Analysis of bowel cancer outcomes for the National Bowel Cancer Screening Program

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Contents

Acknowledgments

Abbreviations

χ^2	Chi-square statistic
ABS	Australian Bureau of Statistics
ACT	Australian Capital Territory
AIHW	Australian Institute of Health and Welfare
CI	Confidence interval
DoHA	Department of Health and Ageing (now the Department of Health)
FOBT	Faecal Occult Blood Test
GP	General Practitioner
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases, 10th edition
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition
NBCSP	National Bowel Cancer Screening Program
NDI	National Death Index
NHMRC	National Health and Medical Research Council
No.	Number
NOS	Not otherwise specified
NPV	Negative predictive value
NSW	New South Wales
PPV	Positive predictive value
WHO	World Health Organization

Symbols

%	per cent
—	nil or rounded to zero
. .	not applicable
n.a.	not available

Summary

The National Bowel Cancer Screening Program (NBCSP) was introduced in Australia in 2006 with the aim of reducing morbidity and mortality from bowel cancer, by actively recruiting and screening the target population for early detection or prevention of the disease. This study set out to evaluate and to quantify the effectiveness of the NBCSP against this aim.

The study linked NBCSP, cancer incidence and mortality data to identify 22,051 people diagnosed with bowel cancer:

- 4,327 had been invited to participate in the NBCSP in 2006–2008, as part of the target population turning 50, 55 or 65 (NBCSP invitees)

- 17,724 were aged 50–69 in 2006–2008, but did not turn 50, 55 or 65 during that period and were therefore not invited to screen then (non-invitees).

The report presents a comparison of the outcomes (mortality) and cancer characteristics for these two populations, and shows that NBCSP invitees (particularly those who participated) had less risk of dying from bowel cancer, and were more likely to have less-advanced bowel cancers when diagnosed, than non-invitees. These findings demonstrate that the NBCSP is contributing to reducing morbidity and mortality from bowel cancer in Australia.

Bowel cancer mortality rates were lower for NBCSP invitees than non-invitees

Of people in this study who were diagnosed with bowel cancer in 2006–2008, non-invitees had a 68% higher risk of bowel cancer death by 31 December 2011, compared with NBCSP invitees. Even after correcting for lead-time bias in screen-detected cancers (where an earlier diagnosis may not affect eventual date of death, yet give a seemingly longer survival time), the mortality risk was still a statistically significant 15% higher for non-invitees.

Among the NBCSP invitees specifically, the risk of death from bowel cancer was over 2 times as high in those who did not participate but later had a bowel cancer diagnosed, compared with those whose cancer was diagnosed through participation in bowel cancer screening.

On average, bowel cancers were less advanced for NBCSP invitees than non-invitees

Detection of bowel cancer at an earlier stage in its development is linked with better treatment options and prognosis, and is a key reason behind the reduced mortality risk. Of the bowel cancers in this study that had 'summary stage at first presentation' data available, non-invitees were found, on average, to have more advanced (worse prognosis) bowel cancers compared with NBCSP invitees. Specifically, bowel cancers in non-invitees had 38% higher odds of being more advanced than those diagnosed in NBCSP invitees.

Among the NBCSP invitees, those with screen-detected bowel cancers were much more likely to be diagnosed at an earlier summary stage (121% higher odds), compared with bowel cancers later diagnosed in the invitees who did not participate.

Screening test performance

Of the NBCSP invitees who participated, 83% of those diagnosed with bowel cancer within 2 years of their screen had received a positive screening result, and 93% of those who were not diagnosed with bowel cancer had received a negative result. These figures suggest that the screening test has a high degree of accuracy.

1 Introduction

Background

Bowel cancer, which includes cancers of the colon, recto-sigmoid junction and rectum, is a major cause of morbidity and mortality in Australia. According to the latest available data, it was the second most common cancer diagnosed in 2010 (excluding non-melanoma skin cancer), with 14,860 new cases. Bowel cancer was also the second most common cause of cancer mortality in 2011, with almost 4,000 deaths. One in 12 Australians are likely to develop bowel cancer in their lifetime (AIHW & AACR 2012).

Several randomised controlled trials have demonstrated that bowel cancer mortality could be reduced by 15–33% through regular bowel screening using a faecal occult blood test (FOBT) to detect bowel cancers earlier, prior to them causing symptoms (Kewenter et al. 1994; Hardcastle et al. 1996; Kronburg et al. 1996; Mandel et al. 1999). Early detection of bowel cancer through population screening programs is therefore predicted to improve prognosis and reduce mortality.

A pilot program was run between November 2002 and June 2004 to test the feasibility, acceptability and cost effectiveness of bowel cancer screening in Australia (DoHA 2005). In 2005, the National Health and Medical Research Council (NHMRC) released guidelines that recommended biennial bowel cancer screening, using FOBT kits, for the Australian population over 50 years of age (CCA & ACN 2005).

In August 2006, the National Bowel Cancer Screening Program (NBCSP) commenced, screening people using immunochemical FOBT kits (Box 1). The Program's goal is to reduce the morbidity and mortality from bowel cancer by actively recruiting and screening the target population for early detection or prevention of the disease.

Box 1: How the National Bowel Cancer Screening program works

The NBCSP is managed by the Australian Government Department of Health, in partnership with state and territory governments.

People who are registered as an Australian citizen or migrant in the Medicare enrolment file, or registered with a Department of Veterans' Affairs gold card, are included in the eligible NBCSP population, and added to the NBCSP register, when they reach one of the target ages. These people are then sent an invitation pack containing a FOBT kit.

The NBCSP has been phased in gradually. The target ages initially invited to screen in 2006 were people turning 55 and 65, with 50-year-olds added from July 2008. The Government-funded NBCSP currently offers immunochemical FOBT screening to Australians turning 50, 55, 60 and 65. The NBCSP will be further expanded from 2015, when a phased implementation of biennial screening will commence. When fully implemented, all Australians aged between 50 and 74 will be offered bowel screening every two years, consistent with the recommendations of the NHMRC (CCA & ACN 2005).

While population screening programs are aimed at the asymptomatic population, at the time of invitation it is currently not known if particular invitees already have symptoms, a diagnosed bowel cancer, or are already undergoing regular surveillance or screening outside the program.

(continued)

Box 1 (*continued*): How the National Bowel Cancer Screening program works

Once an eligible person has completed their FOBT, they post it to the Program's pathology laboratory for analysis. Results are sent to the participant, the participant's nominated GP and the NBCSP register. Participants with a positive result, indicating blood in their faeces, are advised to consult their GP to discuss further diagnostic testing—in most cases this will be a colonoscopy.

Responses to invitations, and the outcomes for participants who complete the screening test and receive a positive result, are monitored to the point of diagnostic assessment. (See Appendix A, Figure A.1 for a complete representation of the current screening pathway.)

The AIHW publishes monitoring reports on the NBCSP each year. These reports provide the most up-to-date national data available for the NBCSP. The latest monitoring report, *National Bowel Cancer Screening Program Monitoring report: 2012–13* (AIHW 2014b), is available online at <www.aihw.gov.au>. To date, final screening outcome data (that is, diagnostic assessment data) for NBCSP participants have been limited, mainly due to inadequate NBCSP reporting by colonoscopists and histopathology laboratories. Performance evaluation of some aspects of the NBCSP has consequently been somewhat hindered, and this in turn became the trigger for this project, which is aimed at identifying bowel cancer outcomes for 2006–2008 NBCSP invitees. (See Appendix A for further information on the NBCSP.)

Box 2: Report terminology

Key terminology used throughout this report is explained below. Further definitions are included in the Glossary.

Intention-to-screen analysis: In a trial of a screening intervention, patient outcomes are analysed according to the group to which subjects were randomised, irrespective of whether those in the screening group (the 2006–2008 NBCSP invitee study group) and the control group actually participated in screening. The importance of this principle lies in ensuring that randomisation is preserved, thus maintaining an equal distribution of important factors that may influence the outcome in both the control and intervention groups. Using intention-to-screen analysis also reflects more closely the population benefit that can be expected, given participation rates that are likely to be encountered in practice (Barratt et al. 2002).

Invitation: An NBCSP FOBT screening kit sent to those turning a target age (see Box 1).

Participation: An NBCSP invitee is considered to have participated when they return a completed FOBT kit for analysis, regardless of its screening result.

Positive result: A positive screening result occurs when blood is found in a completed screening kit when tested. Blood in faeces may indicate a bowel abnormality (including cancer or adenomas) that requires further investigation.

Non-positive result: Includes negative screening results, and also inconclusive or unsatisfactory screening results where there was no successful re-test recorded.

Non-responder: A person was considered a non-responder if they were sent an invitation as part of the 2006–2008 NBCSP study group, but did not return their screening kit for analysis.

Screen-detected cancer: A bowel cancer was considered screen-detected if it was diagnosed any time after a positive screening test result, as it was likely diagnosed as part of follow-up investigation from the screening test.

(continued)

> **Box 2 (*continued*): Report terminology**
>
> **Interval cancer:** A bowel cancer was considered an interval cancer if it was diagnosed within 2 years of a negative or inconclusive screening result. A 2-year cut off was used for interval cancers as that is the recommended rescreening interval, where later cancers should normally be discovered by a rescreening test.
>
> **Down-staging:** If cancers diagnosed in a group of people exposed to a particular treatment are on average at a less-advanced stage (see Box 3) than those diagnosed in a similar group of people who were not exposed to the treatment, 'down-staging' of cancers in the treatment group is said to have occurred. As cancers at a less-advanced stage when diagnosed generally have better morbidity and mortality outcomes than those at a more-advanced stage, down-staging can be assumed to be an improvement for those people.

Project objectives

This project's aim was to evaluate the effectiveness of the NBCSP in reducing morbidity and mortality, and to quantify the impact of the program in identifying bowel cancer earlier, in line with the program goal of early detection or prevention of the disease. We investigated differences in bowel cancer outcomes between individuals who were invited into the NBCSP (between 2006 and 2008), and those aged 50–69 who were diagnosed with bowel cancer over the same time period who were not invited into the NBCSP. Further comparisons were made between the 2006–2008 NBCSP invitees who participated, and the invitees who did not participate.

To do so, we linked the 2006–2008 NBCSP invitees' data to jurisdictional cancer registry data and national deaths data—the latter through the National Death Index (NDI).

Overall, there were five project objectives:

Primary objectives

1. *Describe differences in bowel cancer mortality between 2006–2008 bowel cancer diagnoses in those invited to screen and those aged 50–69 who were not invited into the NBCSP.*
   Even though only a small number of years had passed since the NBCSP invitations analysed in this project, it would be of great value to see if the available data showed any differences in bowel cancer mortality between those invited and not invited into the NBCSP.
2. *Describe differences in bowel cancer summary stage (see Box 3) in those whose bowel cancer was diagnosed after a 2006–2008 invitation to screen in the NBCSP, compared with those aged 50–69 who were not invited into the NBCSP.*
   It was hypothesised that bowel cancers diagnosed in people invited into the NBCSP would, on average, be less advanced than those diagnosed in people of a similar age who were not invited to screen. This is referred to as 'down-staging'.

Secondary objectives

3. *Investigate characteristics of interval bowel cancers.*
   People with a negative or inconclusive screening result who then had a bowel cancer diagnosed within 2 years of that result were considered to have an interval cancer. Meeting this objective involved investigating if there were any different characteristics in interval cancers compared with screen-detected bowel cancers.

4. *Describe the positive predictive value (PPV) and negative predictive value (NPV) of the screening test.*
   This involved investigating how many people who received a positive screening result actually had bowel cancer, and how many people who received a negative screening result did not have bowel cancer. These statistics are often evaluated in screening programs to ensure potential harm (including psychological) is minimised from incorrect screening test results.

5. *Demonstrate the feasibility of, and gain experience in, the linkage of data from the NBCSP register, cancer registries and the NDI to evaluate NBCSP outcomes, with a view to repeated future linkages if successful.*

Box 3: What is bowel cancer stage, and why is it analysed?

Bowel cancer summary stage at first presentation (more simply called 'summary stage' in this report) refers to the extent, or spread, of cancer at the time of diagnosis. Staging is usually based on the size of the cancer, whether lymph nodes also contain cancer (a sign of cancer spread), and whether the cancer has spread to other locations in the body—a sign of poorer prognosis (O'Connell, Maggard & Ko 2004; Morris, Lacopetta & Platell 2007).

The key indication that a cancer screening program is being effective is reduced bowel cancer mortality outcomes for those participating in the program. However, as the number of years of follow-up data were limited at the time of this study, and full evaluations of the effect on mortality can take more than 10 years (Day & Walter 1984), another way to show the potential effect of screening on mortality outcomes is to compare differences in cancer stage with those not invited to screen. This is because a lower stage at diagnosis (that is, less spread or growth of a cancer) is generally related to improved treatment and disease outcomes, and thus survival. A similar South Australian study by Cole and colleagues (2013) also used this approach. Stage analyses are used in this study, in addition to the mortality analyses, to provide more detail and explanation.

In this report, bowel cancer staging data were based on the 'summary stage at first presentation' system. (See Appendix A for further details on cancer stage, and how it was analysed in this report.)

Structure of this report

Chapter 2 describes the data sources and methods used, along with technical issues that should be considered when interpreting the information in this report. Chapter 3 then describes the study group details after the data linkages. Chapter 4 contains the findings against Objectives 1–4. Summaries of rationale, data and methods are presented before each set of findings and results. Chapter 5 combines and discusses the findings to aid interpretation and summarise the project. Consideration of Objective 5 is incorporated into this overall discussion.

Additional methodological details are provided in Appendix A.

2 Data and methods

Data sources

This project linked screening details of people invited to screen in the NBCSP in 2006–2008 (Box 4) with two other data sets—a population-based dataset of bowel cancer diagnoses, and national deaths information—in order to improve the amount of bowel cancer outcome information for those NBCSP invitees. A separate collection of bowel cancer diagnoses in those of similar age who were not invited in 2006–2008 could also then be created.

These linkages allowed for comparisons of cancer characteristics and mortality risk across NBCSP invitees and non-invitees. The predictive value of the screening test could also then be determined.

Box 4: Why were those invited to screen in 2006–2008 chosen for this report?

There were two main reasons for setting the NBCSP study group for this project to the 2006–2008 invitees:

- Bowel cancer can take many years to grow and show symptoms before being diagnosed (Brenner et al. 2011). Bowel cancer screening aims to detect cancers before symptoms are noticed by the person. In order to compare outcomes (including bowel cancer summary stage) in those invited and not invited, sufficient time must have elapsed for symptoms to manifest and cancers to be detected in the not-invited (and interval) population.

- Additionally, data on cancer incidence and mortality are not available until a number of years after those events have occurred. The use of invitations from 2006–2008 optimised the data available for linkage.

NBCSP invitee study group

The invitee study group used were those invited between August 2006 (the start of the NBCSP) and 31 December 2008. Within this time period, the eligible NBCSP invitee population consisted of those turning 55 and 65, as well as 50-year-olds from 1 July 2008. (See Table A.1, Appendix A, for NBCSP target population changes.)

As the NBCSP invitee study group chosen were those invited in the first 2 years of the program, most screening invitations were initial invitations (known as prevalent screens) and not rescreening invitations. An exception was the small number of people who had been invited as part of the NBCSP pilot, about 6 years earlier. This should be taken into account when interpreting these results, as prevalent screening test results may differ from rescreening test results (incident screens) which will occur in future years of the NBCSP (once biennial screening is fully rolled out).

Bowel cancer diagnosis data

Bowel cancer diagnosis data from jurisdictional cancer registries were used to identify bowel cancer diagnoses (ICD-10 C180–C209) in both the NBCSP invitee study group and, by process of elimination, those not invited into the NBCSP. For this report, bowel cancer diagnoses from 1 January 2006 to the latest available at the time of selection from the 8 jurisdictions were merged to form a 'national' bowel cancer diagnosis dataset.

The use of bowel cancer information directly from jurisdictional registries was preferred to using the AIHW's Australian Cancer Database (ACD) because more recent bowel cancer diagnosis data were available directly from registries than were held in the ACD at the time of the project. Further, additional fields were also requested for the bowel cancer diagnoses, such as the 6th digit of morphology (a code describing how much or how little a tumour resembles the normal tissue from which it arose) and any bowel cancer staging data—these are not currently contained in the ACD. Some of these additional fields were not available for all jurisdictions, and this affected analyses in this report. (See Appendix A for details.)

