g. Secretaries, Data Managers, lab managers) in your lab/unit:

Position	No. of Staff	Full Time Equivalent
Secretaries		
Data Managers		
Lab Manager		
Technicians / Assistants		
Other (please specify)		

3. RESEARCH ENVIRONMENT

a) Physical Location

Please indicate the physical location of your Unit/Centre (tick more than one if appropriate):

Teaching Hospital / Cancer Centre	☐
Cancer Centre / not Teaching Hospital	☐
District General Hospital / Cancer Unit	☐
Primary care	☐
Hospice	☐
University department	☐
Research Institute	☐
Other (please describe)	

b) Managerial Links

Is your Unit/Centre/ Laboratory managed within a:

University department of Oncology/Cancer Medicine	☐
University department of Anatomy	☐
University department of Pathology	☐
University department of Genetics	☐
University department of Pharmacology	☐
University department of Behavioural/Social Sciences	☐
University department of Nursing	☐
Other (please describe)	

c) Focus

Is the focus of the research conducted in your lab / unit / clinic:

Purely lung cancer (incl. mesothelioma)	☐
Predominantly lung cancer	☐
Various disease sites incl. lung cancer	☐
Lung cancer studied infrequently	☐

d) Academic Links

Please describe any key lung cancer research collaborations (including mesothelioma) you have, within or outside your Unit/Centre.

4. APPOINTMENTS

Do any staff in your Unit/Centre have any relevant research appointments (e.g. Grant awarding bodies/ committees; Research Advisory Groups; Research Network Leads etc.)? Please give details OR attach brief CVs such as those used for research grant applications:

5. FUNDING

In the last five years what have been your main sources of research funding (and amounts). Please include sources of funding not explicitly named:

	<£50Kp.a	£50k - £100K p.a	£101K – £200K p.a	£201 - £500K p.a	>£500K p.a.
Cancer Research UK	☐	☐	☐	☐	☐
Medical Research Council	☐	☐	☐	☐	☐
Department of Health R&D or devolved equivalent	☐	☐	☐	☐	☐
Macmillan Cancer Relief	☐	☐	☐	☐	☐
AICR	☐	☐	☐	☐	☐
BBSRC	☐	☐	☐	☐	☐
Roy Castle Lung Cancer Foundation	☐	☐	☐	☐	☐
Industry	☐	☐	☐	☐	☐
Other (Please specify)	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐
	☐	☐	☐	☐	☐

6. RESEARCH TOPICS

We are interested to get a clearer picture of the breadth of current research activity. Please use the table below to indicate the research topics that your Unit/Centre/department is currently researching. Tick the box you feel most appropriate. (Feel free to send an annual report, or equivalent, as well if you wish).

Research Topic	Research sub-topic	Major current activity	Currently active	Have capacity to explore in future	Would require further resources	Unlikely to contribute
Basic Biology of Lung	Fundamental research	☐	☐	☐	☐	☐
Cancer	Stem cells	☐	☐	☐	☐	☐
	Cellular / animal models	☐	☐	☐	☐	☐
	Cancer initiation	☐	☐	☐	☐	☐
	Cancer progression	☐	☐	☐	☐	☐
	Other	☐	☐	☐	☐	☐
Aetiology of Lung Cancer	Genetic risk	☐	☐	☐	☐	☐
	Environmental risk	☐	☐	☐	☐	☐
	Other	☐	☐	☐	☐	☐
Risk and Prevention of Lung Cancer	Epidemiology	☐	☐	☐	☐	☐
	Tobacco control	☐	☐	☐	☐	☐
	Chemoprevention	☐	☐	☐	☐	☐
Early Detection and Diagnosis	Screening	☐	☐	☐	☐	☐
	Imaging	☐	☐	☐	☐	☐

7. TISSUE BANKING

We are aware that access to tissue samples is critical for some cancer research. We wish to determine the number, type and location of lung cancer tissue samples in the UK to determine if lack of access is a problem for researchers.

