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In Practice

Capacity of the 45 and Up Study to mobilise evidence-based improvements in cancer control: lung cancer case study

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Key points

- With prospectively linked data on registry-notified cancers, the 45 and Up Study has increased our understanding of cancer causes, care, costs, and outcomes in Australia
- Evidence on the effects of smoking, lung cancer risk prediction and costs based on data from the Study has supported policy decisions in tobacco control and lung cancer screening
- Patterns of care and cancer survivorship studies using the data have highlighted potential areas of unmet need for lung cancer patients, which can be monitored over time as treatments evolve

Abstract

Objective: Over the 15 years since the 45 and Up Study (the Study) was established, researchers have harnessed its capacity for enabling rigorous, comprehensive investigation of cancer causes, care, and outcomes. For the first time in Australia, the entire cancer-control continuum could be investigated by linking questionnaire data with cancer registry notifications, hospital records, outpatient medical services and prescription medications at scale. Here, we use lung cancer as a case study to demonstrate the Study's potential to improve cancer control.

Method: Narrative description.

Results: Between 2006–2013, approximately 1200 participants in the Study cohort who had no prior history of cancer were diagnosed with lung cancer, allowing the generation of novel, policy- and practice-relevant evidence for tobacco control, screening, and systems of care. The Study produced evidence on the continuing impact of smoking, including that 'light smoking' (1–5 cigarettes/day) is associated with nine times the risk of lung cancer compared to never-smoking; and that 54% of lung cancers could be avoided long-term if all Australians who smoked were to quit. The Study was used to validate a lung cancer screening risk prediction tool, correctly identifying 70% of the participants with a history of smoking who developed lung cancer within a 6-year period as 'high-risk'. Potential inequities in lung cancer care were identified using the Study cohort, including suboptimal levels of radiotherapy utilisation, below benchmark levels of systemic therapy for patients with metastatic disease, and high numbers of emergency department presentations prior to diagnosis. Participants with lung cancer reported poorer quality of life than those with almost any other cancer type, and about 50% reported severe physical functioning limitations. The Study also provided the infrastructure for the first comprehensive report on lung cancer health system costs.

Lessons learnt: As a statewide, population-based cohort, the Study provides reliable estimates of cancer risk, health services utilisation, and person-centred outcomes that can inform policy and practice decision making; and has provided the backbone for localising policy-relevant insights from international experience. We have found that the direct involvement of clinicians and policy makers in research design, and engagement with community networks, can yield tractable, policy-relevant, and ultimately impactful scientific insights.

Introduction

An improved understanding of the causes of, and outcomes after cancer, was a key motivation for the establishment of the 45 and Up Study. Inspired by large prospective cohort studies like the Million Women Study in the UK[1], the 45 and Up Study (hereafter 'the Study') was launched in Australia with a significant funding contribution from Cancer Council NSW, among other funding partners. Cancer is the leading cause of disease burden in Australia[2], accounting for three in 10 Australian deaths, yet every cancer type is different, complex and, in most cases, unexpected. Fifteeen years since its inception, the Study is now a robust source for investigating both known and unknown cancer risk factors; a primary objective that has been met with important contributions to the global evidence base for many exposures and cancer types to date (see supplementary Table S, available from https://figshare.com/articles/figure/Weber_et_al_2022_PHRP_Supplementary_table_pdf/21550608). Because of its large size (>250 000 participants) and population-based sampling frame, the Study has also contributed enormously to understanding cancer care and outcomes in Australia. It has been used to document pathways to cancer diagnosis and screening; patterns of care; inequities in care and outcomes; the survivorship experience; health system costs; and estimates of the population-wide burden of disease. It has proven to be a powerful, highly cost-efficient tool for informing evidence-based, priority-driven cancer control policy. Here, we describe some key established and potential applications of the Study to cancer control in the Australian setting, using lung cancer as a case study.

Background: the evolving landscape of lung cancer control

While lung cancer has remained the leading cause of cancer death in the 15 years since the inception of the Study in 2006, the lung cancer policy and practice landscape has changed enormously. Smoking rates (the primary modifiable risk factor for lung cancer) have declined over the study period (from 16.6% daily smoking in 2007 to 11% in 2019 among Australians aged 14 years and older[3]). However, e-cigarettes have become increasingly pervasive.[3] Given that individuals who have never smoked combustible cigarettes are three times as likely to take up smoking if they have used e-cigarettes[4], the long observed annual decline in smoking prevalence may be in jeopardy, which would significantly impact future lung cancer rates.[5] The results of the first randomised controlled trials demonstrating the effectiveness of lung cancer screening with low dose computed tomography (LDCT) were published in 2011[6,7], with many countries, including Australia, now tackling the prospect of embedding lung cancer screening into the health system.[8] Therapeutic innovation for treating patients with metastatic lung cancer has burgeoned, with 13 new drugs listed on the Australian Pharmaceutical Benefits Scheme (Government-subsidised prescription medicines) since 2016. This has resulted in survival benefits for many patients but with an estimated cost exceeding $600 million in 2021 (see Figure 1).[9] With linkage to routinely collected health records, the Study has enabled timely, locally relevant evidence for addressing the health impact of these evolving issues in lung cancer control.