At the time of this project, the calendar years of available cancer registry data from each jurisdiction differed, with some supplying data from 2006 to 2010 or later, but others only supplying data from 2006 to 2008 (Figure 1). These end-point differences were taken into account in the analyses where required, as outlined later in this chapter in the descriptions of data and methods for each objective.
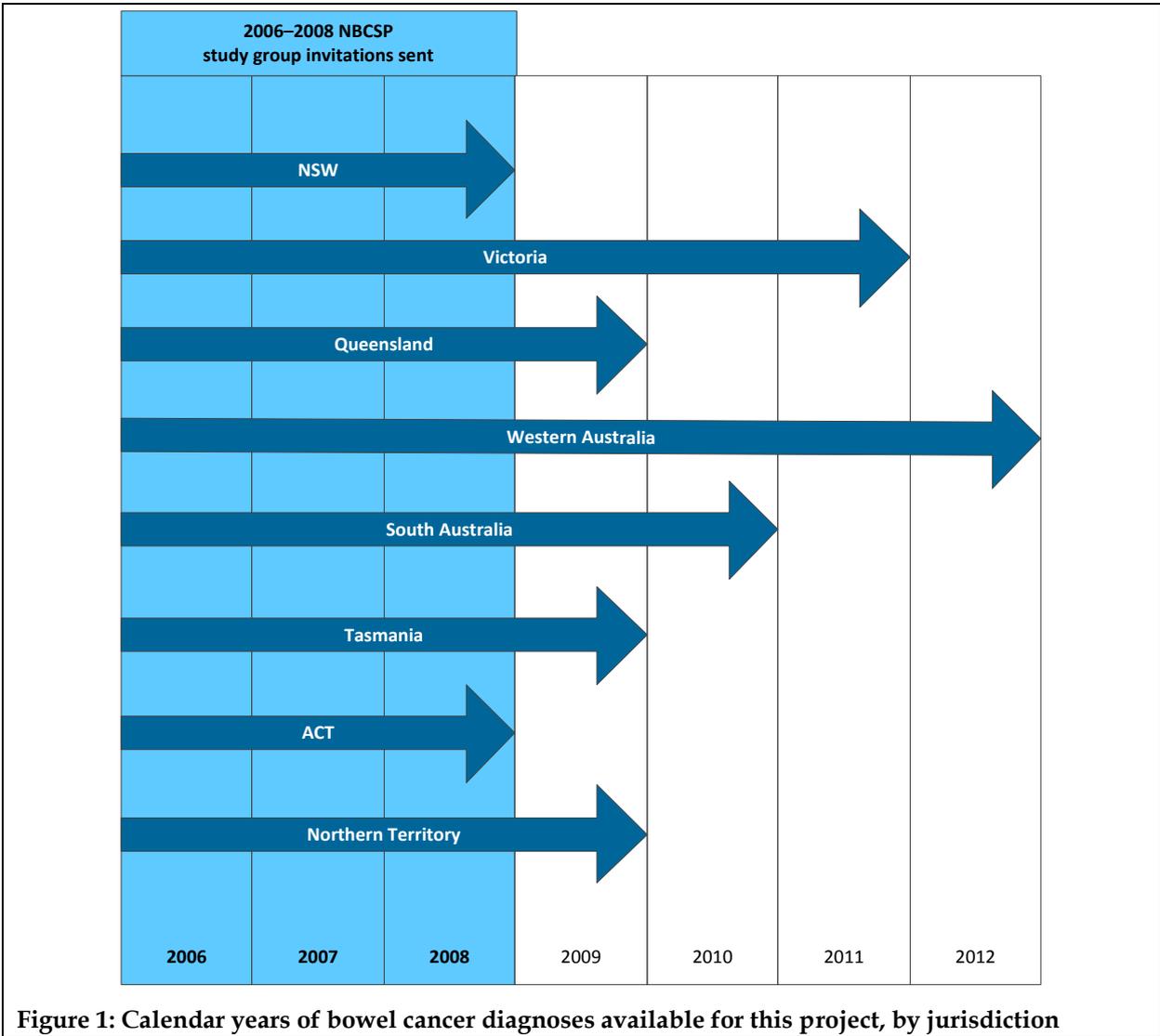
Figure 1: Calendar years of bowel cancer diagnoses available for this project, by jurisdiction

National deaths data

The National Death Index (NDI) is a database of all deaths that have occurred in Australia since 1980, and is maintained by the AIHW for the purposes of record linkage—for example,

record linkages that help determine outcome differences, such as in this study. These data are supplied monthly by the state and territory Registrars of Births, Deaths and Marriages. While fact-of-death information is generally up to date in the NDI, underlying-cause-of-death information—required for this project—is normally some years behind. At the time of data linkage for this project, underlying-cause-of-death data contained in the NDI were only available up to 31 December 2011.

See Appendix A for more detail of the data sources, including data issues and caveats.

Methods

Ethics approvals

To gain access to the data required for this linkage project, ethics approvals were obtained from the AIHW Ethics Committee, the Department of Health Ethics Committee, and jurisdictional Human Research Ethics Committees responsible for their relevant cancer registry's data. Approval was also obtained from the Department of Human Services (formerly Medicare Australia) for extracting the NBCSP study group data from the NBCSP register. Individuals were matched across databases and then de-identified by an independent third party (the AIHW Data Linkage Unit) before analysis by investigators, as described below.

Data linkage phase

The AIHW Data Linkage Unit performed probabilistic data linkages between the National Bowel Cancer Screening Program, jurisdictional bowel cancer diagnosis, and National Death Index data sets. The AIHW Cancer and Screening Unit analysed the resulting linked and de-identified data (Figure 2). Specifically, the NBCSP invitee study group was linked to the bowel cancer diagnosis data and deaths information from the NDI. Lastly, the bowel cancer diagnosis data were linked to the deaths data.
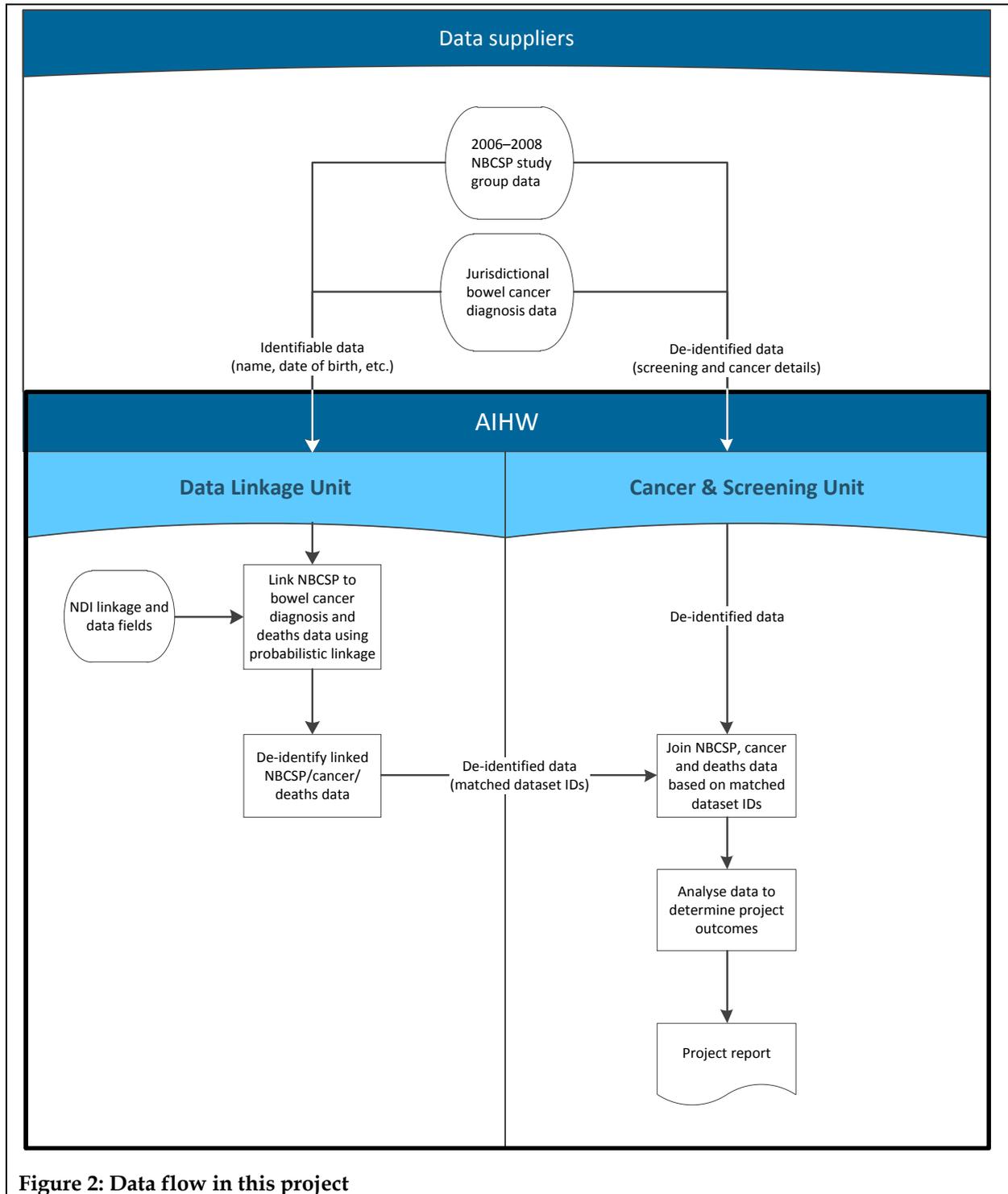
Figure 2: Data flow in this project

The linkage process involved creating record pairs by matching records from one dataset with records from another dataset based on similarities in characteristics such as surname, given name(s), sex, and day, month and year of birth. Probabilistic linkage techniques such as these do not necessarily result in an exact match between two records, but indicate a high degree of similarity between records. For each matched record pair, a comparison weight is calculated. The weight quantifies the degree of similarity between records in a given pair. This can be used to ascertain the extent to which a given record pair is likely to be the same person, with a higher record pair comparison weight suggesting a given record pair is more

likely to be the same person than a lower comparison weight. Due to the nature of probabilistic linkage, there may be some unavoidable inaccuracy in the linkage process, and while statistical significance testing was used in most analyses, this should be taken into account when interpreting the results.

Linkage of the three data sources

The linkage across the three project data sources is depicted in Figure 3.

(a)   Those in the 2006–2008 NBCSP invitee study group who had a bowel cancer diagnosis, but no bowel cancer death link (n = 3,835).

(b)   Those in the 2006–2008 NBCSP invitee study group who had a bowel cancer diagnosis and bowel cancer death link (n = 492).

(c)   Those in the 2006–2008 NBCSP invitee study group who had a bowel cancer death link, but no recorded bowel cancer diagnosis. This may have been due to deaths data being more recent than diagnosis data. As these had no date of diagnosis, survival from diagnosis to death could not be calculated, so they were excluded from the Objective 1 analysis (n = 381).

(d)   Bowel cancers diagnosed 2006–2008+[e] in those 50–69 who also had a bowel cancer death link (n = 3,088).

(e)   The end-point of bowel cancer diagnosis data differed by jurisdiction, ranging from 2008 to 2012.

Figure 3: Linkage outcomes across the three project data sources

For the 'NBCSP invitee study group to bowel cancer diagnosis' data linkage, 6,758 presumed correct bowel cancer diagnosis matches to invitees were made. However, 2,431 were then

excluded from the analyses due to diagnoses before invitation (2,115), or more than 2 years after a negative screen (316).

The linkages using the NDI data set resulted in 3,961 presumed correct bowel cancer death matches—873 to NBCSP invitees, and 3,088 to non-invitees (see footnotes (b), (c) and (d), Figure 3).

After linkage across the three datasets, it was possible to summarise the bowel cancer diagnoses into 4 subgroups (with bowel cancer death information included where appropriate): screen-detected cancers, interval cancers, non-responder cancers and never-invited cancers. These are described more completely below.

2006–2008 NBCSP invitee study group. These 3 subgroups are contained within the '1 + 2' and '1 + 2 + 3' intersections in Figure 3:

1. Screen-detected cancers

These were bowel cancers diagnosed in individuals following NBCSP invitation and subsequent positive FOBT. This subgroup included those who were invited to participate when they turned one of the target ages in 2006–2008. Any bowel cancer diagnosis after a positive screening result, regardless of the time between screening and diagnosis, was considered screen-detected.

2. Interval cancers

These were defined as bowel cancers diagnosed in individuals who were invited and participated in the NBCSP and received a negative or inconclusive screen result, but were later diagnosed with bowel cancer within a 2-year follow-up period. A 2-year cut-off was chosen because the recommended rescreening interval is 2 years (CCA & ACN 2005).

3. Non-responder cancers

These were bowel cancers diagnosed in those invited to participate in the NBCSP who did not participate. That is, invitees in this subgroup never returned a completed screening test for analysis but were diagnosed with bowel cancer after their invitation. The exact reason for non-participation by individuals in this group is unknown, and this needs to be taken into account when interpreting the results in this report. Any bowel cancer diagnosis after an invitation with no response, regardless of the time between invitation and diagnosis, was considered a non-responder cancer.

Never-invited study group. This subgroup captures the remainder of the bowel cancer diagnoses not contained within the '1 + 2' and '1 + 2 + 3' intersections in Figure 3:

4. Never-invited cancers

These were bowel cancers diagnosed in individuals aged 50–69 who were not invited to participate in the NBCSP in 2006–2008. As can be seen in Figure 3, these are the bowel cancer diagnoses that did not link to a NBCSP invitee record. This subgroup included those who were not invited into the NBCSP over the time period examined, as they did not have a target age birthday (that is 50th, 55th, or 65th) in that time. As most jurisdictions included bowel cancer diagnosis data later than 2008 (Figure 1), and only NBCSP invitees from 2006 to 2008 were linked to these diagnosis data, individuals aged 50, 55 or 65 at a time of diagnosis after 2008 may be due to participation in the NBCSP from 2009 onwards. These individuals were therefore excluded from the never-invited subgroup to remove any potential bias in the results.

For analysis by intention-to-screen (in Objectives 1 and 2), data for screen-detected, interval and non-responder groups were combined as the 'NBCSP invitee' group. Results were compared with the outcomes of the 'never-invited' group. Invitees with a bowel cancer diagnosed before invitation or screening test completion were excluded.

With an intention-to-screen design, it is assumed that people invited to screen who were then diagnosed with a bowel cancer either: participated by completing the screening test provided, or as a result of the information provided, had increased awareness of bowel cancer symptoms which may have led to other medical investigations outside the program that diagnosed the bowel cancer—earlier than if they had never been invited. This design also allows the benefit of the overall program, even including those who do not participate, to be understood.

Age-at-diagnosis differences between NBCSP invitee and never-invited groups

As the NBCSP invitee group was comprised of those reaching their 50th, 55th or 65th birthday in 2006–2008, a higher proportion of diagnoses in this group were at those ages, or within a year or two afterwards. This gave a different age structure for the NBCSP invitee compared with the never-invited group (Table 1). Differences in age at diagnosis between groups were adjusted for in relevant analyses.

Table 1: Age-at-diagnosis differences for 2006–2008 NBCSP invitee and never-invited groups

	Age at diagnosis						
	50	**51–54**	**55**	**56–64**	**65**	**66–69**	**Total number**
Group	Proportion of diagnoses (%)						
NBCSP invitee	2.4	3.1	15.7	22.4	27.2	29.2	4,327
Never-invited	1.9	12.7	1.1	53.5	2.1	28.7	17,724
Total							**22,051**

Assumptions for statistical analysis

In this project, variability across the NBCSP invitee and never-invited groups warranted the need for statistical significance testing of differences observed across groups. The variability within data could be due to:

- Potential minor inaccuracies in the probabilistic data linkage process, as discussed earlier.

- Limitations in cancer staging data. For this project, only 3 jurisdictions were found to have suitable cancer staging data for the study time period—New South Wales, Tasmania and the Australian Capital Territory. These jurisdictions provided about 27% of the total bowel cancer cases, which serves as a preliminary estimate for the stage profile of cancer at the national level.

- Differences in age-group-at-diagnosis structures between invited and non-invited groups. The NBCSP invitees were those turning 50, 55 and 65 years of age. They were compared with 5-year age groups in the non-invited group (that is, 50–54, 55–59, 60–64 and 65–69), which, while incorporating the NBCSP target ages, also include ages up to 69.

- Potential variability in the screening test. For example, there is a small margin of error in which the positivity cut-off between screening kits may slightly differ.

Statistical analyses

Each objective could be considered a separate analysis, as each used a different subgroup of the overall linked dataset, along with different methods. They are therefore discussed individually below.

Objective 1 data and methods

Describe differences in bowel cancer mortality between 2006–2008 bowel cancer diagnoses in those invited to screen and those aged 50–69 who were not invited into the NBCSP.