1. Do you use lung cancer tissue samples in your research?	In the past ☐	Presently ☐	Never ☐		
2. "Lack of access to lung cancer samples is a significant barrier to progress in the field"	Strongly Agree ☐	Agree ☐	Neutral ☐	Disagree ☐	Strongly Disagree ☐
3a. Where do you obtain your samples from?	Own collection ☐	Dep/Instit collection ☐	University collection ☐	Commercial UK ☐	Commercial Abroad ☐
3b. On average, how many lung cancer tissue samples do you use per month	0-10 ☐	11-20 ☐	21-30 ☐	>30 ☐	

3c.Will your future demands for lung tissue samples	Sputum	Blood	Buccal swabs	Fixed	Frozen	DNA/RNA	Other
Increase	☐	☐	☐	☐	☐	☐	☐
Decrease	☐	☐	☐	☐	☐	☐	☐
Stay the same	☐	☐	☐	☐	☐	☐	☐

4a. Do you currently hold / manage a tissue collection? (If yes, continue with questionnaire, if no answer question below)	Own use only ☐	Own use / formal collaborators ☐	Dept/Inst/Uni Access ☐	Open Access ☐	
4b. Would you be interested in participating in further discussions to aid the establishment of a National Cancer Tissue Resource?	Yes* ☐	No ☐			

4c. What no. of lung cancer samples does your collection currently hold?	Sputum	Blood	Buccal swabs	Fixed	Frozen	DNA/RNA	Other
10s	☐	☐	☐	☐	☐	☐	☐
100s	☐	☐	☐	☐	☐	☐	☐
1000s	☐	☐	☐	☐	☐	☐	☐

4d. What percentage of your collection is currently linked to clinical outcome data?	Sputum	Blood	Buccal swabs	Fixed	Frozen	DNA/RNA	Other
0-20%	☐	☐	☐	☐	☐	☐	☐
21-50%	☐	☐	☐	☐	☐	☐	☐
51-80%	☐	☐	☐	☐	☐	☐	☐
> 80%	☐	☐	☐	☐	☐	☐	☐

4e.To meet future demand for lung cancer tissue samples will your rate of collection	Sputum	Blood	Buccal swabs	Fixed	Frozen	DNA/RNA	Other
Increase (need additional capacity)	☐	☐	☐	☐	☐	☐	☐
Increase (within current capacity)	☐	☐	☐	☐	☐	☐	☐
Stay the same	☐	☐	☐	☐	☐	☐	☐
Decrease	☐	☐	☐	☐	☐	☐	☐

*In question 4b you are asked if you are willing to enter into further discussions regarding the establishment if the National Cancer Tissue resource. If you answer yes to this question, your details will be passed onto the NCTR team and they may contact you in due course.

The questionnaire was targeted at principal investigators thought to be currently involved in lung cancer research within the remit of the SPG. The main aim was to map out the research workforce involved in lung cancer research and gain some information to assess the current and future activities of these groups.

When an address was available questionnaires were sent by e-mail, if not a copy was sent by post. The form was designed to be filled out electronically and returned by e-mail, but respondents could also post or fax their replies. Several reminders were issued.

In the first round 108 questionnaires were sent out. 10 e-mail addresses appeared to be defunct, and the correct addresses could not be sourced. Respondents were asked to provide the names of other recipients not on the list, and this generated a further seven contacts who were subsequently sent the questionnaire, totalling 105 questionnaires sent to apparently functional e-mail and postal addresses. Of these 105 questionnaires sent out, 58 responses were received. 4 did not complete the questionnaire satisfactorily, 7 thought that they were not suitable for the survey, 5 had retired from active research and 7 referred us to more suitable colleagues. This resulted in a total of 35 completed questionnaires suitable for the analysis.

As the number of returned questionnaires was relatively low, additional efforts were taken to ensure that all centres with a significant interest in lung cancer had been given the opportunity to participate. The list of recipients was cross-referenced against a list of names and addresses from the bibliometric analysis, representing all UK scientists who had published a lung cancer paper from 1999-2003. Only one centre with more than one lung cancer publication did not respond to the questionnaire.

The profile of the profession of the respondents is shown in **Figure 5a** in the main body of the report. The 'other' professions included an epidemiologist, a psychologist and a geneticist. These 35 PIs oversee groups with a total of 160 researchers active in lung cancer, with a full time equivalent of 72. The average number of researchers per group was 4.5 with the largest group having 15.

Recipients were asked to name their main sources of funding, to cross reference with the analysis of the Cancer Research Database, and to identify if there are any significant sources of funding for lung cancer outwith the NCRI partnership. The North West Cancer Research Fund provides funding to 3 labs, and there is significant "soft" money coming from local charities and trusts, and charities associated with hospitals and research institutes.

The current research topics of the labs are shown in **Figure 7** in the main body of the report. In addition to their current activities we asked recipients to highlight any activities they may wish to pursue in the future. Stem cell research and chemoprevention, areas which do not occur frequently in the current activities, are listed as areas which some labs may wish to pursue in the future. Some labs currently involved in clinical research are also interested in developing capacity for health services research.

At the request of onCore UK, the national tissue banking initiative, we also asked recipients a series of questions on tissue banking. This confirmed that at present, access to lung cancer tissue samples and suitable controls is limited, with most researchers procuring samples from in-house, closed collections. Researchers active in tissue-based research are predicting an increase in the demand for blood, fixed and frozen tissue samples and DNA/RNA.