Using the Study to facilitate continued momentum in tobacco control

Research using data from the Study has produced evidence on the continuing impact of smoking in the modern era and for the first time, smoking-related relative risk estimates of death and disease for the Australian population.[10-13] While tobacco smoke has been a known carcinogen since 1964[14], smoking patterns and cigarette products differ markedly across generations and populations, and cohort studies can play a vital role in facilitating evidence-based public health gains in tobacco control. Beyond the significance of the period and setting of the Study itself, these analyses contributed novel findings, including that:

- 'Light smoking' (1–5 cigarettes/day) is associated with a nine-fold risk of lung cancer compared to never smoking[10]
- More than half (54%) of lung cancers could be avoided in the long-term and 18% in the short-term, if

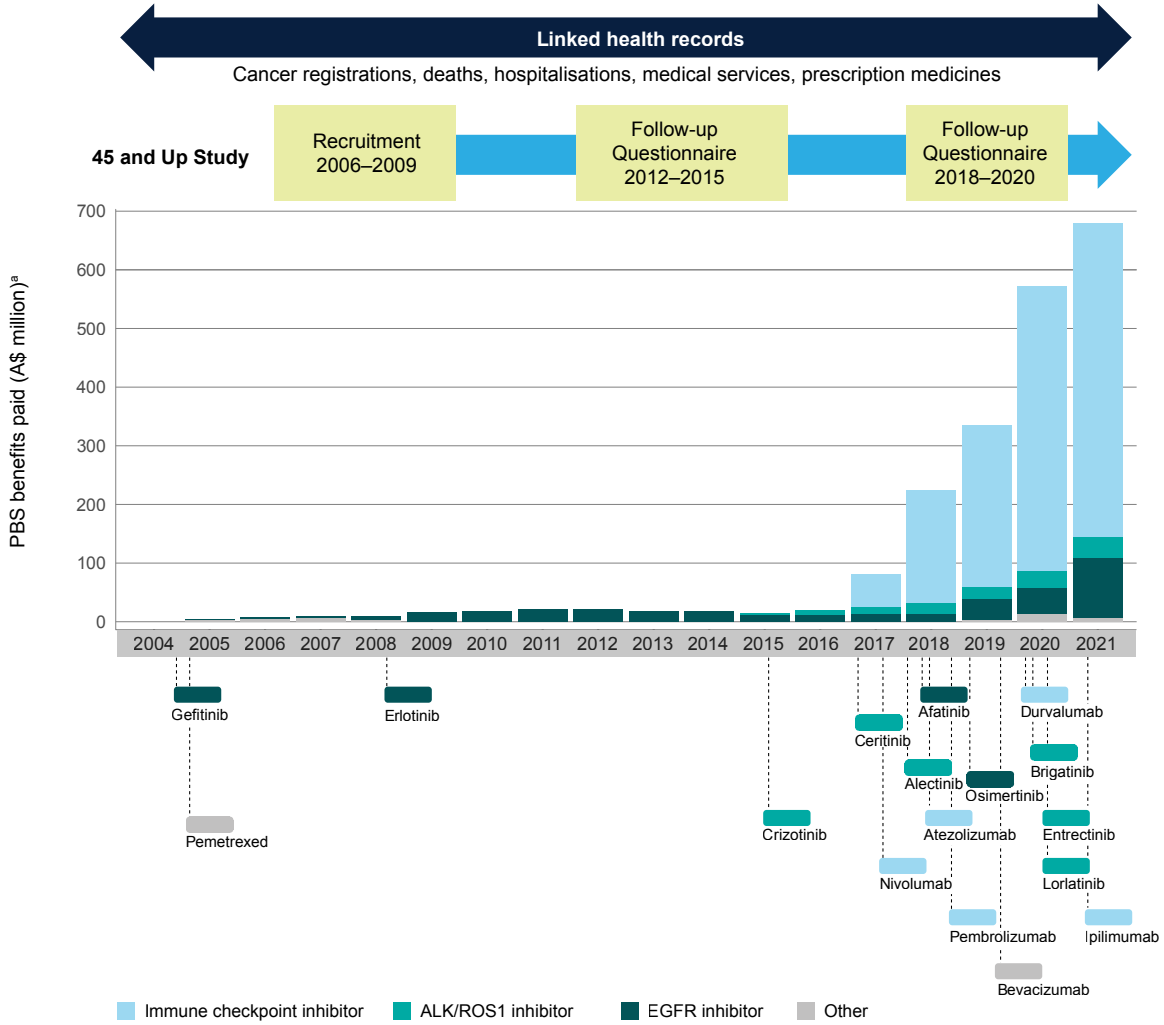
all individuals who currently smoke in Australia were to quit[11]
- Up to two-thirds of individuals currently smoking will die prematurely from their habit if they do not quit[12]
- In Aboriginal and Torres Strait Islander peoples, smoking is responsible for 37% of all deaths and 50% among those aged ≥45 years.[13]