To ensure the people analysed in this objective had at least 3 years of follow-up time available, only those diagnosed with bowel cancer between 1 August 2006 and 31 December 2008 were included. These were followed up until 31 December 2011 (the latest date of deaths information available in the NDI data set). Bowel cancers that linked to participants within the 2006–2008 NBCSP invitee study group were classified as 'NBCSP invitee' bowel cancers for the intention-to-screen analysis (regardless of whether they were screen-detected, interval or non-responders). This group was compared with bowel cancers in those aged 50–69 at time of diagnosis that did not link to a 2006–2008 NBCSP invitee—the 'never-invited' bowel cancer study group. This first comparison was considered an intention-to-screen analysis; however comparisons between mortality outcomes for the NBCSP subgroups were also made.

Time from diagnosis to death due to bowel cancer (ICD 10 C180–C209 recorded as the underlying cause of death) was the event being measured. Otherwise, those diagnosed with bowel cancer had their follow-up time ended either at the date of death from another cause, or at the end of the follow-up period (31 December 2011). Therefore, the groups compared in the intention-to-screen analysis were:

- NBCSP invitees who had been diagnosed with bowel cancer (298 bowel cancer deaths and 2,311 with follow-up ended). This group was further divided into screen-detected, interval and non-responder subgroups in a secondary mortality analysis.

- Those aged 50–69 when diagnosed with bowel cancer who had not been a 2006–2008 NBCSP invitee (1,973 bowel cancer deaths and 8,107 with follow-up ended).

Hazard ratios were calculated in this objective. They are generated from the Cox proportional hazards regression, which is used for person-time multivariable modelling. They are essentially the same as rate ratios.

A hazard ratio indicates how many times as high the probability of an event is in one group of people with a particular characteristic than in another group of people without that characteristic, after adjusting for other factors in the model. This gives an indication of the strength of the association and can help decide whether the characteristic of interest could be a cause of an event (in this case, death from bowel cancer after a bowel cancer diagnosis). Factors such as individual screening or testing behaviours might affect the survival analyses (see the section 'A note on lead-time bias' that follows).

Ninety-five per cent confidence intervals are also presented as an indication of statistical precision and significance. If the interval does not cross the value of 1 then the result is interpreted as having a statistically significant impact (that is, not due to chance) (Kalbfleisch & Prentice 1980).

A note on lead-time bias

Cancer survival is based on the time between cancer diagnosis and death, and is therefore sensitive to anything that affects the timing of either date. Effective treatment and management of cancer can improve survival by delaying the time until death. However, the timing of cancer diagnosis can also be brought forward, potentially without impacting death outcomes. This time shift in the detection of cancer, without changing the natural course of the disease, is known as lead-time bias, which results in an artificial or inflated increase in survival (Duffy et al. 2008; Gigerenzer et al. 2008; de Vries et al. 2010). Cancers that can be diagnosed asymptomatically through screening are prone to lead-time bias.

It should be emphasised that screening and earlier detection can also lead to genuine gains in survival as early-stage bowel cancers can be treated more successfully than late-stage cancers (Siegel et al. 2012). There is a need to better understand the extent to which increases in survival are due to earlier detection, improvements in treatment, or a combination of the two.

Mortality trends have been suggested as an alternative to survival for measuring cancer control without the influence of lead-time bias. However, mortality trends in isolation can also be misleading as an expression of survival since they are influenced by incidence trends. Therefore, the most appropriate way of evaluating progress in cancer control is to consider all three measures of incidence, mortality and survival together (Dickman & Adami 2006). An improved understanding of these factors in relation to bowel cancer may not be possible until enough time has passed since the NBCSP commenced (in 2006) for its impact to affect longer-term mortality and survival rates.

Therefore, to factor in lead-time bias in this study, additional analyses were undertaken that used estimated sojourn times for bowel cancer (the time period from asymptomatic but screen-detectable to symptomatic cancers) (Brenner et al. 2011), to correct for lead time in screen-detected diagnoses (Duffy et al. 2008). (See 'Additional statistical methods', Appendix A, for further details.)

Objective 2 data and methods

Describe differences in bowel cancer summary stage (see Box 3) in those whose bowel cancer was detected after a 2006–2008 invitation to screen in the NBCSP, compared with those aged 50–69 who were not invited into the NBCSP.

The analyses in this objective were based on the subset of people diagnosed with bowel cancer from the 3 jurisdictions that supplied staging data that could be combined into a summary stage system (New South Wales, Tasmania and the Australian Capital Territory). There were small differences in the years of cancer diagnosis data available from the 3 jurisdictions for this report. New South Wales and the Australian Capital Territory had bowel cancer diagnoses from 2006 to the end of 2008 available, while Tasmania had diagnoses up until the end of 2009. (See the 'Additional data source details', Appendix A, for more information.)

This analysis also contained a main intention-to-screen component, with additional analyses between the NBCSP invitee subgroups. For the intention-to-screen analysis, the 1,016 participants within the 2006–2008 NBCSP invitee study group diagnosed with bowel cancer were categorised as 'NBCSP invitee' bowel cancers (regardless of whether they were screen-detected, interval or non-responders). Using logistic regression, this group was compared with the 4,884 people aged 50–69 at time of bowel cancer diagnosis who did not receive a 2006–2008 NBCSP invitation—the 'never-invited' bowel cancer group.

As a second analysis, the NBCSP invitee group was further divided into screen-detected (512) and non-responder (449) subgroups, for comparison.

Logistic regression involves calculating the probability of the event occurring for varying levels of characteristics in a study population. It is especially appropriate when the outcome of interest is a categorical variable (in this case, summary stage). Results derived from logistic regression are expressed as odds ratios, with 95% confidence intervals presented to give an indication of statistical precision and significance of the result.

Odds ratios compare the odds of a specified event occurring (for example, a particular summary stage) in people with a particular characteristic (for example, invitation to the NBCSP) with the odds in people without that characteristic, while controlling for other factors in the model, such as age and sex. An odds ratio of 1 implies that there is no association between the characteristic and the outcome. An odds ratio greater than 1 indicates that those with the characteristic have a greater risk of having the outcome, while an odds ratio of less than 1 indicates reduced risk.

Objective 3 data and methods

Investigate characteristics of interval bowel cancers.

Meeting this objective involves using bowel cancer data from invitees in the screen-detected and interval cancer subgroups. In total, there were 1,575 people in the screen-detected subgroup, and 265 in the interval cancer subgroup.

However, for some of the characteristics under investigation, the counts were lower (see Table 2 in Chapter 3). This was because not all cases had valid socioeconomic status, remoteness and summary stage data available.

As with Objective 2, the summary stage data available for Objective 3 only related to cancers diagnosed in New South Wales, the Australian Capital Territory and Tasmania.

Analyses for Objective 3 were undertaken using χ^2 analysis.

Objective 4 data and methods

Describe the positive predictive value (PPV) and negative predictive value (NPV) of the screening test.

This objective necessarily involved using data only for members of the 2006–2008 NBCSP invitee study group who participated (that is, the screen-detected and interval cancer subgroups). As the recommended FOBT rescreening interval for bowel cancer is 2 years (CCA & ACN 2005), this time period was used as a cut-off for screen-detected cancer diagnoses. However, some jurisdictions did not supply at least 2 years of cancer data, that is, data up until 31 December 2010 for all those invited within the 2006–2008 NBCSP invitee study period (Figure 1). Hence, calculations for predictive values only considered invitees with a bowel cancer diagnosis after screening who had at least 2 years of follow-up data available after their screen, regardless of when their cancer was diagnosed in that follow-up period.

The analyses carried out under this objective used standard 2 x 2 contingency tables.

3   Details of study subjects

Descriptive statistics

The linkage of the 2006–2008 NBCSP invitee study group to bowel cancer diagnosis data found that 4,327 cases of bowel cancer were diagnosed in individuals invited to participate in the NBCSP (Table 2). Of these, 1,575 (36.4%) were screen-detected, 265 (6.1%) were interval cancers and the remaining 2,487 (57.5%) were diagnosed in individuals who were invited but did not participate. There were an additional 2,115 diagnoses made before a person's invitation, and 316 bowel cancers were diagnosed in the interval group more than 2 years after screening test analysis, but, as discussed in the Methods section in Chapter 2, these diagnoses were excluded from further analysis.

> **Box 5: Did the data linkage in this project identify additional NBCSP screening-related bowel cancer diagnoses?**
>
> Using data returned to the NBCSP register from histopathology forms only, there were 337 bowel cancers confirmed in the 2006–2008 invitee study group following positive screening tests. After linkage to the bowel cancer diagnosis dataset in this project, a total of 1,575 bowel cancer diagnoses followed a positive screening test in this group. Therefore the linkage identified 1,250 additional bowel cancer diagnoses in this group that had not been previously attributed to NBCSP participation.

Among individuals aged 50–69 who had not been invited to participate (the never-invited group), 17,724 cancer cases were diagnosed.

After the exclusions mentioned, the total number of bowel cancers in the study was 22,051.

Table 2: Characteristics of those in the study groups who were diagnosed with bowel cancer

| | 2006–2008 NBCSP invitees | | | | | | | | Never-invited | | Total | |
| | Screen-detected | | Interval | | Non-responder | | *Total* | | | | | |
Characteristic	No.	%	No.	%	No.	%	*No.*	%	No.	%	No.	%
Sex												
Male	974	61.8	132	49.8	1,532	61.6	*2,638*	*61.0*	10,527	59.4	13,165	59.7
Female	601	38.2	133	50.2	955	38.4	*1,689*	*39.0*	7,197	40.6	8,886	40.3
Age at diagnosis[a]												
50–54	77	4.9	14	5.3	143	5.7	*234*	*5.4*	2,583	14.6	2,817	12.8
55–59	531	33.7	73	27.5	923	37.1	*1,527*	*35.3*	3,606	20.3	5,133	23.3
60–64	31	2.0	8	3.0	83	3.3	*122*	*2.8*	6,069	34.2	6,191	28.1
65–69	936	59.4	170	64.2	1,338	53.8	*2,444*	*56.5*	5,466	30.8	7,910	35.9
Socioeconomic status[b][c]												
1 (most disadvantage)	320	20.5	53	20.2	536	21.7	*909*	*21.2*	n.a.	n.a.	909	21.2
2	343	22.0	61	23.3	517	21.0	*921*	*21.5*	n.a.	n.a.	921	21.5
3	331	21.2	39	14.9	515	20.9	*885*	*20.6*	n.a.	n.a.	885	20.6
4	301	19.3	52	19.8	491	19.9	*844*	*19.7*	n.a.	n.a.	844	19.7
5 (least disadvantage)	265	17.0	57	21.8	406	16.5	*728*	*17.0*	n.a.	n.a.	728	17.0
Remoteness area[b][c]												
Major cities	964	61.7	158	60.4	1,643	66.5	*2,765*	*64.4*	n.a.	n.a.	2,765	64.4
Inner regional	378	24.2	71	26.9	500	20.3	*949*	*22.1*	n.a.	n.a.	949	22.1
Outer regional	193	12.4	30	11.4	269	10.9	*492*	*11.5*	n.a.	n.a.	492	11.5
Remote	18	1.2	1	0.4	41	1.7	*60*	*1.4*	n.a.	n.a.	60	1.4
Very remote	10	0.6	2	0.8	16	0.7	*28*	*0.6*	n.a.	n.a.	28	0.6

(continued)

Table 2 (continued): Characteristics of those in the study groups who were diagnosed with bowel cancer

Characteristic	Screen-detected No.	Screen-detected %	Interval No.	Interval %	Non-responder No.	Non-responder %	Total No.	Total %	Never-invited No.	Never-invited %	Total No.	Total %
Cancer site[d]												
Right-sided colon	392	24.9	115	43.4	706	28.4	1,213	28.0	5,229	29.5	6,442	29.2
Left-sided colon	754	47.9	74	27.9	904	36.3	1,732	40.0	6,504	36.7	8,236	37.3
Rectum	395	25.1	63	23.8	801	32.2	1,259	29.1	5,422	30.6	6,681	30.3
Colon, not otherwise specified	34	2.2	13	4.9	76	3.1	123	2.8	569	3.2	692	3.1
Summary stage[e]												
Localised	236	46.1	28	50.9	139	31.0	403	39.7	1,666	34.1	2,069	35.1
Regionalised	190	37.1	19	34.5	200	44.5	409	40.3	1,911	39.1	2,320	39.3
Distant	31	6.1	6	10.9	70	15.6	107	10.5	904	18.5	1,011	17.1
Unknown	55	10.7	2	3.6	40	8.9	97	9.5	403	8.3	500	8.5
Morphology[f]												
Adenocarcinomas	1,524	96.8	249	94.0	2,357	94.8	4,130	95.4	16,720	94.3	20,850	94.6
Other types	51	3.2	16	6.0	130	5.2	197	4.6	1,004	5.7	1,201	5.4
Total	**1,575**		**265**		**2,487**		**4,327**		**17,724**		**22,051**	

Notes

(a) 2006–2008 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

(b) Socioeconomic status and remoteness area could not be determined for the never-invited group as information on residence (postcode) was not available.

(c) Those with missing data for this characteristic were excluded. Therefore, the sum of numbers in this characteristic does not equal the total.

(d) Definitions for cancer sites are in Appendix A.

(e) Only summary stage data for New South Wales, Tasmania and the Australian Capital Territory were used. Therefore, the sum of numbers in this characteristic does not equal the total.

(f) Morphology groupings based on IARC international rules for multiple primary cancers using ICD-O-3 (IARC 2004). See Appendix A for further information.

Figure 4 presents cancer and adenoma (pre-cancerous lesions) outcomes for the 3 subgroups of the 2006–2008 NBCSP invitee group only, based on their progression through the NBCSP screening pathway.

(a)   Bowel cancer diagnoses after 1 January 2006 but prior to the person's invitation date.

(b)   Bowel cancer diagnoses in those who did not screen (non-responders), using available cancer registry data (Figure 1).

(c)   Includes both negative and inconclusive screening results.

(d)   Bowel cancer diagnoses, using available cancer registry data (Figure 1), by length of time between screen and diagnosis.

(e)   Adenoma counts were only available for positive screens that had relevant colonoscopy and histopathology forms returned. Therefore, they may be underreported due to incomplete form return.

Figure 4: Cancer and adenoma outcomes for the 2006–2008 NBCSP invitee study group

Study subject differences

The male to female ratio of those diagnosed with bowel cancer in the study groups was generally about 60:40; however, for interval cancers, the ratio was 50:50 (Table 2).

As discussed earlier, due to the NBCSP invitee study group having specific invitation ages, the split of age at diagnosis across the invitee subgroups is different to that for the never-invited group.

Bowel cancer differences

Cancer type

The most common type of bowel cancers diagnosed were adenocarcinomas (the malignant evolution of previously benign adenomas). They represented over 94% of bowel cancers diagnosed for each subgroup (Table 2).

Cancer site

The specific site of cancers within the bowel is of interest as it is known to affect mortality risk, with left-sided bowel cancers having a lower mortality rate than right-sided bowel cancers (Wray et al. 2009). There were marked differences in the site of cancers within the bowel between the subgroups (see Appendix A for a description of bowel cancer sites). The proportion of left-sided bowel cancers was higher in the screen-detected subgroup (48%) than in other subgroups (28–37%), and the proportion of right-sided cancers was higher in the interval subgroup (43%) than in other subgroups (25–30%) (Table 2). In general, the proportions across the bowel cancer sites were similar between the non-responder and the never-invited subgroups.

For all bowel cancer diagnoses combined, the proportion of right-sided cancers per age group increased with age, from 25% in those aged 50–54 to 34% in those aged 65–69 (Table 3). Conversely, left-sided and rectal cancer proportions decreased with age.

Analysis of bowel cancer site by sex showed that males had a higher proportion of rectal cancers. Females had a higher proportion of right-sided bowel cancers.

Table 3: Bowel cancer site[a] **by age group and sex**

	Right-sided	Left-sided	Rectum	Colon, NOS	Total	Right-sided	Left-sided	Rectum	Colon, NOS	Total
	No.					**%**				
Age group at diagnosis[b]										
50–54	695	1,085	968	69	2,817	24.7	38.5	34.4	2.4	100.0
55–59	1,297	1,970	1,704	162	5,133	25.3	38.4	33.2	3.2	100.0
60–64	1,802	2,299	1,905	185	6,191	29.1	37.1	30.8	3.0	100.0
65–69	2,648	2,882	2,104	276	7,910	33.5	36.4	26.6	3.5	100.0
Sex										
Males	3,279	5,031	4,452	403	13,165	24.9	38.2	33.8	3.1	100.0
Females	3,163	3,205	2,229	289	8,886	35.6	36.1	25.1	3.3	100.0
Total	**6,442**	**8,236**	**6,681**	**692**	**22,051**	**29.2**	**37.3**	**30.3**	**3.1**	**100.0**

NOS Not otherwise specified.

(a)   Definitions for cancer sites are in Appendix A.

(b)   2006–2008 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

Summary stage

Of the 5,900 individuals with bowel cancer summary stage data available (see Appendix A for further details on cancer stage, and how it was analysed in this report), those diagnosed within the NBCSP invitee group were more likely to be at an earlier (less-advanced) summary stage than those diagnosed in the never-invited group and this difference was statistically significant (χ^2=40.58, P<0.001) (Table 2). (This is investigated further in the 'Objective 2' section in Chapter 4.)