APPENDIX VI

ENHANCING LUNG CANCER BIOSAMPLE COLLECTION

1. INTRODUCTION

The NCRI Strategic Planning Group on Lung Cancer has identified the lack of lung cancer tissue as an obstacle to research. They asked Dr Tim Eisen, Chair of the NCRI Lung Cancer Clinical Studies Group, and Dr Brian Clark, Chief Executive of onCoreUK to advise on a plan to enhance lung cancer tissue collection. They have prepared this framework for the development of such a plan. Implementation will be subject to the statutory provisions of the Human Tissue Act (2004) and other requirements of research governance including patient consent.

2. TISSUES TO BE TARGETED FOR COLLECTION

Common lung cancers

Non-small cell lung cancer (NSCLC) makes up 80% of all lung cancers. These cancers can occur in any part of the lung, although those closer to the mid-line tend to be squamous cell carcinomas, with those occurring distally more likely to be adenocarcinoma. Patients with the earlier stages of these types of cancer are the most likely to undergo surgery and a possible opportunity to obtain samples exists from these patients.

Rarer lung cancers

Small cell lung cancer accounts for 20% of all lung cancers. This is a particularly aggressive cancer that tends to develop distant metastases rapidly. As surgery is rarely performed on affected patients, there are few tissue collections in existence.

Mesothelioma is a cancer of the outer covering of the lungs (and other organs) and is related to asbestos exposure. The tumour occurs decades after the exposure and the current epidemic of the disease is not predicted to peak until 2015. Research in this cancer is difficult, as there are no highly effective treatments, the pathology of the condition is challenging and patients with mesothelioma may deteriorate rapidly. No substantial sample collections in the UK can be identified.

Dysplasia

One of the priority areas highlighted by the SPG is the need for a better understanding of the cellular processes that result in a normal cell becoming cancerous. One of the intermediate and potentially reversible stages in this process is dysplasia. Dysplastic cells show characteristics that may indicate they are at a greater risk of becoming cancerous. However, it appears that this process can spontaneously reverse, with cells reverting to normal type. Understanding this process could help design interventions to prevent dysplastic cells from progressing to becoming cancerous.

To be most useful, multiple samples are needed from the same patient over time. Even though the procedure to collect samples can be uncomfortable, and the patients may see no direct benefit, ongoing small studies suggest that they are willing to participate. Generating tissue collection by this method may be challenging, but the potential rewards in the longer term should make the challenge worth while.

3. SPECIMENS REQUIRED

The choice of sample and how it is treated and stored will affect its utility for different types of research. For example, for diagnosis of a primary tumour it is common to take a needle biopsy from a suspect area. This sample is then processed by chemical fixation, embedding in wax, and

staining with dyes before microscopic examination. However, this process damages some components of cells, so if the intention is to study protein or nucleic acid structure, it is often better to freeze the sample. This needs to be done as soon as the material is removed from the body which can be logistically more difficult and require resourcing.

Whilst tissue biopsies might provide the most direct information on the cancer or precancerous cells, other samples, such as blood, broncho-alveolar lavage fluid and sputum may be more abundant or are easier to collect, and can also provide valuable contextual or surrogate information. Tumour samples from metastatic disease can also be valuable, although biopsies of such disease sufficient to generate excess tissues for research use are relatively rare.

4. METHODS AND OPPORTUNITIES FOR COLLECTION

The method and opportunity for tissue collection will vary depending on the treatment path of the patient, the samples required and how the sample collection is funded.

The most common point of sample collection from patients is as part of their diagnostic work-up or treatment. For example, blood might be drawn or biopsies taken for diagnosis. These samples are generally not available for further research.

Sample collections are sometimes funded as part of clinical trials and usually the trial protocol will include plans for how the samples will be used. Since the number of lung cancer clinical trials has increased, this provides more opportunity for sample collection than in the past. Funding streams exist for the collection of such samples even if it is not known at the time of collection what hypothesis they will be used to test.

Approximately 4,000 patients with early stage NSCLC have surgery every year, a potential opportunity to collect tissue samples. Since most of these patients are not in clinical trials, a different means of funding sample collection will need to be found. Some hospitals routinely collect prospective samples from their patients for research purposes, but these are usually kept in local collections for local use and with limited access afforded to external groups. Nevertheless, with the provision of increased resources to a few key centres that routinely perform lung cancer surgery, there may be scope to encourage hospitals to boost their sample collection activities, make their collections more widely known and also more readily available for research.