Local estimates of the risk of death and disease in relation to smoking are invaluable for maintaining momentum in tobacco control; for example, some of these research findings have been used by the Australian Government to support three annual, 12.5% increases in tobacco excise, a tobacco control measure known to be the single most effective intervention to reduce smoking rates[15], which has proven effective in reducing smoking rates in both the general population[16] and in Aboriginal communities.[17]

Evidence to support lung cancer screening recommendations

Primary prevention through tobacco control is likely to remain the most effective strategy for reducing the burden of lung cancer over the longer term.[5] However, given the 20–30-year lag between population-level tobacco exposure and lung cancer incidence, the full benefits of these interventions will not be realised for decades to come.[5] For many people with a history of heavy tobacco use, lung cancer may be inevitable, and a high proportion will be diagnosed with advanced disease with poor prognosis and quality of life.[18] Two large international, randomised controlled trials found that low-dose CT scans (LDCT) for people with high lung cancer risk (those with a history of heavy smoking) could detect cancer at an earlier stage and thus reduce lung cancer mortality by 20–24%.[6,7]

Figure 1. Timeline of systemic therapies solely indicated for lung cancer, newly listed on the Australian Pharmaceutical Benefits Scheme and annual benefit paid during the 45 and Up Study period.



Data source: Services Australia. Pharmaceutical Benefits Schedule Item Reports. 2022: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

[a] Costs do not account for the confidential costs recovered by the Government through special pricing arrangements.

ALK/ROS1 inhibitor = anaplastic lymphoma kinase/ROS proto-oncogene 1 receptor tyrosine kinase; EGFR inhibitor = epidermal growth factor receptor inhibitor; PBS = Pharmaceutical Benefits Scheme

These findings accelerated efforts to refine lung cancer risk prediction tools and screening selection criteria to support implementation. Currently, the most promising tool is $PLCO_{m2012}$, an algorithm based on demographic, health and smoking factors – these were able to be ascertained in the 45 and Up Study, making it the ideal setting to test the tool's predictive accuracy in an Australian population.[19] $PLCO_{m2012}$ risk was estimated for 95 822 participants with a history of smoking at baseline, a sample larger than the development dataset and about five times larger than any other validation dataset. Over 6 years of follow-up, the tool accurately identified 70% of the participants who went on to develop lung cancer as 'high-risk'.[19] In 2020, the research was included in an Australian Government enquiry into the feasibility of establishing a national targeted lung cancer screening program.[8]

The government screening enquiry also included key data on the health care costs of lung cancer established from the Study data, to inform a health economic evaluation.[20] Previous studies of lung cancer care costs were limited to smaller, hospital-based samples, and lacked data on general practice or specialist consultations. Via linkage with routinely collected, administrative health records, the Study allowed for comprehensive capture of excess health services costs attributed to lung cancer, without restriction to a specific hospital catchment or treatment type. The results could also be detailed by factors essential to reliable cost-effectiveness analyses, such as age, sex and extent of disease at diagnosis.

The Australian Government enquiry found in favour of targeted lung cancer screening and the Australian Medical Services Advisory Committee gave the Government a positive recommendation regarding introducing a national lung screening program for high-risk individuals .[8] Embedding a national screening program into the Australian health system would entail many challenges.[21] However, the Study can be harnessed to update evaluations of the economic impact of screening as evidence emerges, including on the further evolution of lung cancer therapy utilisation and costs.

