Australian Government
Australian Institute of Health and Welfare

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

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AIHW

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Contents

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Abbreviations

ABS	Australian Bureau of Statistics
ACD	Australian Cancer Database
AIHW	Australian Institute of Health and Welfare
GP	general practitioner
IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases, Tenth Edition
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
iFOBT	immunochemical Faecal Occult Blood Test
IRSD	Index of Relative Socioeconomic Disadvantage
NBCSP	National Bowel Cancer Screening Program
NDI	National Death Index
NHMRC	National Health and Medical Research Council
NPV	negative predictive value
PPV	positive predictive value

Symbols

χ^2	chi-square statistic
—	nil or rounded to zero
. .	not applicable
<	less than
>	more than
≥	more than or equal to
n.a.	not available
n.o.s.	not otherwise specified
n	number
%	per cent
P	The probability that the observed difference or association could have occurred by chance alone. If that probability is less than 5% (0.05), it is conventionally held that the observed difference is unlikely enough to be due to chance that it is evidence of a true difference or association.

Summary

The National Bowel Cancer Screening Program (NBCSP) started in Australia in 2006. Its aim is to reduce morbidity and mortality from bowel cancer by actively recruiting and screening the target population for early detection or prevention of the disease. An earlier study (AIHW 2014) quantified and evaluated the effectiveness of the NBCSP for 2006–2008 invitees against this aim. This current report extended those findings by linking a larger NBCSP invitee cohort (2006–2010) to more recent cancer incidence and mortality data to analyse 51,832 people diagnosed with bowel cancer in 2006–2015. Of these:

- 15,454 were invited to participate in the NBCSP in 2006–2010 as part of the target population's turning 50, 55 or 65 (NBCSP invitees)
- 36,378 were aged 50–74 when diagnosed, but did not turn 50, 55 or 65 in 2006–2010 and were therefore not invited to screen in that period (non-invitees).

This report compares the outcomes (mortality) and cancer characteristics of these two populations. It 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 confirm that the NBCSP is contributing to reducing morbidity and mortality from bowel cancer in Australia.

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

Of the people diagnosed with bowel cancer in this study, non-invitees had a 28% higher risk of bowel cancer death by 31 December 2015 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 13% higher for non-invitees. The all-cause mortality risk was also found to be a statistically significant 7% higher for non-invitees.

Among 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 the NBCSP.

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 associated with better treatment options and prognosis, and is a key reason behind the reduced mortality risk. Of the bowel cancers in this study with '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 12% higher odds of being more advanced than those diagnosed in NBCSP invitees.

Among NBCSP invitees, those with screen-detected bowel cancers were much more likely to be diagnosed at an earlier summary stage (171% higher odds), compared with bowel cancers later diagnosed in the invitees who did not participate.

Bowel cancers diagnosed within 2 years of a negative or inconclusive screening test

Compared with screen-detected bowel cancers, those diagnosed within 2 years of a negative or inconclusive screening test were more likely to be in the right side of the bowel, be of a non-adenocarcinoma cell type, and less likely to be localised.

Screening test performance

Of the NBCSP invitees who participated, 85% of those diagnosed with bowel cancer within 2 years of their screen received a positive screening result, and 92% of those who were not diagnosed with bowel cancer received a negative result. These figures suggest that the screening test used at the time of this study had 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. In 2018, an estimated 17,004 people will be diagnosed with bowel cancer (50% will be in the National Bowel Cancer Screening Program (NBCSP) 50–74 target age group) and an estimated 4,129 will die from bowel cancer (AIHW 2018). However, deaths from bowel cancer are likely to be underestimated (ABS 2016). It is estimated that, in 2018, bowel cancer will be the third most commonly diagnosed cancer in Australia (after breast and prostate cancer).