Cancer site versus cancer stage

The relationship between cancer site and cancer stage was also examined (Table 4).

Table 4: Bowel cancer summary stage, by study group and cancer site[a]

	Summary stage								
	Localised	Regional	Distant	Unknown	Total	Localised	Regional	Distant	Unknown
Cancer site			No.					%	
2006–2008 NBCSP invitee									
Right-sided	101	132	37	10	280	36.1	47.1	13.2	3.6
Left-sided	165	178	42	43	428	38.6	41.6	9.8	10.0
Rectum	127	85	20	36	268	47.4	31.7	7.5	13.4
Colon, NOS	10	14	8	8	40	25.0	35.0	20.0	20.0
All sites	*403*	*409*	*107*	*97*	*1,016*	*39.7*	*40.3*	*10.5*	*9.5*
Never-invited									
Right-sided	441	636	271	85	1,433	30.8	44.4	18.9	5.9
Left-sided	614	716	330	111	1,771	34.7	40.4	18.6	6.3
Rectum	561	514	231	169	1,475	38.0	34.8	15.7	11.5
Colon, NOS	50	45	72	38	205	24.4	22.0	35.1	18.5
All sites	*1,666*	*1,911*	*904*	*403*	*4,884*	*34.1*	*39.1*	*18.5*	*8.3*
All study groups									
Right-sided	542	768	308	95	1,713	31.6	44.8	18.0	5.5
Left-sided	779	894	372	154	2,199	35.4	40.7	16.9	7.0
Rectum	688	599	251	205	1,743	39.5	34.4	14.4	11.8
Colon, NOS	60	59	80	46	245	24.5	24.1	32.7	18.8
All sites	**2,069**	**2,320**	**1,011**	**500**	**5,900**	**35.1**	**39.3**	**17.1**	**8.5**

NOS   Not otherwise specified.

(a)   Definitions for cancer sites are in Appendix A.

Across all bowel cancer sites, the proportion of distant summary stage cancers was lower for the NBCSP invitee group (11%), compared with the never-invited group (19%). Regarding specific sites:

- In the invitee group, a greater proportion of rectal cancers were diagnosed at a localised summary stage (47%) than in the never-invited group (38%).

- In the invitee group, the greatest proportion of 'colon, not otherwise specified' cancers was at the regional summary stage. In the never-invited group, the greatest proportion of these cancers was at the distant summary stage.

4   Results

Objective 1

The first objective was to describe any differences in bowel cancer mortality between 2006–2008 bowel cancer diagnoses in those invited to screen and those aged 50–69 who were not invited into the NBCSP.

Rationale	There would be great value in knowing if there were any early differences in bowel cancer mortality (after a bowel cancer diagnosis) between those invited to screen in 2006–2008 and those aged 50–69 who were not invited into the NBCSP.
Data used in meeting this objective	In meeting this objective we used three types of data sources: the NBCSP invitee study group; bowel cancer diagnosis data; and national deaths data. Only people with a bowel cancer diagnosis in 2006–2008 were included in this analysis.
	Time from diagnosis to death due to bowel cancer was the survival event being measured. Otherwise, those diagnosed with bowel cancer had their follow-up time ended either at the date of death from another cause, or at the end of the follow-up period (31 December 2011, which was the latest date deaths information were available in the NDI dataset).
	See the Methods section in Chapter 2 for more information.
Analyses	This objective included an intention-to-screen bowel cancer mortality analysis, and a comparison of mortality outcomes for screen-detected and non-responder bowel cancer diagnoses.
	The results are presented as hazard ratios, converted to percentages, that show how much higher the probability of death occurring is in one group than in another 'reference' group.
Guide to interpretation	Re-analysis with more years of outcome data would help mitigate potential lead-time bias issues.

Key findings

When comparing people diagnosed with bowel cancer in 2006–2008 between the NBCSP invitee and never-invited groups:

- Of the 2,609 people in the NBCSP invitee group with a bowel cancer diagnosis, 298 (11.4%) had died of bowel cancer before 2012. Of the 10,080 never-invited people with a bowel cancer diagnosis, 1,973 (19.6%) had died of bowel cancer by the same date.

- Using proportional hazards regression, the risk of death from bowel cancer was 68% higher for people diagnosed with bowel cancer in the never-invited group, relative to the NBCSP invitees. After correcting for potential lead time bias, the result was still statistically significant (15% higher risk in the never-invited group).

When comparing NBCSP invitees only:

- The risk of death from bowel cancer was considerably higher for people diagnosed with bowel cancer in the interval and non-responder subgroups (over 3 and 4 times the risk of death respectively) relative to the screen-detected group, after adjusting for age group at diagnosis, and cancer site, type and summary stage. However, after correcting for potential lead-time bias, the risk only remained higher in the non-responder group (over 2 times the risk) and this difference was statistically significant.

Of all bowel cancers diagnosed:

- People with more-advanced summary stage cancers, right-sided or 'colon, not otherwise specified' cancers, or non-adenocarcinoma cancers had a higher risk of bowel cancer death.

Results

## Intention-to-screen bowel cancer mortality analysis

The first comparison of bowel cancer mortality outcomes was between people in the NBCSP invitee and the never-invited groups with a diagnosis recorded between 1 August 2006 and 31 December 2008—in an intention-to-screen bowel cancer mortality analysis. Of the 10,080 never-invited people with a bowel cancer diagnosis, 1,973 (19.6%) had died of bowel cancer before 2012 (Table 5). Of the 2,609 people in the NBCSP invitee group with a bowel cancer diagnosis, 298 (11.4%) had died of bowel cancer by the same date. The mean follow-up time to bowel cancer death for all diagnoses was 18.6 months (range 0–64.3 months, standard deviation 13.9 months).

Table 5: Cumulative bowel cancer deaths in those diagnosed 2006–2008, by study group

			Bowel cancer deaths			
		2006–2008 diagnoses	Years since diagnosis			
Study group			1	2	3	at 31/12/2011
NBCSP invitee	No.	2,609	123	212	268	298
	Proportion (%)		4.7	8.1	10.3	11.4
Never-invited	No.	10,080	766	1,350	1,715	1,973
	Proportion (%)		7.6	13.4	17.0	19.6

Intention-to-screen survival plots

The general logrank test statistic of $\chi^2=86.3$ with 1 degree of freedom (P<0.001) showed there was a strong study group effect (NBCSP invitee versus never-invited) on bowel cancer mortality outcome. Members of the NBCSP invitee group with a bowel cancer diagnosis had better bowel cancer survival (Figure 5).

Figure 5: Survival plots for the NBCSP invitee and never-invited groups
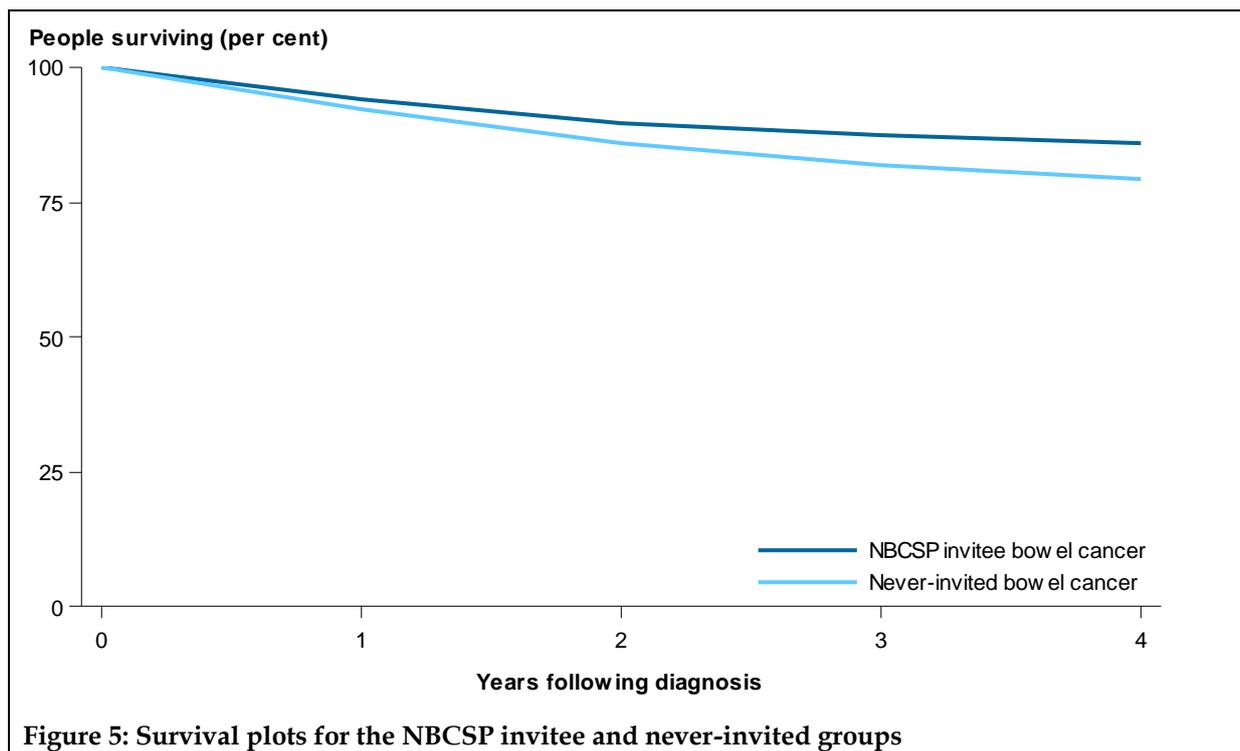
Intention-to-screen hazard ratios

The Cox proportional hazards regression model was used to quantify the relationship between survival and a set of explanatory variables for those diagnosed with bowel cancer. Simple Cox regression models were fitted to each variable: bowel cancer study group (NBCSP invitee versus never-invited), sex, age group at diagnosis, cancer site, histological type and summary stage of cancer. The crude hazard ratios are presented in Table 6.

Table 6: Crude bowel cancer mortality hazard ratios (HR) for intention to screen[a]

Variable	Crude HR	95% CI	P value
Study group			
NBCSP invitee	1.0	. .	. .
Never-invited	1.77	1.57–2.00	<0.0001
Sex			
Males	1.0	. .	. .
Females	0.95	0.88–1.04	0.26
Age group at diagnosis[b]			
50–54	1.0	. .	. .
55–59	0.79	0.69–0.91	0.001
60–64	0.96	0.84–1.10	0.57
65–69	0.84	0.74–0.96	0.01
Cancer site[c]			
Left-sided colon	1.0	. .	. .
Right-sided colon	1.19	1.07–1.31	0.001
Rectum	1.05	0.95–1.17	0.32
Colon, not otherwise specified	2.45	2.03–2.96	<0.0001
Summary stage[d]			
Localised	1.0	. .	. .
Regionalised	3.41	2.65–4.38	<0.0001
Distant	24.02	18.87–30.59	<0.0001
Unknown	3.03	2.14–4.29	<0.0001
Morphology[e]			
Adenocarcinomas	1.0	. .	. .
Other histological types	1.33	1.12–1.57	0.001

Notes

(a) A hazard ratio of 1.0 with no confidence interval indicates the reference category.

(b) 2006–2008 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

(c) Definitions for cancer sites are in Appendix A.

(d) Only summary stage data for New South Wales, Tasmania and the Australian Capital Territory were used. See Appendix A for further information.

(e) Morphology groupings based on IARC international rules for multiple primary cancers using ICD-O-3 (IARC 2004). See Appendix A for further information.

The crude hazard ratio for the bowel cancer diagnosis study groups showed that, compared with the NBCSP invitee group, the risk of death from bowel cancer for individuals who were never-invited was increased and this difference was statistically significant (hazard ratio 1.77, 95% CI: 1.57–2.00). Regression was then performed against a number of other explanatory variables, to look for potential confounding variables.

There were differences in unadjusted mortality hazard ratios across the age-at-diagnosis groups. Other statistically significant crude hazard ratio outcomes included cancer site, type and summary stage of cancer.

People with right-sided (hazard ratio 1.19, 95% CI: 1.07–1.31) or 'colon, not otherwise specified' bowel cancers (hazard ratio 2.45, 95% CI: 2.03–2.96) both had a higher risk of

bowel cancer death than cancers located in the left side of the colon (see Appendix A for a description of bowel cancer sites).

People with non-adenocarcinoma cancer types had a higher risk of bowel cancer death (hazard ratio 1.33, 95% CI: 1.12–1.57) compared with adenocarcinomas, and individuals with bowel cancers of more advanced summary stage, that is, regionalised and distant cancers (hazard ratio of 3.41 and 24.02, respectively), had a higher risk of bowel cancer death than localised cancers. Thus, summary stage had the greatest effect on mortality risk; however, as differences in summary stage between the groups is considered the main reason for any mortality risk differences (see Objective 2), this was not adjusted for in the final model.

A person's gender did not have a significant effect on the risk of bowel cancer death. Remoteness area and socioeconomic status could not be included in the intention to screen analysis as postcode data were not available for the never-invited group.

After adjusting for the statistically significant effects of age group at diagnosis, and bowel cancer site and type, the adjusted hazard ratio for the never-invited group was 1.68 (95% CI: 1.48–1.92) when compared with the invitee group. That is, after a bowel cancer diagnosis in 2006–2008, the risk of death from bowel cancer before 2012 was 68% higher for people in the never-invited group compared with the NBCSP invitee group.

Lead-time bias due to earlier diagnosis (but not necessarily a change in date of death) is generally considered a factor when investigating screening outcomes (Day & Walter 1984). Therefore methods to correct for lead time (Duffy et al. 2008; Brenner et al. 2011) were also analysed. When using these to correct for potential lead-time in screen-detected cancers, the risk of death from bowel cancer was still significantly higher in the never-invited group (hazard ratio 1.15, 95% CI: 1.01–1.31).

NBCSP invitee subgroup bowel cancer mortality analysis

The second comparison of bowel cancer mortality outcomes was between people in the NBCSP invitee subgroups who were diagnosed with bowel cancer between 1 August 2006 and 31 December 2008 (Table 7). Of the 1,352 NBCSP invitees with a screen-detected bowel cancer diagnosis, 62 (4.6%) had died of bowel cancer before 2012. Of the 130 NBCSP invitees with an interval bowel cancer diagnosis, 19 (14.6%) had died of bowel cancer by the same time, and of the 1,127 non-responders with a bowel cancer diagnosis, 217 (19.3%) had also died of bowel cancer. The mean follow-up time to bowel cancer death for all NBCSP invitee diagnoses was 17.4 months (range 0–49.8 months, standard deviation 12.5 months).

Table 7: Cumulative bowel cancer deaths in those diagnosed 2006–2008, by study subgroup

| Study subgroup | | 2006–2008 diagnoses | Bowel cancer deaths | | | |
| | | | Years since diagnosis | | | at 23/12/2011 |
			1	2	3	
Screen-detected	No.	1,352	11	34	57	62
	Proportion (%)		0.8	2.5	4.2	4.6
Interval	No.	130	7	15	18	19
	Proportion (%)		5.4	11.5	13.8	14.6
Non-responder	No.	1,127	105	163	193	217
	Proportion (%)		9.3	14.5	17.1	19.3
Never-invited	No.	10,080	766	1,350	1,715	1,973
	Proportion (%)		7.6	13.4	17.0	19.6

NBCSP invitee subgroup survival plots

The general logrank test statistic of $\chi^2 = 149.2$ with 2 degrees of freedom (P<0.001) showed a strong effect of subgroup (screen-detected, interval and non-responder) on risk of bowel cancer mortality. The survival curves (Figure 6) show that people with screen-detected bowel cancer had the longest survival times after diagnosis, followed by people with interval bowel cancers. Non-responders with bowel cancer had the shortest survival times. (Never-invited people with bowel cancers are included in Figure 6 for comparison.)