Another possibility for tissue collection is via autopsy retrieval. For the many lung cancer patients who are not surgical candidates, the tissue biopsies that are removed for diagnosis or staging are usually too small to provide sufficient material for research. Autopsy retrieval, on the other hand, could provide quantities of samples from the most aggressive fatal tumours and also provide samples from metastases as well as primary tumours, although sample quality is diminished relative to surgically derived samples. It is possible that lung cancer patients and their families would be willing to contribute to the research effort by donating tissues post mortem. This option is successfully pursued in other disease areas, most notably in neurodegenerative diseases where donation of brain tissue after death is well supported by affected patients and families. In the context of lung cancer, it would be useful to first attempt to gauge patient and public opinion before this option is further explored.

5. FUNDING FOR SAMPLE COLLECTION

It is possible to gain funding for sample collection associated with clinical trials through existing peer review mechanisms, for example the Cancer Research UK Translational Research in Clinical Trials Committee (TRICC). It can be less easy to obtain funds for free-standing collections – it would be helpful for NCRI Partners to consider whether there is anything they could do to facilitate this. Any programme for autopsy retrieval will need special funding which would need to be discussed once feasibility has been established.

6. PLAN OF ACTION

- ❑ NCRI Partners to consider whether their funding processes provide sufficient opportunity for the support of free-standing tissue collection, for example from patients undergoing surgery, as an important component of research infrastructure.

- ❑ The Lung Cancer Clinical Studies Group to ensure that all new clinical trials in lung cancer patients include tissue collection, where appropriate.

- Members of the NCRI Cancer Biobanking Confederation to examine the extent of privately or locally held collections of lung cancer materials and to help provide information on materials available for sharing or collaborative research.

- The lung cancer communications working party, led by Roy Castle Lung Cancer Foundation, will pursue the possibility of commissioning a survey of public opinion to determine the acceptability of the collection of tissue post mortem. If positive, onCore UK to follow up with plan for collection, which will need specific funding.

- The Lung Cancer Clinical Studies Group and onCore UK to work together to devise a plan to extend and standardise the collection of tissues from people with dysplasia.

APPENDIX VII

EXPERTS INVITED TO GIVE EVIDENCE TO THE LUNG CANCER STRATEGIC PLANNING GROUP

Dr Corri Black
Clinical Lecturer, Department of Public Health, University of Aberdeen

Dr Brian Clark
Chief Executive, onCoreUK

Professor Jessica Corner
Professor in Cancer and Palliative Care, University of Southampton, Macmillian Director for Improving Cancer Services

Professor Stephen Duffy
CR-UK Professor of Cancer Screening, Wolfson Institute for Preventative Medicine

Dr Tim Eisen
Consultant Medical Oncologist, Royal Marsden and Institute for Cancer Research (from September 2006, of CR-UK Cambridge Research Institute)

Professor John Field
Director of Research, Roy Castle Lung Cancer Research Programme, University of Liverpool Cancer Research Centre

Dr Serban Ghiorghiu
Global Clinical Research Physician, AstraZeneca UK Ltd

Sir Muir Gray
National Screening Committee

Dr James Mulshine
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APPENDIX VIII

GLOSSARY OF TERMS AND ACRONYMS

ABPI	Association of British Pharmaceutical Industry
BBSRC	Biotechnology & Biological Sciences Research Council
CRD	Cancer Research Database
CSDG	Clinical Studies Development Group
CSG	Clinical Studies Group
CSO	Common Scientific Outline
CT	Computed Tomography
CTAAC	Clinical Trials Awards & Advisory Committee
ESRC	Economic & Social Research Council
FTE	Full Time Equivalent
GP	General Practitioner
HSE	Health and Safety Executive
HTA	Health Technology Assessment
ICRP	International Cancer Research Partnership
MRC	Medical Research Council
NCI	National Cancer Institute, USA
NCRN	National Cancer Research Network
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NLST	National Lung Cancer Screening Trial
NPRI	National Prevention Research Initiative
NSC	National Screening Committee
NSCLC	Non-Small Cell Lung Cancer
PCCSDG	Primary Care Clinical Studies Development Group
PCRN	Primary Care Research Network
PI	Principal Investigator
PIC	Potential Impact Category
RC	Relative Commitment
RCT	Randomised Control Trial
ROD	Research Outputs Database
SCI	Science Citation Index
SCLC	Small Cell Lung Cancer
SPG	Strategic Planning Group
SuPaC	Supportive & Palliative Care
TRICC	Translational Research in Clinical Trials Committee
UKCRC	UK Clinical Research Collaboration
UKLCC	UK Lung Cancer Coalition


NCRI
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