Several randomised controlled trials have shown that bowel cancer mortality could be reduced by 15%–33% through regular screening, using an immunochemical faecal occult blood test (iFOBT) to detect bowel cancers earlier, before they cause symptoms (Hardcastle et al. 1996; Kewenter et al. 1994; 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 bowel cancer screening program was undertaken 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 iFOBT kits, for the Australian population aged over 50 (CCA & ACN 2005). These guidelines have recently been revised but support the same screening method (CCACCGWP 2017).

In August 2006, the NBCSP started screening people using iFOBT kits (Box 1.1). The Program's goal is to reduce morbidity and mortality from bowel cancer by actively recruiting and screening the target population for early detection or prevention of the disease.

Box 1.1: How the National Bowel Cancer Screening Program works

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

People 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 when they reach one of the target ages, and are sent an invitation pack containing an iFOBT 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. From 2019, the government-funded NBCSP will offer all Australians aged 50–74 bowel screening every 2 years, consistent with the clinical guidelines endorsed by the NHMRC (CCACCGWP 2017).

Population screening programs are aimed at the asymptomatic population; however, 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. Steps to limit invitations to those who are asymptomatic and not under surveillance are currently being investigated.

(continued)

Box 1.1 (continued): How the National Bowel Cancer Screening Program works

Once an eligible person completes their iFOBT, they post it to the program's pathology laboratory for analysis. Results are sent to the participant, his or her nominated general practitioner (GP) and the NBCSP register. Participants with a positive result, indicating blood in their faeces (which might be a sign of bowel cancer or other bowel abnormalities), are advised to consult their GP to discuss further diagnostic testing—in most cases, 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.

The Australian Institute of Health and Welfare (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 2018* (AIHW 2018), 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 in monitoring reports, mainly due to inadequate NBCSP reporting of colonoscopy and histopathology results. Hence, performance evaluation of some aspects of the NBCSP has been somewhat hindered. This, in turn, became the trigger for the previous 2014 report (AIHW 2014), which aimed to identify bowel cancer outcomes for 2006–2008 NBCSP invitees. This current report extends these outcome analyses for 2006–2010 invitees. See Appendix A for more information on the NBCSP.

Project objectives

This project's aim was to help 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 outcomes for bowel cancer—and all-cause mortality—between individuals invited into the NBCSP (between 2006 and 2010) and those aged 50–74 diagnosed with bowel cancer over the same time period who were not invited into the NBCSP. This is known as an intention-to-screen design (see Box 1.2), which is of most interest for program evaluation.

Further comparisons were also made between the 2006–2010 NBCSP invitees who participated, and the invitees who did not participate. To do so, we linked the data for 2006–2010 NBCSP invitees to jurisdictional cancer registry data and national deaths data—the latter through the National Death Index (NDI).

Box 1.2: Report terminology

Key terms used in this report are explained here. Further definitions are in the Glossary.

Down-staging: 'Down-staging' of cancers in a group exposed to a particular treatment is said to occur if cancers diagnosed in that group are, on average, at a less-advanced stage (see Box 1.3) than those diagnosed in a similar group of people not exposed to the treatment. As cancers diagnosed at a less-advanced stage generally have better morbidity and mortality outcomes than those at a more-advanced stage, down-staging can be assumed to be an improvement in prognosis for those people.

(continued)

Box 1.2 (continued): Report terminology

Intention-to-screen analysis: In screening intervention trials, patient outcomes are analysed according to the group to which subjects were randomised, irrespective of whether those in the screening group (the 2006–2010 NBCSP invitee study group) and the control group participated in the screening. This principle is important as it ensures that randomisation is preserved, thus maintaining an equal distribution of important factors that may influence the outcome in both groups. Using intention-to-screen analysis also reflects more closely the population benefit that can be expected, given participation rates are likely to be met in practice (Barratt et al. 2002).

Interval cancer: A bowel cancer 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.

Invitation: A NBCSP iFOBT screening kit is sent to those turning a target age (see Box 1.1).

Non-responder: A person sent an invitation as part of the 2006–2010 NBCSP study group who did not return the screening kit for analysis.

Participation: Occurs when an NBCSP invitee returns a completed iFOBT kit for analysis, regardless of its screening result.