People surviving (per cent)

Legend:
— Screen-detected bowel cancer
— Interval bowel cancer
····· Non-responder bowel cancer
- - - - Never-invited bowel cancer

Years following diagnosis
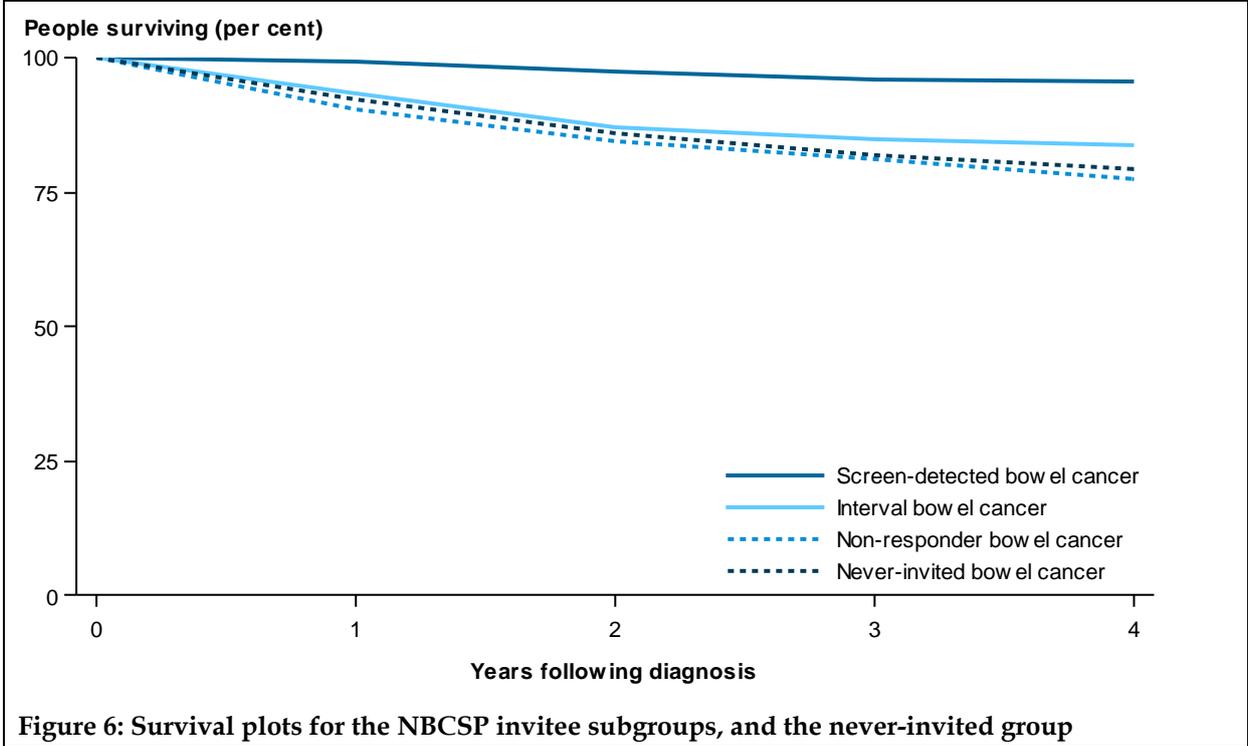
Figure 6: Survival plots for the NBCSP invitee subgroups, and the never-invited group

NBCSP invitee subgroup hazard ratios

The Cox proportional hazards regression model was used to quantify the relationship between survival and a set of explanatory variables for those NBCSP invitees diagnosed with bowel cancer. Simple Cox regression models were fitted to each variable: NBCSP invitee subgroup (screen-detected, interval and non-responder), sex, age group at diagnosis, socioeconomic status quintiles, remoteness area, cancer site, histological type and summary stage of cancer. The crude hazard ratios are presented in Table 8.

Table 8: Crude bowel cancer mortality hazard ratios (HR) for NBCSP invitees only[a]

Variable	Crude HR	95% CI	P value
NBCSP invitee subgroup			
Screen-detected	1.0	. .	. .
Interval	3.63	2.17–6.08	<0.0001
Non-responder	4.92	3.71–6.53	<0.0001
Sex			
Males	1.0	. .	. .
Females	1.25	0.99–1.57	0.05
Age group at diagnosis[b]			
50–54	1.0	. .	. .
55–59	2.10	0.67–6.60	0.21
60–64	1.40	0.34–5.86	0.64
65–69	2.08	0.66–6.51	0.21
Socioeconomic status			
1 (most disadvantage)	1.0	. .	. .
2	1.0	0.71–1.41	1.00
3	1.0	0.71–1.41	1.00
4	0.96	0.67–1.38	0.83
5 (least disadvantage)	0.85	0.58–1.24	0.40
Unknown quintile	1.26	0.40–4.00	0.70
Remoteness area			
Major cities	1.0	. .	. .
Inner regional	0.94	0.71–1.23	0.63
Outer regional	0.83	0.56–1.23	0.34
Remote & very remote	0.47	0.12–1.91	0.29
Unknown remoteness area	1.04	0.26–4.17	0.96
Cancer site[c]			
Left-sided colon	1.0	. .	. .
Right-sided colon	1.60	1.20–2.12	0.001
Rectum	1.35	1.01–1.80	0.041
Colon, not otherwise specified	3.67	2.19–6.15	<0.0001
Summary stage[d]			
Localised	1.0	. .	. .
Regionalised	3.03	1.62–5.70	0.0006
Distant	24.25	13.10–44.88	<0.0001
Unknown	1.98	0.75–5.22	0.17
Morphology[e]			
Adenocarcinomas	1.0	. .	. .
Other histological types	2.01	1.29–3.14	0.002

Notes

(a) A hazard ratio of 1.0 with no confidence interval indicates the reference category.

(b) 2006–2008 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

(c) Definitions for cancer sites are in Appendix A.

(d) Only summary stage data for New South Wales, Tasmania and the Australian Capital Territory were used. See Appendix A for further information.

(e) Morphology groupings based on IARC international rules for multiple primary cancers using ICD-O-3 (IARC 2004). See Appendix A for further information.

The crude hazard ratio for the NBCSP invitee bowel cancer subgroups showed that, compared with people in the screen-detected subgroup, the risk of death from bowel cancer for people in the non-responder subgroup (hazard ratio 4.92, 95% CI: 3.71–6.53) and interval cancer subgroup (hazard ratio 3.63, 95% CI: 2.17–6.08) was significantly increased. Regression was then performed against a number of other explanatory variables, to look for potential confounding variables.

There were differences in the unadjusted mortality hazard ratios across the age-at-diagnosis groups (Table 8). Other statistically significant crude hazard ratio outcomes included cancer site, type and summary stage of cancer.

Invitees with right-sided (hazard ratio 1.60, 95% CI: 1.20–2.12), rectum (hazard ratio 1.35, 95% CI: 1.00–1.80) and 'colon, not otherwise specified' bowel cancers (hazard ratio 3.67, 95% CI: 2.19–6.15) all had a higher risk of death than invitees with cancers located in the left side of the colon (see Appendix A for a description of bowel cancer sites).

Invitees diagnosed with non-adenocarcinoma cancer types had a higher risk of death (hazard ratio 2.01, 95% CI: 1.29–3.14) compared with adenocarcinomas, and invitees with bowel cancers of more advanced summary stage, that is, regionalised and distant cancers (hazard ratio of 3.03 and 24.25, respectively), had a higher risk of death than those with localised cancers. Once again, differences in summary stage across groups were not adjusted for in the final model. Sex, socioeconomic status or remoteness area of invitees did not have statistically significant effects on the risk of bowel cancer death.

After adjusting for the statistically significant effects of age group at diagnosis, and bowel cancer site and type, the adjusted bowel cancer mortality hazard ratio was 3.41 (95% CI: 2.03–5.77) for people in the interval subgroup and 4.77 (95% CI: 3.58–6.35) for people in the non-responder subgroup, when compared with the screen-detected subgroup. That is, the risk of death from bowel cancer was higher for invitees in the interval and non-responder subgroups compared with the screen-detected subgroup (over 3 and 4 times the risk, respectively), and these differences were statistically significant.

After correcting for potential lead-time bias in screen-detected cancers, the mortality risk for people with interval cancers was no longer significantly higher (hazard ratio 1.63, 95% CI: 0.96–2.77), but the risk for people in the non-responder group was still significantly higher (hazard ratio 2.29, 95% CI: 1.69–3.11). With only 19 deaths in the interval cancer subgroup, its results should be interpreted with caution; more follow-up time may increase the sample size—and statistical precision—for this subgroup.

Objective 2

The second objective was to describe differences in summary stage between those whose bowel cancer was diagnosed after a 2006–2008 NBCSP invitation, and those aged 50–69 who were not invited into the NBCSP.

Rationale	As a second method to investigate likely differences in mortality—because mortality risk is known to differ by cancer stage—differences in bowel cancer summary stage between those invited and those not invited were investigated.
	It was hypothesised that bowel cancers diagnosed in people invited into the NBCSP would, on average, be at a less-advanced summary stage than those diagnosed in people of a similar age who were not invited to screen.
Data used in meeting this objective	The analyses in this objective were based on the subset of people diagnosed with bowel cancer from the 3 jurisdictions that supplied staging data that could be combined into a summary stage system. (See the 'Additional data source details' section, Appendix A, for more information.)
	For the various analyses, these people were grouped into 'NBCSP invitee' and 'never-invited' study groups, or screen-detected and non-responder subgroups, as appropriate. (See the Methods section in Chapter 2 for more information.)
Analyses	This objective included an intention-to-screen analysis and a comparison of summary stage between screen-detected and non-responder NBCSP invitee subgroups.
	Summary stage refers to how much the cancer had already developed when first diagnosed. The summary stage system used has three stage levels, from the least advanced (localised summary stage), to regionalised, then to the most advanced summary stage (distant). Distant summary stage cancers generally have the worst prognosis.
	Analyses undertaken included investigation of summary stage differences by Chi-square (χ^2) analysis, with multivariable logistic regression performed to control for possible differences between the study groups' age, sex and other characteristics.
Guide to interpretation	Summary stage data were available for only 3 jurisdictions. While there are no known reasons why there would be jurisdictional differences in bowel cancer summary stage across Australia, this should be kept in mind when generalising these findings to a national context.

Key findings

When comparing summary stage between the NBCSP invitee and never-invited groups:

- Bowel cancers diagnosed within the NBCSP invitee group were more likely to be at a less advanced summary stage than those diagnosed in the never-invited group and this difference was statistically significant (P<0.001). The percentage of people diagnosed

with a bowel cancer at a localised (least advanced) summary stage was 40% for NBCSP invitees compared with 34% for those who were never invited to participate.

- After adjusting for differences in age at diagnosis between groups, people in the never-invited group had an odds ratio of 1.38 for more advanced (worse prognosis) bowel cancers. This means that the people diagnosed with bowel cancer in the never-invited group had 38% higher odds of it being at a more-advanced summary stage than for diagnoses in the NBCSP invitee group. This indicates down-staging of cancer (related to better prognosis) for NBCSP invitees compared with the never-invited group.

When comparing summary stage between the screen-detected and non-responder NBCSP invitee subgroups:

- There were statistically significant differences in the cancer summary stage profile. In the screen-detected subgroup, the percentage of people with bowel cancers in the localised (least advanced) stage was 46% compared with 31% in the non-responder subgroup.

- After adjusting for differences in sex between the subgroups, people in the non-responder subgroup had 121% higher odds of having a more-advanced (worse prognosis) bowel cancer than for those diagnosed in the screen-detected subgroup.

Results

The first summary stage comparison was an intention-to-screen analysis.

Intention-to-screen summary stage analysis

There was a shift towards earlier bowel cancer summary stage for cancers diagnosed in the NBCSP invitee group, when compared with the never-invited group (Figure 7).

(a)   Includes bowel cancer in people invited into the NBCSP in 2006–2008 (screen-detected, interval and non-responder) as 'intention to screen'.

(b)   Cancer stage was not known.

Note: Only summary stage data for New South Wales, Tasmania and the Australian Capital Territory were used. See Appendix A for further information.

Figure 7: Summary stage of bowel cancer diagnosed in individuals invited to the NBCSP[a] **and those not invited, 2006–2008**

The proportion of people diagnosed with a localised (least advanced) bowel cancer was 40% for NBCSP invitees compared with 34% for those who were never invited to participate in

the NBCSP between 2006 and 2008. Similarly, the proportion of people diagnosed with a distant (most advanced) bowel cancer was 11% for NBCSP invitees compared with 19% for those in the never-invited group. Excluding the 'Unknown' summary stage bowel cancer diagnoses, the difference in the summary stage profile of the NBCSP invitee group compared with the never-invited group was highly statistically significant (χ^2=39.12, P<0.001).

To ensure potential differences in the proportion of 'Unknown' summary stage cancers between the groups did not affect the result, the analysis was re-run with the inclusion of the 'Unknown' summary stage diagnoses; this had no effect on the statistical significance of the findings.

Using multivariable logistic regression, earlier summary stage was clearly associated with the NBCSP invitees when compared with the never-invited group (χ^2=28.88, P<0.001). Age group at diagnosis was also associated with summary stage (older age groups had higher odds of more advanced summary stage) (χ^2=25.54, P<0.001). There was no association between sex and summary stage (χ^2=0.71, P=0.40).

After adjusting for age group at diagnosis, the odds for more-advanced summary stage for NBCSP non-invitees was 1.38. In other words, bowel cancers diagnosed in the never-invited group had 38% higher odds of being more advanced than the odds for those diagnosed in the NBCSP invitee group. This indicates down-staging of bowel cancers—related to better prognosis—for the NBCSP invitees compared with the never-invited group.

To determine whether simply receiving an invitation but not participating led to down-staging, the summary stage profile of cancers diagnosed in individuals within the NBCSP invitee group who did not participate (that is, the non-responder subgroup) was then compared with the summary stage profile of those who were not invited (the never-invited group). There was no statistically significant difference in summary stage profile between these two groups (χ^2=6.39, P=0.09). Therefore, the statistically significant difference observed above, between the NBCSP invitees and the never-invited group, was mainly due to better summary stage diagnoses in the screen-detected and interval subgroups, not the non-responder subgroup (Table 2).

NBSCP invitee subgroup summary stage analysis

The summary stage profiles of NBCSP invitees diagnosed following a positive FOBT (screen-detected subgroup) were compared with those who were invited but did not participate (non-responder subgroup) (Figure 8).

Per cent
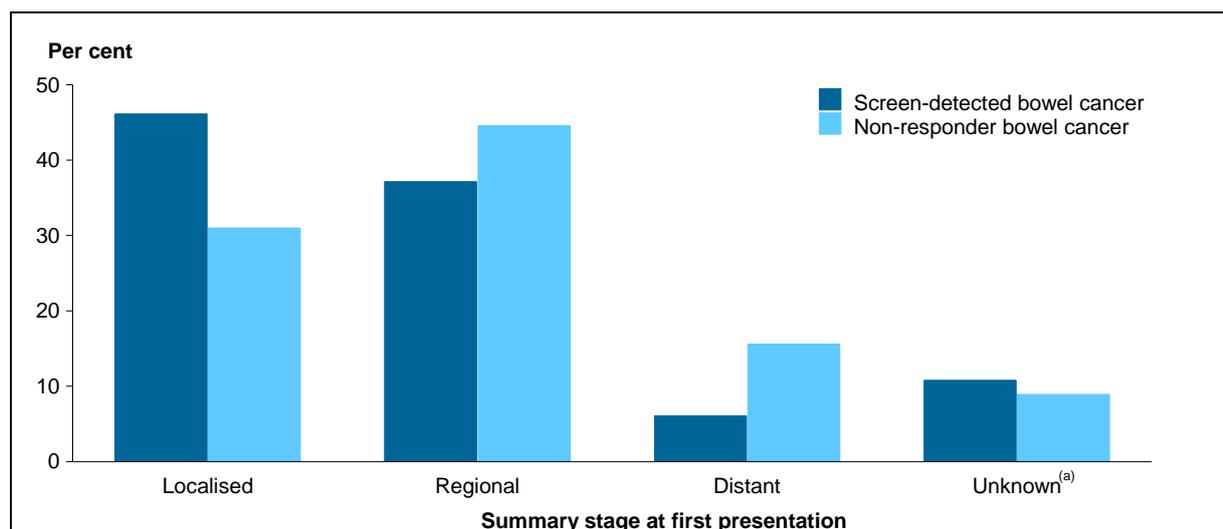
(a)   Cancer stage was not known.

Note: Only summary stage data for New South Wales, Tasmania and the Australian Capital Territory were used. See Appendix A for further information.

Figure 8: Summary stage of bowel cancer of invitees with a screen-detected cancer and invitees who did not respond to their invitation

In the screen-detected subgroup, the proportion of localised (least advanced) cancers was 46% compared with 31% in the non-responder subgroup. Further, the proportion of distant (most advanced) cancers was 6% in the screen-detected subgroup compared with 16% in the non-responder subgroup. After excluding the 'Unknown' summary stage diagnoses, the differences in summary stage profiles between the 2 groups were highly statistically significant (χ^2=38.82, P<0.001).

To ensure potential differences in the proportion of 'Unknown' summary stage cancers between the subgroups did not affect the result, the analysis was re-run with the inclusion of the 'Unknown' summary stage diagnoses; this had no effect on the statistical significance of the findings.

Using multivariable logistic regression, the difference in the summary stage profiles for invitees diagnosed with screen-detected cancers and cancers in non-responders was found to be statistically significant (χ^2=35.85, P<0.001). There was also a significant effect on summary stage based on invitee sex (χ^2=5.32, P=0.02), with female invitees having a higher risk of a more-advanced cancer. Invitee age group did not significantly affect summary stage (χ^2=0.46, P=0.93).