Documenting real-world patterns in lung cancer care

Evidence-based treatment is critical to improving health outcomes. Prior to the establishment of the 45 and Up Study, little had been published on lung cancer care pathways, and pathways to diagnosis in particular. The Study has provided capacity for researchers to connect data across the entire cancer-control continuum by linking patient-level information with hospital records, outpatient medical services and prescription medications. While Study cohort participants are known to be healthier than the general population[22], on a large scale, these types of analyses can identify potentially unwarranted variations and inequities in care, highlight evidence gaps, and serve as benchmarks with which to compare the impact of emerging interventions or unforeseen disruptions (for example, a global pandemic). Importantly, the availability of extensive sociodemographic and lifestyle information prior to cancer diagnosis allows researchers to identify whether gaps in care are particularly apparent for specific subgroups of the population, which could not be investigated based on hospital and medical records alone.

Between 2006 and 2013, approximately 1200 Study participants without a prior history of cancer had a registry-notified lung cancer diagnosed[10], with approximately 160–178 new cases of lung cancer occurring each year.[20] There were 226 cases diagnosed between 2006–2013 in participants who never smoked.[23] Many participants had been admitted to a hospital emergency department in the 3 months prior to lung cancer diagnosis[24,25], and for 14%, it was the only health service event identified prior to diagnosis.[24] Suboptimal levels of radiotherapy utilisation were reported[26] and below benchmark levels of systemic therapy for patients with metastatic disease at diagnosis.[27] Almost one-third of Study participants diagnosed with non-small cell lung cancer up to 2010 received no anti-cancer treatment.[25]

However, innovations in systemic therapy (Figure 1), surgery and radiotherapy are changing the standard of care for lung cancer in unprecedented ways, and lung cancer survival is improving over time.[18] The first Australian evidence-based clinical practice guidelines for lung cancer were published in 2004. In 2012, they were updated and converted to an electronic version that incorporated new evidence over time. Under an evolving standard of care, resources like the Study will continue to be critical in monitoring the uptake, fidelity, and impact of new technologies and highlighting areas of unmet need.

Quantifying the social and psychological impacts of lung cancer

Administrative datasets are ideal for capturing health service events but miss a vitally important aspect of cancer care – that is, patient preference. While the Study does not directly capture patient-reported preferences and outcomes, one of its most powerful aspects is the connection between administrative health records and questionnaire data on mental health, disability, social participation, and quality of life. Before the 45 and Up Study was established, most studies on the quality of life of cancer survivors were limited to a single cancer type.[28] Around 24 000 participants joined the Study with a personal history of invasive cancer, providing an opportunity for systematic comparison of unmet needs for people diagnosed with different cancer types. Compared to almost every other cancer type, participants with lung

cancer in the Study had the poorest quality of life and self-rated health, the highest levels of psychological distress[28,29], and were more likely to be out of the workforce.[30] Almost half the participants with lung cancer had severe physical functioning limitations.[28] While lung cancer clinicians, patients, and carers have a keen understanding of the impact that a lung cancer diagnosis has on quality of life, having large-scale, robust local estimates of the magnitude of these adverse outcomes documented in the scientific literature are critical for underpinning investment in lung cancer research, support systems, and policy and practice improvements.

Lessons learnt

The value of the investment in the 45 and Up Study is only now being fully realised,15 years from its inception. When the Study was established, there was no NHMRC clinical trials and cohort funding scheme, so many studies were established with major partnerships. With its robust population-wide sampling frame and large-scale collection of linked health records, researchers have generated outputs from the 45 and Up Study that will support improvements in cancer control and provide a compelling case for continued investment in such shared infrastructure.

Our successes in using the Study to inform wider policy considerations, for example, on issues around lung cancer screening, have largely been driven by the engagement of multidisciplinary research teams. These include clinicians and key lung cancer experts within cancer policy, public health, and epidemiology. In addition, ongoing involvement with organisations in the not-for-profit sector, such as Cancer Council and the Lung Foundation Australia, has been integral to identifying community-relevant issues, evidence gaps, and stakeholders. These active networks have taught us that large-scale health data are most powerful when harnessed within the broader framework of lived experience, including patient and clinician perspectives and the constraints and needs of public policy.

Thanks to the thousands of participants who consented to share their de-identified information, the 45 and Up Study is fast becoming a reliable mechanism to mobilise evidence-based improvements in cancer control so that future generations may age free from the harms of cancer.

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EB was the Scientific Director of the 45 and Up Study from 2003–2018 and a senior adviser to the Sax Institute from 2018–2022.

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Peer review and provenance

Externally peer reviewed, invited.

Competing interests

None declared.

Author contributions

MW was responsible for the design, drafting, and editing of the manuscript. PN was responsible for the analysis of data and contributed to manuscript review and editing. PG contributed to manuscript review and editing and DG, JS, EB and KC contributed to manuscript design, review and editing.

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