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

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

Overall, there were four project objectives for this linkage project:

Primary objectives

1. *Describe differences in bowel cancer and all-cause mortality between 2006–2010 bowel cancer diagnoses in those invited to screen and those aged 50–74 who were not invited into the NBCSP.*
   Even though there were only a few years between the NBCSP invitations analysed in this project and the latest available outcome data, it would be of great value to see if the available data showed any differences in bowel cancer and all-cause mortality between those invited and not invited into the NBCSP.
2. *Describe differences in bowel cancer summary stage (see Box 1.3) in those whose bowel cancer was diagnosed after a 2006–2010 NBCSP invitation, compared with those aged 50–74 who were not invited into the NBCSP.*
   It was hypothesised that bowel cancers diagnosed in people invited into the NBCSP would be, on average, less advanced than those diagnosed in people of a similar age who were not invited to screen. This is referred to as ‘down-staging’ (see Box 1.2).

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 the characteristics of interval bowel cancers and screen-detected cancers differed.

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 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 harms (including psychological) are minimised from incorrect screening test results.

Box 1.3: What is bowel cancer stage, and why is it analysed?

Bowel cancer summary stage at first presentation (referred to as 'summary stage' in this report) refers to the extent, or spread, of cancer when diagnosed. 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 (Morris et al. 2007; O'Connell et al. 2004).

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) used this approach; it was also used in the previous 2014 AIHW outcomes report (AIHW 2014). Thus, stage analyses are used in this study, as well as mortality analyses, to provide more detail and explanation.

In this report, bowel cancer staging data were based on a 'summary stage at first presentation' system. (See Appendix A for more 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 describes the study group details after the data linkages. Chapter 4 outlines the findings against Objectives 1–4 for this project. 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.

Further 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 2006–2010 (Box 2.1) with two other data sets—a population-based data set of bowel cancer diagnoses, and national deaths information—in order to improve information on bowel cancer outcomes for those NBCSP invitees. A separate collection of bowel cancer diagnoses in those of similar age who were not invited in 2006–2010 was also created with these data sets.

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

Box 2.1: Why were those invited to screen in 2006–2010 chosen for this report?

There were two main reasons for setting the NBCSP study group for this project to those invited in 2006–2010:

- 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 a person notices symptoms. To compare outcomes (including by bowel cancer summary stage) in those invited and not invited, enough time must have elapsed for symptoms to emerge and cancers to be detected in the not-invited (and interval) population.
- Further, data on cancer incidence and mortality are not available until several years after those events have occurred. The use of invitations from 2006–2010 optimised the outcome data available for linkage and analysis.

NBCSP invitee study group

The invitee study group used were those invited between 1 August 2006 (the start of the NBCSP) and 31 December 2010. Within this time period, the eligible NBCSP invitee population consisted of those turning 55 and 65, with 50-year-olds also invited from 1 July 2008. (See Table A1, Appendix A, for NBCSP target population changes.)

As the NBCSP invitee study group chosen were those invited in the first 4 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); this will be more common 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 (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, or ICD-10: C18.0–C20.9) 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 eight jurisdictions were merged to form a ‘national’ bowel cancer diagnosis data set.

Using bowel cancer information directly from jurisdictional registries was preferred to using the AIHW's Australian Cancer Database (ACD) as, at the time of the project, the data registries held on bowel cancer diagnoses were more recent than ACD data. Further, extra fields were also requested for the bowel cancer diagnoses, such as any bowel cancer staging data that individual jurisdictions may collect; these are not currently contained in the ACD. Bowel cancer staging data 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 (Figure 2.1). 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.