After adjusting for sex, the odds ratio for later summary stage for the non-responders was 2.21 (95% CI: 1.71–2.87). This means that bowel cancers diagnosed in the non-responder subgroup had 121% higher odds of being at a more-advanced summary stage than the odds for those diagnosed through the NBCSP.

Therefore, there was a statistically significant increase in localised (better-prognosis) cancers and a decrease in distant cancers in those who participated in the NBCSP and were diagnosed with a screen-detected bowel cancer, compared with non-responders.

Objective 3

People with a negative (or inconclusive) screening result who then had a bowel cancer diagnosed within 2 years of that screen result were considered to have an interval cancer. The third objective was to compare characteristics of interval cancers with those of screen-detected cancers.

Rationale	Details of the bowel cancers diagnosed through the NBCSP have been under-reported (see Box 5), and, until the data linkages carried out for this report, data on interval cancers have not been available.
	This objective involved investigating if there were any different characteristics found in interval cancers when compared with screen-detected bowel cancers.
Data used in meeting this objective	We used bowel cancer data from the screen-detected and interval cancer subgroups. (See the Methods section in Chapter 2 for more information.)
Analyses	Analyses in this objective were undertaken using χ^2 analysis.
Guide to interpretation	While statistically significant results were found, the small number of cancers in the analyses of some characteristics may affect their statistical reliability.

Key findings

Compared with screen-detected bowel cancers:

- A higher proportion of interval cancers were located within the right side of the colon (44% versus 25%), which were related to a higher risk of death (see 'Objective 1' earlier in this chapter).

- The gender ratio for interval cancers was approximately equal whereas more screen-detected cancers were found in men than women (62% versus 38%).

- Interval cancers were significantly more likely to be non-adenocarcinoma cancer types (6% of interval cancers were, compared with 3% of screen-detected cancers).

Results

The characteristics of bowel cancers diagnosed in individuals with a negative or inconclusive FOBT who were later found to have bowel cancer (the interval cancer subgroup) were analysed and compared with the screen-detected subgroup (Table 9).

For this analysis, the small number of individuals in the interval cancer subgroup (265), while encouraging for program performance, may affect the interpretability/reliability of the findings below. Therefore, these statistical analyses should be interpreted with caution.

Table 9: Characteristics of individuals diagnosed with bowel cancer in the screen-detected and interval cancer subgroups

Characteristic	Screen-detected		Interval[a]		P value
	No.	%	No.	%	
Sex					
Male	974	61.8	132	49.8	
Female	601	38.2	133	51.2	0.0002
Age at diagnosis[b]					
50–54	77	4.9	14	5.3	
55–59	531	33.7	73	27.5	
60–64	31	2.0	8	3.0	
65–69	936	59.4	170	64.2	0.19
Socioeconomic status[c]					
1 (most disadvantaged)	320	20.3	53	20.0	
2	343	21.8	61	23.0	
3	331	21.0	39	14.7	
4	301	19.1	52	19.6	
5 (least disadvantaged)	265	16.8	57	215	0.11
Remoteness[c]					
Major cities	964	61.7	158	60.4	
Inner regional	378	24.2	71	26.9	
Outer regional	193	12.4	30	11.4	
Remote	18	1.2	1	0.4	
Very remote	10	0.6	2	0.8	0.72
Site[d]					
Right-sided colon	392	24.9	115	43.4	
Left-sided colon	754	47.9	74	27.9	
Colon, not otherwise specified	34	2.2	13	4.9	
Rectum	395	25.1	63	23.8	<0.0001
Summary stage[e]					
Localised	236	46.1	28	50.9	
Regionalised	190	37.1	19	34.5	
Distant	31	6.1	6	10.9	
Unknown	55	10.7	2	3.6	0.20
Morphology[f]					
Adenocarcinomas	1,524	96.8	249	94.0	
Other histological types	51	3.2	16	6.0	0.02
Total	**1,575**		**265**		

Notes

(a)   Interval cancers include all bowel cancer diagnoses within 2 years of a negative or inconclusive screening result.

(b)   2006–2008 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

(c)   Those with missing data for this characteristic were excluded. Therefore, sum of numbers in this characteristic do not equal the total.

(d)   Definitions for cancer sites are in Appendix A.

(e)   Only summary stage data for New South Wales, Tasmania and the Australian Capital Territory were used. Therefore, sum of numbers in this characteristic do not equal the total.

(f)   Morphology groupings based on IARC international rules for multiple primary cancers using ICD-O-3 (IARC 2004). See Appendix A for further information.

Statistically significant differences in the site of tumours within the bowel were observed between the subgroups (χ^2=55.1, P=<0.0001), with the screen-detected subgroup having a higher proportion of left-sided cancers (48%) and lower proportion of right-sided cancers (25%) than the interval subgroup (28% and 43% respectively). Proportions for rectal and 'colon, not otherwise specified' cancers were similar between the two subgroups. (See Appendix A for a description of the four bowel cancer site groupings.)

When further comparing screen-detected cancer site proportions with those of the never-invited and non-responder groups (Table 2), of all groups, the highest proportion of left-sided cancers was in the screen-detected group.

There was a significant difference in the proportions of male and female diagnoses across the two subgroups (χ^2=13.7, P=0.0002). The sex split in the interval cancer subgroup was close to equal, whereas there were more men than women with screen-detected cancers.

Analysis of bowel cancer types (morphology), by adenocarcinoma or other types, found that there was a significant difference in these morphology groups across the screen-detected and interval cancer subgroups (χ^2=5.07, P=0.02). The interval cancer subgroup had a higher proportion of non-adenocarcinoma cancer types (6% versus 3%).

Differences in age, socioeconomic status quintiles, remoteness area and summary stage between individuals in the screen-detected and interval subgroups were also analysed. No statistically significant differences were found for these characteristics.

Objective 4

Objective 4 was to describe the positive predictive value (PPV) and negative predictive value (NPV) of the screening test.

Rationale	The PPV, NPV, sensitivity and specificity of the NBCSP screening test have not been calculated previously, so the findings of this objective are of interest.
Data used in meeting this objective	Meeting this objective necessarily involved only using data from members of the 2006–2008 NBCSP invitee study group who participated (that is, the screen-detected and interval cancer subgroups). Calculations for predictive values only considered invitees with a bowel cancer diagnosis after screening that had at least 2 years of follow-up data available after their screen, regardless of when their cancer was diagnosed in that follow-up period. See the Methods section in Chapter 2 for more information.
Analyses	The analyses in this objective used standard 2 x 2 contingency tables.
Guide to interpretation	It is important to note that these values are for initial (prevalent) screens which may have different detection rates than for rescreening. This is because initial screens are testing a population that may have had bowel cancers (or adenomas) growing asymptomatically for many years, whereas rescreens are testing for cancers that should have only appeared since the previous screen. Therefore, these statistics are likely to be different once biennial rescreening is fully implemented, which will include both rescreening, and older target ages (older invitees are generally at higher risk of a positive screening test—and bowel cancer). A 2-year cut off for follow-up was chosen as this is the recommended bowel cancer rescreening interval (CCA & ACN 2005). If participants from jurisdictions that did not have 2 years of follow-up available were also included, it would potentially bias the statistics as some participants with less than 2 years of follow-up data and a 'Cancer not diagnosed' outcome may yet record a bowel cancer before their full 2-year follow-up period is complete. The analysis in this objective therefore provides the most accurate results available, within current limitations, on the overall performance of the FOBT.

Key findings

- The positive and negative predictive values of the screening kit for bowel cancer were 3.6% and 99.9% respectively. That is, 3.6% of those with a positive screen were diagnosed with bowel cancer, and less than 0.1% of those with a negative screen were diagnosed with bowel cancer within 2 years.

- Of people in the 2006–2008 NBCSP invitee group who participated, 83% of those who were diagnosed with a bowel cancer within 2 years had received a positive screening test, and 93% of those who were not diagnosed with bowel cancer within 2 years had

received a negative screening test. This level of accuracy compares favourably with other international FOBT screening studies.

Results

Of those in the 2006–2008 NBCSP invitee group who participated, the sensitivity of the FOBT was 83% and the specificity was 93% (Table 10). That is, 83% of all who screened and were later diagnosed with a bowel cancer had a positive screening test, and 93% of those who were not diagnosed with bowel cancer had received a negative screening result. The positive and negative predictive values of the screening kit were 3.6% and 99.9% respectively. These measures reflect high validity for the screening test in diagnosing bowel cancer (Burch et al. 2007; Levi et al. 2007; Shin et al. 2013).

Table 10: Performance of faecal occult blood test for diagnosing bowel cancer, 2006–2008 NBCSP invitees[a]

| Screening result | Actual cancer outcome[a] | | Total |
	Cancer diagnosed	Cancer not diagnosed	
Positive FOBT	887	23,899	**24,786**
	(3.6% PPV)		
Negative FOBT	176	297,378	**279,554**
	(0.06% false negatives)	(99.9% NPV)	
Total	**1,063**	**321,277**	**322,340**
	(83.4% sensitivity)	(92.6% specificity)	

(a)   Includes all cancer outcomes of individuals from jurisdictions where 2 years of follow-up data were available.

Therefore, the chance that a participant who received a positive screening test result had a bowel cancer diagnosed was about 1 in every 28 positive screens.

5   Discussion

This project has linked bowel screening records of people invited into the NBCSP in 2006–2008 with population-based datasets of bowel cancer diagnoses and national deaths information. These linkages allowed comparisons of the characteristics of bowel cancers diagnosed across the NBCSP invitee group to be compared with those in similar-aged non-invitees. The analyses by intention-to-screen (in Objectives 1 and 2) are important as these findings can provide information to examine the mortality impact of the NBCSP overall.

Bowel cancer mortality rates were lower in the NBCSP invitee study group

The results demonstrated the positive impact of NBCSP invitation on bowel cancer mortality risk. Population hazards analysis found that, with the data available, the risk of bowel cancer death before 2012 after a diagnosis in 2006–2008 was 68% higher in the never-invited group, compared with the NBCSP invitees. Even after correcting for potential lead-time bias, this risk was still a statistically significant 15% higher in the never-invited group. Within the NBCSP invitee group specifically, the risk of death from bowel cancer was considerably higher for the non-responder subgroup compared with the screen-detected subgroup.

Because evaluations of cancer mortality outcomes from screening programs are known to be affected by lead-time bias (Day & Walter 1984; Walter & Stitt 1987), some studies can use 10 or more years of follow-up data and lead-time correction to mitigate it. Repeating this data linkage with more years of follow-up data is expected to strengthen the significant difference between the invitee and never-invited groups. This is because the method for correcting for lead-time bias assumes that all bowel cancers follow the same trajectory from asymptomatic to symptomatic. However, it is likely, with only a small number of years of follow-up data, that the screen-detected bowel cancers that have already resulted in death would have been more aggressive and had a shorter time to symptoms than allowed for in the correction method. This issue would be reduced with a longer follow-up time.

Nevertheless, the results of these population-based analyses support findings from earlier randomised trials (which are not affected by such lead-time effects) that faecal occult blood test screening reduces mortality from bowel cancer (Winawer et al. 1993; Kewenter et al. 1994; Hardcastle et al. 1996; Kronburg et al. 1996; Mandel et al. 1999; Towler et al. 1998).

The other mortality finding of interest was that the main contributor towards increased bowel cancer mortality risk was more advanced bowel cancer summary stage at diagnosis.

Bowel cancer 'down-staging' was found for the NBCSP invitee study group

'Down-staging' (that is, cancers diagnosed in one group of people being on average at a less-advanced stage than in another comparison group) has been used as a proxy for a reduction in bowel cancer mortality in other studies (Cole et al. 2013). As hypothesised, we observed a shift in the summary stage distribution of NBCSP invitee bowel cancers, with cancers diagnosed within the never-invited population having higher odds of being more advanced than those diagnosed in the NBCSP invitee group. After adjusting for differences by age group, bowel cancers diagnosed in the never-invited group had 38% higher odds of

being more advanced than those diagnosed in the NBCSP invitee group. Further, within the NBCSP invitee group specifically, bowel cancers diagnosed in the non-responder subgroup had 121% higher odds of being more advanced than the odds for bowel cancers diagnosed in those whose cancer was detected by a positive screening test (the screen-detected subgroup).

Further analysis showed no statistically significant difference between the summary stage profile of cancers diagnosed in the non-responder subgroup and the never-invited subgroup. This indicated that better summary stage outcomes for NBCSP invitees diagnosed with bowel cancer were largely influenced by the shift in summary stage distribution in the screen-detected and interval subgroups, not the non-responder subgroup. Hence, bowel cancer down-staging was more highly associated with participation in the NBCSP than invitation alone.

Cancers diagnosed at an earlier summary stage are more likely to have better prognoses and be managed curatively (Cole et al. 2013). Therefore, this finding agrees with a main objective of the NBCSP—to detect cancers at an early stage to maximise the effectiveness of treatment and improve outcomes for the disease. Further, these results add support to the mortality findings from Objective 1.

These findings were based on bowel cancer summary staging data from 3 of the 8 Australian jurisdictions (New South Wales, Tasmania, and the Australian Capital Territory). There is no reason to expect bowel cancer staging outcomes would differ in the other jurisdictions in comparison with these three.

Characteristics of screen-detected bowel cancers

This study found that screen-detected bowel cancers have different characteristics to those diagnosed symptomatically. Screen-detected cancers were diagnosed more commonly in males than females (even though more women than men participate in screening, see the *NBCSP monitoring report 2012–13* [AIHW 2014b]), and are more likely to be found in the left side of the colon. These findings are consistent with other studies (Ananda et al. 2009; Steele et al. 2012; Morris et al. 2012; Cole et al. 2013).

Site of bowel cancer affects prognosis

As discussed above, screen-detected bowel cancers were more likely to be left-sided when compared with the never-invited population, and left-sided bowel cancers had improved mortality outcomes than right-sided (and 'colon, not otherwise specified') bowel cancers. This finding was also consistent with similar studies (Wray et al. 2009; Gonzalez et al. 2001; Haug et al. 2011).

Descriptive statistics showed that right-sided bowel cancers were more likely to be diagnosed at a more advanced summary stage, and were diagnosed in higher proportions in females, and as age-at-diagnosis increased. However, of these, only more advanced summary stage was associated with a higher risk of bowel cancer death.

Screening was more likely to detect adenocarcinomas

The NBCSP diagnosed a higher proportion of adenocarcinomas than were diagnosed in the never-invited population, and adenocarcinomas had a slightly lower risk of death than other cancer cell types.

Overall, these findings indicate that there may be reduced mortality risk for left-sided cancers and adenocarcinomas diagnosed by screening. However, of the 3 main differences

between screen-detected and never-invited bowel cancers (cancer site, type, and summary stage), the characteristic with the greatest mortality risk effect was summary stage. This may help explain why outcomes for bowel cancers diagnosed through NBCSP screening were more favourable.

Interval cancers differed from screen-detected cancers

Another important finding from this project was the number and characteristics of interval cancers. The small number of interval cancers in this study (265), while positive for the program, means the statistical findings related to interval cancers should be interpreted with caution.

Compared with screen-detected bowel cancers, interval cancers were more likely to be located in the right side of colon, and less likely to be adenocarcinomas. While there was a statistically significant difference between the screen-detected and interval cancer subgroups for adenocarcinoma cancers, 94% of interval cancers were still adenocarcinomas (compared with 97% of screen-detected cancers). It was not possible to determine if these interval cancers existed at screening time but were not detected, or developed some time after the screening test.

If we assume that the interval cancers appeared in the 2 years following a screening test, it may be that they were faster-growing bowel cancer types. However, they had a less-advanced summary stage profile — and no worse mortality — than non-responder and never-invited cancers, even though these 3 groups would be thought to have cancers found at a similar symptomatic time in their progression.

Interval cancers, perhaps due to increased participant awareness due to screening, were therefore detected at an earlier symptom stage than the other symptomatic diagnoses, yet had differences to screen-detected cancers. These factors together mean that additional investigation into the specifics of interval cancers is required to determine if unique properties of interval cancers could be clarified further. Examples of these specifics could include microsite instability or methylation differences (Arain et al. 2010; Gervaz, Bucher & Morel 2004; Iacopetta 2002; Sawhney et al. 2006), or differences in family history of bowel cancer (Samadder et al. 2014).

Screening test performance

In this project, the positive and negative predictive values of the screening test for bowel cancer were 3.6% and 99.9% respectively. A similar positive predictive value was reported by Shin and colleagues (2013). In addition, the high sensitivity (83%) and specificity (93%) of the FOBT for cancer are similar to the findings of Levi and colleagues (2007).

These results together indicate the high degree of accuracy of the screening test.