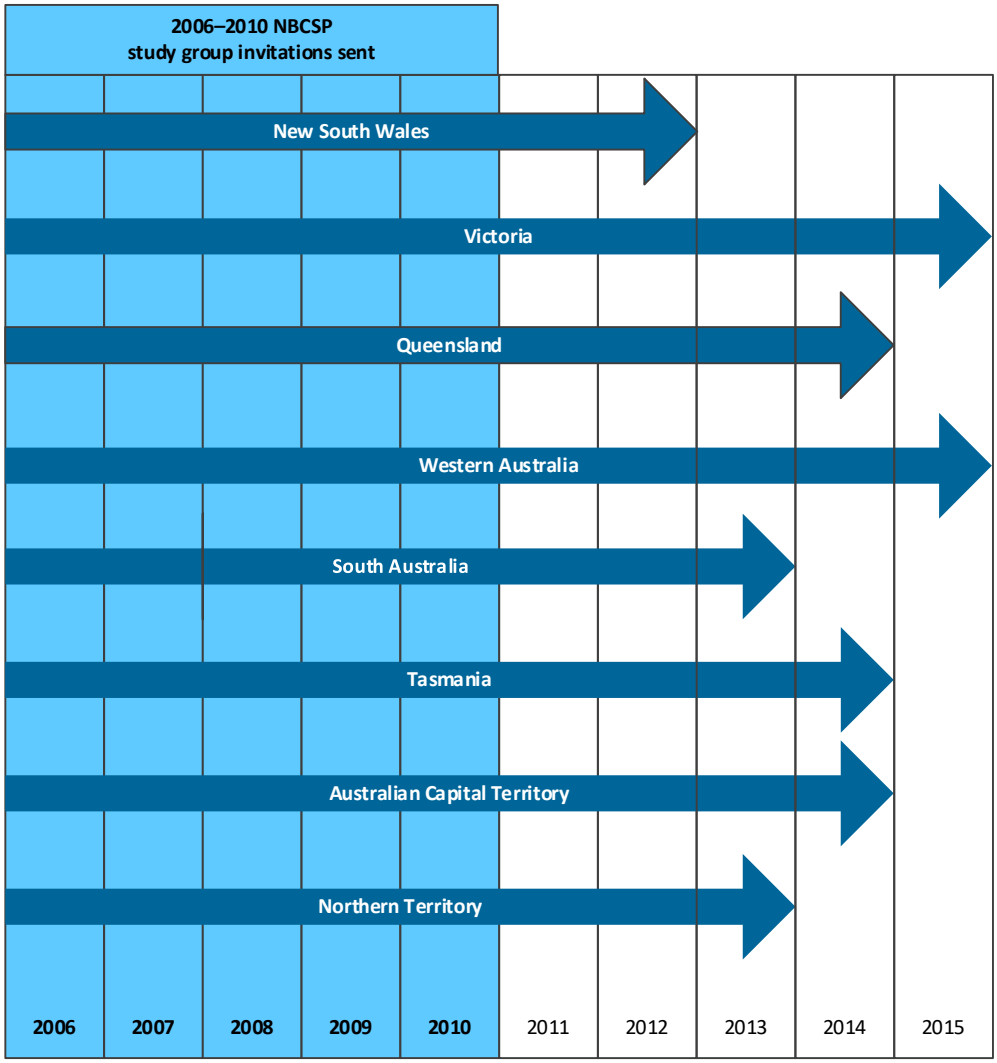


Figure 2.1: Calendar years of bowel cancer diagnoses available for this project, by jurisdiction

National deaths data

The NDI is a database of all deaths in Australia since 1980. It 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. The state and territory registrars of births, deaths and marriages supply these data monthly. 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 available only up to 31 December 2015. Death from bowel cancer was considered to be any with an ICD-10 code of C18.0–C20.9—plus C26.0 (Malignant neoplasm of the intestinal tract, part unspecified), which many bowel cancer deaths are coded as in Australia (ABS 2016). All-cause deaths were any deaths recorded, regardless of the underlying cause.

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

Methods

Ethics approvals

To access 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) to extract 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 further in this section.

Data linkage phase

The AIHW Data Linkage Unit performed probabilistic data linkages between the NBCSP, jurisdictional bowel cancer diagnosis, and NDI data sets. The AIHW Cancer and Screening Unit analysed the resulting linked and de-identified data (Figure 2.2). 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.