Project strengths

This project used a whole-of-population design that compared bowel cancer characteristics of populations differing in screening invitation status, while also looking for differences within the invitee study group. The strengths of this project included:

- Data were obtained from independently-held, well-managed and high quality population-based databases.

- Individuals were matched across databases and then de-identified by an independent third party before analysis by investigators.

- Cancer is a notifiable disease in Australia. Therefore, selection bias was minimised as it is unlikely that there were differences in reporting between bowel cancers diagnosed in the NBCSP invitee group and bowel cancers diagnosed outside of the program (the never-invited population).

- There were no systematic biases in the referral or the type of follow-up received by individuals in each group, as all bowel cancer diagnoses in this project resulted from usual care follow-up of patients after testing, through existing public and private primary health care systems.

- Cancer summary stage data were extracted and interpreted from histology reports by experienced staff at cancer registries.

- With the exception of the interval subgroup, all other groups had similar proportions of individuals with an unknown bowel cancer summary stage due to missing or insufficient data (3.6% for the interval group, 8–10% for others).

Project limitations

This project had a number of limitations:

- Data on cancer summary stage were restricted to those jurisdictions where staging data were considered of sufficient completeness for reporting—New South Wales, Tasmania and the Australian Capital Territory. Therefore only 5,900 records were included in analyses involving bowel cancer summary stage (a further 16,151 records from the other jurisdictions did not have summary stage information).

- The small number of interval cancers—while still useful, and encouraging for program performance—limited the accuracy of statistical analysis and data interpretation for this group. This was especially true in relation to the cancer staging analyses, as an even smaller subset of the interval cancers had staging data. With the expansion of the NBCSP, both in terms of target ages and rescreening, larger sample sizes could be included in future projects.

- The limited follow-up time in the mortality analyses may mean lead-time bias has not been corrected for optimally. Re-analysis with more years of outcome data, combined with lead-time bias correction methods, would help mitigate this. We expect that as more outcome data become available, the lead-time effect will become smaller, meaning the risk difference between the invited and never-invited groups should increase from the adjusted 15% risk difference found in this report.

- Complete behaviour and grade data for bowel cancers were not available, meaning other potential comparisons showing pre-cancerous or cell differentiation differences could not be realised. For example, data on benign or in-situ (non-invasive) neoplasms could improve overall evaluation of the program's goal to 'reduce the morbidity and mortality from bowel cancer by actively recruiting and screening the target population for early detection or prevention of the disease'—particularly the prevention component.

- Reasons for non-response (such as already undergoing screening or surveillance) would help clarify the differences in this subgroup.

- Details of the screening (for example, alternative FOB testing) or colonoscopy history of the never-invited study group would allow improved focus on asymptomatic cancers in this group.

- The never-invited study group did not contain geographical location information, so comparisons of socioeconomic status or remoteness areas were not possible for this group.

- As NBCSP form return for adenoma diagnoses is not considered complete (see Box 5 for discussion on the level of missing histopathology outcome information), and there is no practical way to determine the number of adenomas missed by the screening test, the positive and negative predictive values, specificity and sensitivity for adenomas of screening could not be determined.

- Intention-to-screen analyses generally use true randomisation of subjects, something that was implicitly not possible in this population-based observational study.

Future directions of this work

While 10 years of follow-up data would allow mortality reductions due to the program to be fully apparent, and this early study only had access to 3 years of follow-up data, the encouraging findings in this report indicate that there are improved bowel cancer outcomes for those invited into the NBCSP, and particularly for those who participate. As discussed, the statistically significant mortality results support those predicted by the earlier randomised trials of FOBT screening.

This project may therefore, in addition to meeting its primary and secondary objectives, be considered a successful proof-of-concept that viable NBCSP evaluation information can be gathered by the linkage of relevant datasets.

Future analysis with more years of outcome data would improve the evaluation and understanding of bowel cancer outcome differences due to the NBCSP. From July 2013, the NBCSP target ages have expanded to those turning 50, 55, 60 and 65 years of age, with the phasing in, from July 2015 to 2020, of biennial screening for those aged 50 to 74.

Future data linkages, such as those undertaken in this report, would help monitor the effect of the NBCSP on Australian bowel cancer morbidity and mortality outcomes as the program is expanded, especially if bowel cancer staging data become available nationally.

Appendix A

Additional data source details

NBCSP data

NBCSP target population

The NBCSP has been phased in gradually. Table A.1 outlines the start dates of each phase, and the target age groups.

Table A.1: NBCSP phases and target populations

Phase	Start date	End date	Target ages
1	7 August 2006	30 June 2008	55 and 65
2	1 July 2008	30 June 2011[a]	50, 55 and 65
2[b]	1 July 2011	30 June 2013	50, 55 and 65
3	1 July 2013	ongoing	50, 55, 60 and 65
3	1 January 2015		50, 55, 60, 65, 70 and 74
3	1 January 2016		50, 55, 60, 64, 65, 70, 72 and 74
3	1 January 2017		50, 54, 55, 58, 60, 64, 68, 70, 72 and 74
3	1 January 2018		50, 54, 58, 60, 62, 64, 66, 68, 70, 72 and 74
3	1 January 2019		50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72 and 74

(a)   Eligible birthdates, and thus invitations, ended on 31 December 2010.

(b)   Ongoing NBCSP funding commenced.

Note: The eligible population for all Phase 2 and 3 start dates incorporates those turning the target ages from 1 January of that year, onwards.

Once the full rollout of biennial screening for those aged 50–74 is complete, comparisons with a never-invited group will not be possible because all Australians in the target age range (with the exception of those not registered with Medicare) will then be NBCSP invitees.

NBCSP data background

Data are collected about NBCSP participants and their screening outcomes from a variety of sources throughout the screening pathway (Figure A.1), and stored in the NBCSP register. The data are collected on forms completed by participants, GPs, colonoscopists, pathologists, and other specialists or administrative health care staff.
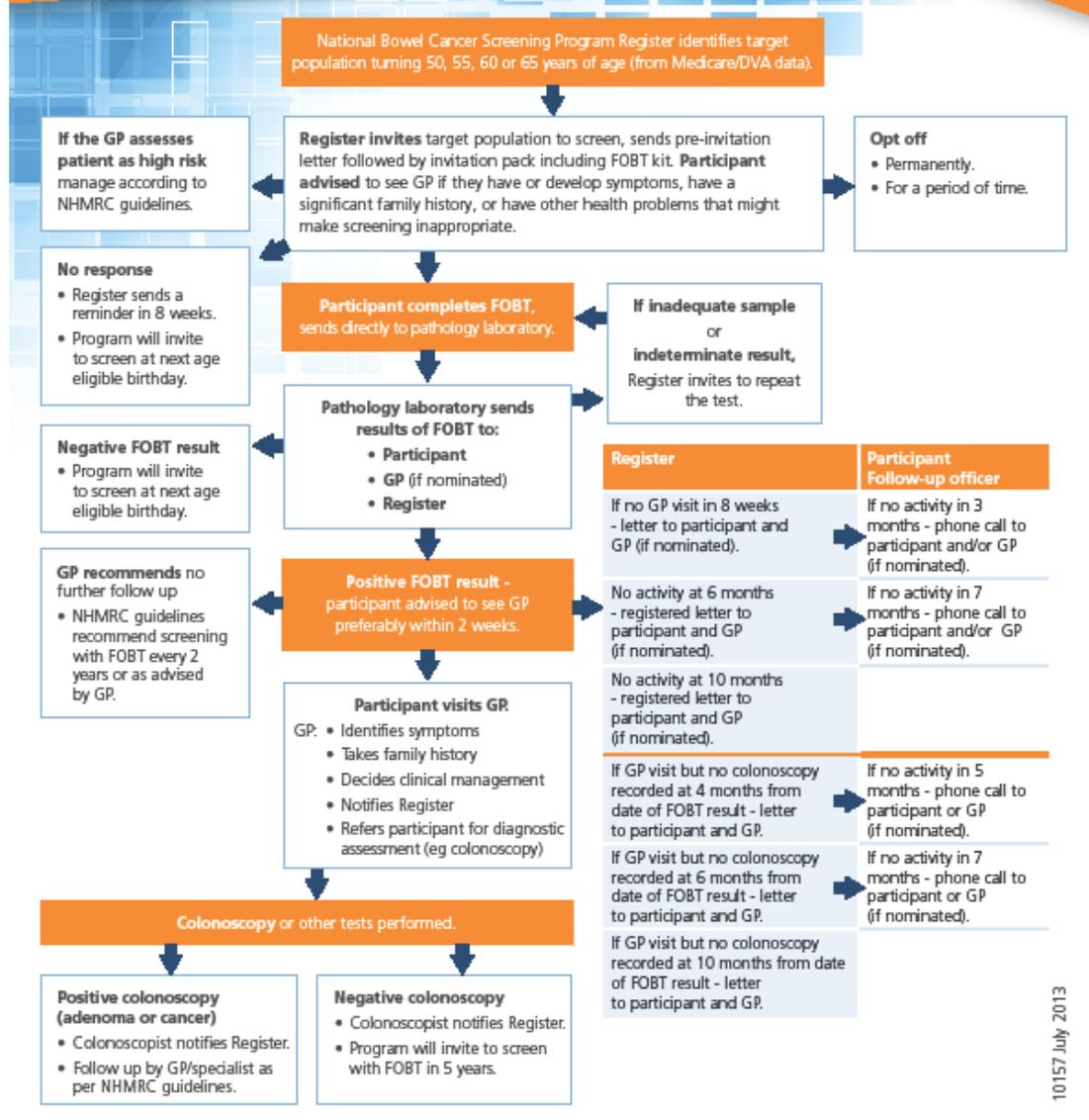
© Commonwealth of Australia 2013.

Source: Health 2013.

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Figure A.1: NBCSP participant screening pathway

Completion of NBCSP forms by practitioners is not mandatory, and there is the possibility of inconsistent reporting, including limited information on participant outcomes. These inconsistencies are noted in the AIHW's NBCSP annual monitoring reports in order to provide an indication of the reliability of the data. In this project, the linkage of the 2006–2008 NBCSP invitee group to jurisdictional cancer registry data and national deaths data was used to improve outcome information for these invitees.

The introduction of a new FOBT kit in December 2008, which was found to be unreliable (AIHW & DoHA 2009), may have had a lowering effect on the positivity rate in this study group; however, this effect would have been minimal, as less than 5% of FOBT kits were affected. Those people invited in December 2008 who were affected by this issue were given the opportunity to re-test in 2009.

2006–2008 NBCSP invitees are counted only once in the reporting period, even if they had more than one abnormality detected due to their invitation. Histopathologically-confirmed results are reported in preference to other suspected findings from the colonoscopist, with the most serious finding chosen where multiple diagnoses were made.

Adenoma classifications

An adenoma (adenomatous polyp) is a benign tumour that arises from epithelial cells. All adenomas have malignant potential. Adenomas in the rectum or colon have a higher chance of developing into cancer (adenocarcinoma) than adenomas in most other organs.

Although nearly all cancers in the colon (adenocarcinomas) arise from adenomas, only a small minority of adenomas (1 in 20 or fewer) progress to cancer (Ahnen & Macrae 2008). While most small tubular adenomas have a low risk of progressing to cancer, the risk is much higher in advanced adenomas.

Adenoma classifications were derived from information reported by colonoscopists and histopathologists, and categorised as:

- Advanced adenoma: Any histopathologically confirmed adenomas that show villous change and/or high grade dysplasia and/or diameter of 10 mm or greater. Or a person with 3 or more histopathology-confirmed adenomas of any kind.

- Other adenoma: All other confirmed adenomas not considered advanced.

Where a person had multiple adenomas, they were classified according to the adenoma having the highest risk.

Jurisdictional cancer registry data

Cancer site

Bowel cancer can occur at any location (site) within the bowel, from its start point at the end of the small intestine, to the rectum. There are known site-specific trends related to bowel cancer. For example they are more likely in certain parts of the bowel depending on age and sex, and survival may be different depending on bowel cancer site (Wray et al. 2009). Therefore, it is important to investigate potential differences in site related to screening activity.

In this report, bowel cancers diagnosed in the appendix, caecum, ascending colon, hepatic flexure and transverse colon (ICD-10 C180–C184) were considered right-sided. Left-sided cancers were those diagnosed at the splenic flexure and in the descending colon, sigmoid colon and the recto-sigmoid junction (ICD-10 C185–C19). The category 'colon, not otherwise specified' included tumours overlapping two sites in the colon (C188) or with no site

specified (C189). Cancers of the rectum were those classified as ICD-10 C208–C209. Anal cancers (C21), which may also be detected by the screening test, are not included in NBCSP outcome analyses.

Cancer stage

Cancer stage at diagnosis refers to extent or spread of cancer at the time of diagnosis. Such information is important for a number of reasons, including determining an individual's prognosis, assisting in the planning and evaluation of treatment, and contributing to cancer monitoring and research.

Currently, stage of bowel cancer at diagnosis is not routinely collected by all jurisdictional cancer registries, meaning there is not complete national stage data. For this project, all jurisdictions were investigated for cancer staging data; however, only 3 jurisdictions were found to have applicable data for the study time period. Therefore, staging analyses in this report only used data from the 3 of the 8 Australian jurisdictions. These 3 jurisdictions, New South Wales (NSW), Tasmania and the Australian Capital Territory (ACT), provided about one-third of the total bowel cancer cases in Australia, and gave a preliminary estimate for the stage profile of cancer at the national level. While this compromise is not optimal, we assumed that any data issues relating to the staging data would be equally spread across the NBCSP invitee and never-invited group diagnoses, thus limiting bias.

Levels of staging

Not only are a number of different staging systems used for different cancers, and in different regions and countries, there are also different levels of staging detail used to determine a stage within these systems.

- **Summary stage at first presentation** is a summary of the most serious extent of cancer spread obtained from pathology reports, inpatient notifications and other treatment facilities within 4 months of the initial diagnosis. It may also be called 'extent of disease at diagnosis'.

- **Clinical stage** uses (pre-operative) information the doctor has gained from physical examination, imaging tests, bowel biopsies and blood tests to estimate the stage of the cancer, which is generally used for determining treatment options.

- **Pathological stage** data are sourced from pathology reports of biopsies, resection surgery and lymph nodes removed at surgery. On their own they may miss detail of the overall cancer stage.

- **Clinico-pathological stage** uses all information gained from the operative findings and relevant pathological data, along with the clinical findings, to provide the most precise information on the cancer stage.

New South Wales and Australian Capital Territory staging data

For this report, NSW and ACT bowel cancer diagnoses included 'Summary stage at first presentation' information, which was supplied in four categories (Table A.2).

Summary stage at first presentation system

According to Tracey and associates (2006), the *Summary stage at first presentation system* is preferred by a number of cancer registries overseas and in Australia (such as the NSW and ACT registries) because the required information can be sourced more readily from the pathology and clinical reports to which the registries have access. In this staging system,

tumours are allocated to one of three categories, as well as an 'Unknown' category, as shown in Table A.2.

Table A.2: Summary stage at first presentation system

Stage	Description
Localised	A malignancy limited to the organ of origin; it has spread no farther than the organ in which it started. There is infiltration past the basement membrane of the epithelium into the functional part of the organ, but there is no spread beyond the boundaries of the organ.
Regional	There is tumour extension beyond the limits of the organ of origin. There is invasion through the entire wall of the organ into surrounding organs and/or adjacent issues or by direct extension or contiguous spread to nearby lymph nodes.
Distant metastases	Tumour cells that have broken away from the primary tumour, have travelled to other parts of the body and have begun to grow at the new location. Distant stage is also called remote, diffuse, disseminated, metastatic or secondary disease. In most cases there is no continuous trail of tumour cells between the primary site and the distant site.
Unknown	These are cases for which sufficient evidence is not available to adequately assign a stage. Examples include occasions when the patient dies before workup is completed, when a patient refuses a diagnostic or treatment procedure, and when there is limited workup due to the patient's age or a simultaneous contraindicating condition. If there is insufficient information the case cannot be assigned a stage.

Source: Tracey et al. 2006.

Tasmanian staging data

Tasmanian bowel cancer diagnoses included staging data with six options (Table A.3)

Table A.3: Tasmanian cancer registry bowel cancer staging system

Stage	Description
Localised	Localised to the tissue of origin (includes in-situ breast and in-situ melanoma).
Regional organs	There is tumour extension beyond the limits of the organ of origin, with invasion of adjacent tissue or organs (includes subcutaneous fat or muscle and organs adjacent to the primary cancer site).
Regional lymph nodes	There is tumour extension beyond the limits of the organ of origin, with invasion of regional lymph nodes.
Distant metastases	Tumour cells that have broken away from the primary tumour, have travelled to other parts of the body, and have begun to grow at the new location.
Other	Not applicable. Applies to lymphatic and haemopoetic cancers.
Unknown	These are cases for which sufficient evidence is not available to adequately assign a stage.

Source: Tasmanian Cancer Registry (personal communication).

Like the NSW and ACT summary-stage-at-first-presentation data, Tasmania generally applies a 4-month-from-initial-diagnosis cut-off rule for staging data. For this report, the 'Other' group (which was not applicable to bowel cancers) was excluded, and 'Regional organs' and 'Regional lymph nodes' stages were merged as per Table A.2 to allow the data to be compatible with the NSW and ACT summary staging data.

To reduce complexity of text in this report, 'summary stage at first presentation' has been more simply called 'summary stage'.

Cancer behaviour and grade

Bowel cancer diagnoses data from jurisdictional cancer registries generally only contain information on malignant cancer; complete information on other cancer behaviours (such as benign, in situ or secondary) was not available at the national level. Therefore, this report could not compare differences in diagnoses other than for malignant cancer behaviours across the groups investigated. It should be noted that a positive result from the NBCSP

screening test could be a result of these other abnormalities—most of which are earlier, better prognosis conditions that may eventually lead to invasive cancer or other problems.

The grade, or differentiation, of cancers describes how much or how little a tumour resembles the normal tissue from which it arose. It is determined by pathologists and coded using the 6th digit of the ICD-O morphology code (Fritz et al. 2000) as follows:

1. Grade I—Well-differentiated or differentiated, not otherwise specified

2. Grade II—Moderately differentiated, moderately well-differentiated or intermediate differentiation

3. Grade III—Poorly differentiated

4. Grade IV—Undifferentiated or anaplastic. That is, a lack of differentiation or loss of structural and functional differentiation of normal cells. This is often a characteristic of aggressive malignancies.

Analysis by grade may have been useful to investigate if there were further differences between NBCSP invitees and non-invitees; however, national data on the grade of bowel cancer were not complete, and this aspect was therefore not investigated.

Morphology

Morphology refers to the histological characteristics of tumours, defined by the type of cell they involve. A tumour that involves skin cells, internal organ tissue, or lining cells is called a carcinoma, and a tumour that involves connective or supportive tissue (muscle cells, bone cells) is called a sarcoma. Each of these broad cellular types can further be categorised by their microscopic properties. The histological type of cancer is associated with different risk factors, natural behaviour history and responsiveness to therapeutic interventions.

In this project, bowel cancers classified as adenocarcinomas were compared with all other cancer morphologies recorded, based on international definitions of multiple primary cancers using ICD-O-3, as recommended by the International Agency for Research on Cancer (IARC) (Table A.4) (IARC 2004).

Table A.4: Grouping of bowel cancer histology types

Type of bowel cancer	Corresponding ICD-O-3 codes
Carcinomas	
1. Squamous and transitional cell carcinoma	8051–8084, 8120–8131
2. Basal cell carcinomas	8090–8110
3. Adenocarcinomas	8140–8149, 8160–8162, 8190–8221, 8260–8337, 8350–8551, 8570–8576, 8940–8941
4. Other specific carcinomas	8030–8046, 8150–8157, 8170–8180, 8230–8255, 8340–8347, 8560–8562, 8580–8671
5. Unspecified carcinomas (NOS)	8010–8015, 8020–8022, 8050
Sarcoma and soft tissue tumours	8680–8713, 8800–8921, 8990–8991, 9040–9044, 9120–9125, 9130–9136, 9140–9252, 9370–9373, 9540–9582
Tumours of haematopoietic and lymphoid tissues	9840, 9860–9931, 9945–9946, 9950, 9961–9964, 9980–9987, 9670–9699, 9728, 9731–9734, 9761–9767, 9769, 9823–9826, 9833, 9836, 9940, 9700–9719, 9729, 9768, 9827–9831, 9834, 9837, 9948, 9650–9667, 9740–9742, 9750–9758, 9590–9591, 9596, 9727, 9760, 9800–9801, 9805, 9820, 9832, 9835, 9860, 9960, 9970, 9975, 9989
Other specified types of cancer	8720–8790, 8930–8936, 8950–8983, 9000–9030, 9060–9110, 9260–9365, 9380–9539
Unspecified types of cancer	8000–8005

Note: All cases included in each of the groups were coded by state and territory cancer registries as primary site, invasive bowel cancers.

Source: IARC 2004.

Classifications of population groups

Cancer data were analysed by remoteness and socioeconomic status for individuals invited to participate in the NBCSP. Remoteness was classified into areas according to the 2006 ABS Australian Standard Geographical Classification (ASGC), while socioeconomic status quintiles were classified using the 2006 ABS Index of Relative Socioeconomic Disadvantage (IRSD). Data on remoteness area of residence and socioeconomic status were not available for the never-invited group; postcode information was only available for the NBCSP invitee study group.

Geographical classification

The ability to access and provide a wide range of services is influenced by the distance between clients and providers, be it for the clients to travel to the service providers or for the providers to travel to deliver services close to a person's home. The geographical location of areas is therefore an important concept in planning and analysing the provision of services.

As noted above geographic location was classified according to the ABS Australian Standard Geographical Classification (ASGC) Remoteness Structure. This groups geographic areas into 6 remoteness categories, defined using the Accessibility/Remoteness Index for Australia (ARIA).

ARIA is a measure of the remoteness of a location from the services provided by large towns or cities. Accessibility is judged purely on distance to one of the metropolitan centres. A higher ARIA score denotes a more remote location. Further information is available on the ABS website at <http://www.abs.gov.au/websitedbs/D3310114.nsf/home/geography>.

Residential address postcodes of invitees (at time of invitation) were mapped to the 2006 Remoteness Structure, classified to 5 main areas: *Major cities*, *Inner regional*, *Outer regional*, *Remote* and *Very remote* (AIHW 2004). The sixth area, *Migratory*, is not used in this project. The category *Major cities* includes Australia's capital cities, with the exceptions of Hobart and Darwin, which are classified as *Inner regional*. Participants whose postcodes were not available in the remoteness correspondence were included in an 'Unknown' geographical location grouping.

As some postcodes can span different Remoteness Areas, a weighting for each Remoteness Area is attributed to the postcode. This can result in non-integer counts for remoteness classifications. For example, the 2006 Northern Territory postal area 0822 was classified as 69.3% *Very remote*, 15.9% *Remote* and 14.8% *Outer regional*. Invitees with postcode 0822 had their counts apportioned accordingly.

Socioeconomic classification

Socioeconomic classifications were based on the 2006 ABS Index of Relative Socioeconomic Disadvantage (IRSD). The IRSD is one of 4 Socioeconomic Indexes for Areas (SEIFAs) developed by the Australian Bureau of Statistics (ABS 2008). This index is based on factors such as average household income, education levels and unemployment rates. Rather than being a person-based measure, the IRSD is an area-based measure of socioeconomic status in which small areas of Australia are classified on a continuum from disadvantaged to affluent. This information is used as a proxy for the socioeconomic status of people living in those areas and may not be correct for each person in that area.

Invitees were assigned into socioeconomic status quintiles according to the IRSD of their residential postcode at the time of invitation. Socioeconomic status (based on IRSD rankings) was calculated with a 2006 Census postal area (POA) correspondence (previously called a concordance) using a population-based method at the Australia-wide level. The first socioeconomic status group (labelled '1') corresponds to geographical areas containing the 20% of the population with the lowest socioeconomic status (most disadvantage) according to the IRSD, and the fifth group (labelled '5') corresponds to the 20% of the population with the highest socioeconomic status (least disadvantage).

Additional statistical methods

Correction for lead-time bias

The following method from Duffy and colleagues (2008) was used to correct for estimated lead-time bias:

$$E(s) = \frac{1 - e^{-\lambda t}}{\lambda}$$

where:

- $E(s)$ equals the estimated sojourn time (lead time) — the period during which the bowel cancer is asymptomatic but screen-detectable.
- t equals the time from screen-detected bowel cancer diagnosis to bowel cancer death (or loss to follow-up). That is, the uncorrected 'survival' time.
- λ equals the rate of transition from asymptomatic but screen-detectable to symptomatic bowel cancer.

The following transition rates from Brenner and colleagues (2011) were used for λ:

Table A.5: Asymptomatic to symptomatic transition rates for bowel cancer

Sex	Age group at diagnosis	Transition rate (λ) per 100 diagnoses, per year
Male	50–59	18.1
	60–64	19.2
	65–69	21.3
Female	50–59	21.3
	60–64	22.5
	65–69	21.9

This simple method relies on strong assumptions and generalisations, but provides a blunt way of taking lead-time into account in the mortality estimates of Objective 1. See the relevant papers for further information.

Glossary

adenoma: An adenoma (adenomatous polyp) is a benign tumour that arises from epithelial cells (cell that line the bowel of a glandular type). All adenomas have malignant potential. Adenomas in the rectum or colon have a higher chance of developing into cancer (adenocarcinoma) than adenomas in most other organs.

adenocarcinoma: The malignant progression of a benign adenoma.

asymptomatic: The situation in which a person has a particular disease, but experiences no symptoms of it.

bowel cancer: Comprises cancer of the colon and cancer of the rectum, collectively known as colorectal cancer.

cancer death: A death where the underlying cause of death is indicated as cancer. Persons with cancer who die of other causes are not counted in the mortality statistics in this publication.

cancer (malignant neoplasm or malignancy): A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems (AIHW 2014a).

colonoscopy: Procedure to examine the bowel using a special scope (colonoscope) usually carried out in a hospital or day clinic.

down-staging: If cancers diagnosed in a group of people exposed to a particular treatment are on average at a less-advanced stage than those diagnosed in a similar group of people who were not exposed to the treatment, down-staging of cancers in the treatment group is said to have occurred. As cancers at a less-advanced stage when diagnosed generally have better morbidity and mortality outcomes than those at a more-advanced stage, down-staging can be assumed to be an improvement.

eligible population: People who are registered as an Australian citizen or migrant in the Medicare enrolment file, or registered with a Department of Veterans' Affairs gold card, are included in the eligible population when they reach one of the target ages.

false negative: A screening test result that incorrectly indicates a person does not have a marker for the condition being tested when they do have the condition. Not all screening tests are completely accurate, so false negative results cannot be discounted. Further, with an FOBT test for bowel cancer, if a polyp, adenoma or cancer is not bleeding at the time of the test, it may be missed by the screening test.

false positive: A screening test result that incorrectly indicates a person has the condition being tested when they do not have the condition. FOBT tests detect blood-in-stool (blood in the faeces), which may be caused by a number of conditions. A false positive finding regarding bowel cancer may still mean the existence of other non-bowel cancer conditions, or pre-cancerous polyps or adenomas.

FOBT: Faecal occult blood test. A test used to detect tiny traces of blood in a person's faeces that may be a sign of bowel cancer. The **immunochemical FOBT** is a central part of Australia's National Bowel Cancer Screening Program.

Pathologists categorise completed NBCSP FOBTs into one of three groups:

1. correctly completed

2. incorrectly completed

3. unsatisfactory.

Participants are provided with specific instructions on how to complete the FOBT. Any tests not completed according to these instructions are classified as incorrectly completed. Unsatisfactory tests refer to those tests that could not be processed due to a problem with the kit (for example, an expired kit, kit samples that have been taken more than 2 weeks apart, or a kit that has taken more than 1 month in transit to arrive). Participants with FOBTs that are not correctly completed are requested to complete another FOBT. See Figure A.1 for details of the participant screening pathway.

FOBT result: FOBT results are classified by pathologists as either:

1. positive (blood is detected in at least one of two samples)

2. negative (blood is not detected)

3. inconclusive (the participant is asked to complete another kit).

histopathology: The microscopic study of the structure and composition of tissues and associated disease.

immunochemical FOBT: A specific type of FOBT test that requires no dietary or medicinal changes prior to the test.

incidence: The number of new cases (of an illness or event, and so on) occurring during a given period. Compare with **prevalence** (AIHW 2014a).

intention to screen: 'In a trial of a screening intervention, patient outcomes are analysed according to the group to which subjects were randomised, irrespective of whether those in the screening and control arms actually participated in screening. The importance of this principle lies in ensuring that randomisation is preserved, thus maintaining an equal distribution of important factors that may influence the outcome in the control and intervention groups. Using intention-to-screen analysis also reflects more closely the population benefit that can be expected, given participation rates that are likely to be encountered in practice' (Barratt et al. 2002).

interval cancer: For this report, an interval cancer is defined as a bowel cancer diagnosed within 2 years of a negative or inconclusive screening test result. A 2-year cut-off was used for interval cancers because that is the recommended rescreening interval, where later cancers should normally be picked up by a rescreening test.

invitee: A person who has been invited to participate in the National Bowel Cancer Screening Program.

lead-time bias: Lead-time bias involves the amount of time a diagnosis of asymptomatic cancer is brought forward by screening. A concern with some cancers diagnosed earlier through screening is that this may cause no difference to the outcome of the disease (that is, the date of death) regardless of the earlier diagnosis. The earlier diagnosis could therefore give an artificial increase (bias) in survival time from that if the cancer was detected symptomatically later.

malignant: Abnormal changes consistent with cancer.

metastasis: The process by which cancerous cells are transferred from one part of the body to another to form a secondary cancer, for example, via the lymphatic system or the bloodstream.

mortality: Death. For this publication specifically, see **cancer death**.

neoplasm: An abnormal ('neo', new) growth of tissue. Can be benign (not a cancer) or malignant (a cancer). Same as **tumour** (AIHW 2014a).

non-positive screening test: Screening tests that had a negative screening result, plus screening test results that were inconclusive or unsatisfactory (and the participant had not successfully re-tested).

non-responder: A person was considered a non-responder if they were sent an invitation as part of the 2006–2008 NBCSP study group, but did not return their screening kit for analysis.

participant: A person who has agreed to participate in the National Bowel Cancer Screening Program by returning a completed FOBT kit and participant details form.

positive predictive value: Proportion of people with a positive FOBT screen who have cancer detected at colonoscopy and confirmed by histopathology.

positive screening test: A positive screening result occurs when blood—even microscopic amounts—is found in a completed screening kit when tested. Blood-in-faeces may indicate a bowel abnormality (including cancer or adenomas) that requires further investigation.

positivity rate: Number of positive FOBT results as a percentage of the total number of valid FOBT results.

prevalence: The number or proportion (of cases, instances, and so forth) in a population at a given time. In relation to cancer, refers to the number of people alive who had been diagnosed with cancer in a prescribed period (typically 1, 5 or 10 years). Compare with **incidence** (AIHW 2014a).

prognosis: The likely outcome of an illness.

Program: The National Bowel Cancer Screening Program.

screen-detected bowel cancer: A bowel cancer was considered screen-detected if it was diagnosed any time after a positive screening test result, as it was likely diagnosed as part of follow-up investigation from the screening test.

screening: Repeated testing, at regular intervals, of apparently well people to detect a medical condition at an earlier stage than would otherwise be the case. Screening tests are not diagnostic (for example, see *false positive*, *false negative* and *positive predictive value*); therefore, people who receive a positive screening result require further assessment and diagnosis to determine whether or not they have the disease or risk marker being screened for.

sensitivity: Sensitivity measures how good a screening test is at identifying people with bowel cancer.

socioeconomic status: See Appendix A for details.

specificity: Specificity measures how good a screening test is at correctly identifying those that do not have bowel cancer.

summary stage at first presentation: Shortened to 'summary stage' in this report. See Appendix A for details.

target population: See Table A.1.

tumour: See **neoplasm**.

underlying cause of death: The condition, disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence that produced the fatal injury (AIHW 2014a).

workup: Intensive diagnostic study, such as a doctor might use to ascertain a patient's cancer stage.

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List of tables

List of figures

List of boxes

Related publications

The following AIHW publications may be of interest:

- AIHW 2014. National Bowel Cancer Screening Program monitoring report: 2012–13. Cancer series no. 84. Cat. no. CAN 81. Canberra: AIHW.

- AIHW 2012. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer Series no. 69. Cat. no. CAN 65. Canberra: AIHW.

- AIHW & AACR 2012. Cancer in Australia: an overview 2012. Cancer series no. 74. Cat. no. CAN 70. Canberra: AIHW.

These and other cancer-related reports can be downloaded free of charge from the AIHW website <http://www.aihw.gov.au/cancer-publications/>.

The website also includes information on ordering printed copies of these reports.

This report presents a comparison of the mortality outcomes and cancer characteristics for two populations: those invited to screen in the National Bowel Cancer Screening Program (NBCSP) in 2006–2008, and those of a similar age who had not been invited to screen in that time period.

Of the 2006–2008 bowel cancer diagnoses in these two groups, non-invitees were found to have a 15% higher risk of dying from bowel cancer than NBCSP invitees, and bowel cancers diagnosed in non-invitees were more likely to be at a more-advanced stage. These outcomes demonstrate that the NBCSP is contributing to reducing morbidity and mortality from bowel cancer in Australia.

The report findings also suggest that the screening test has a high degree of accuracy.