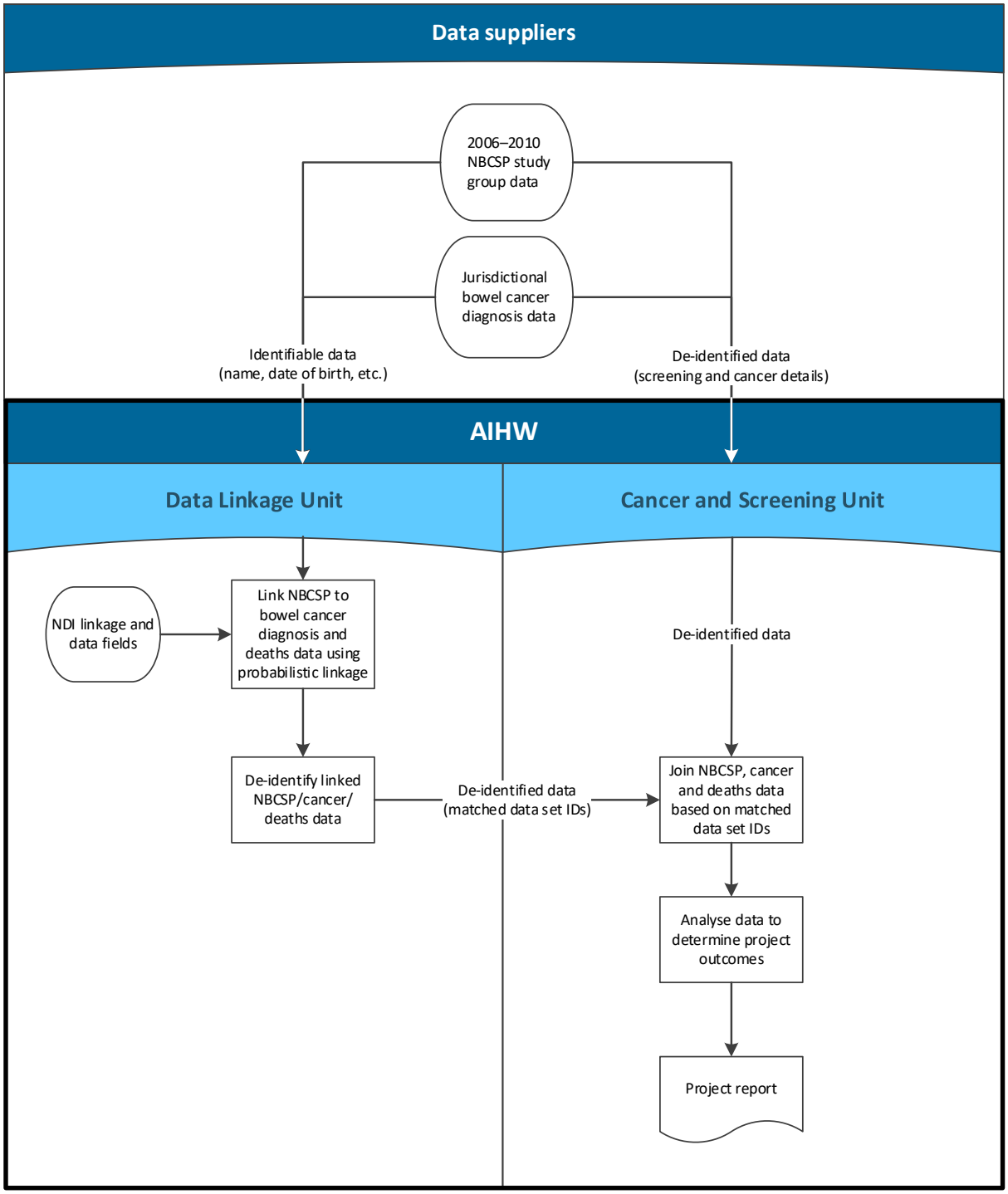


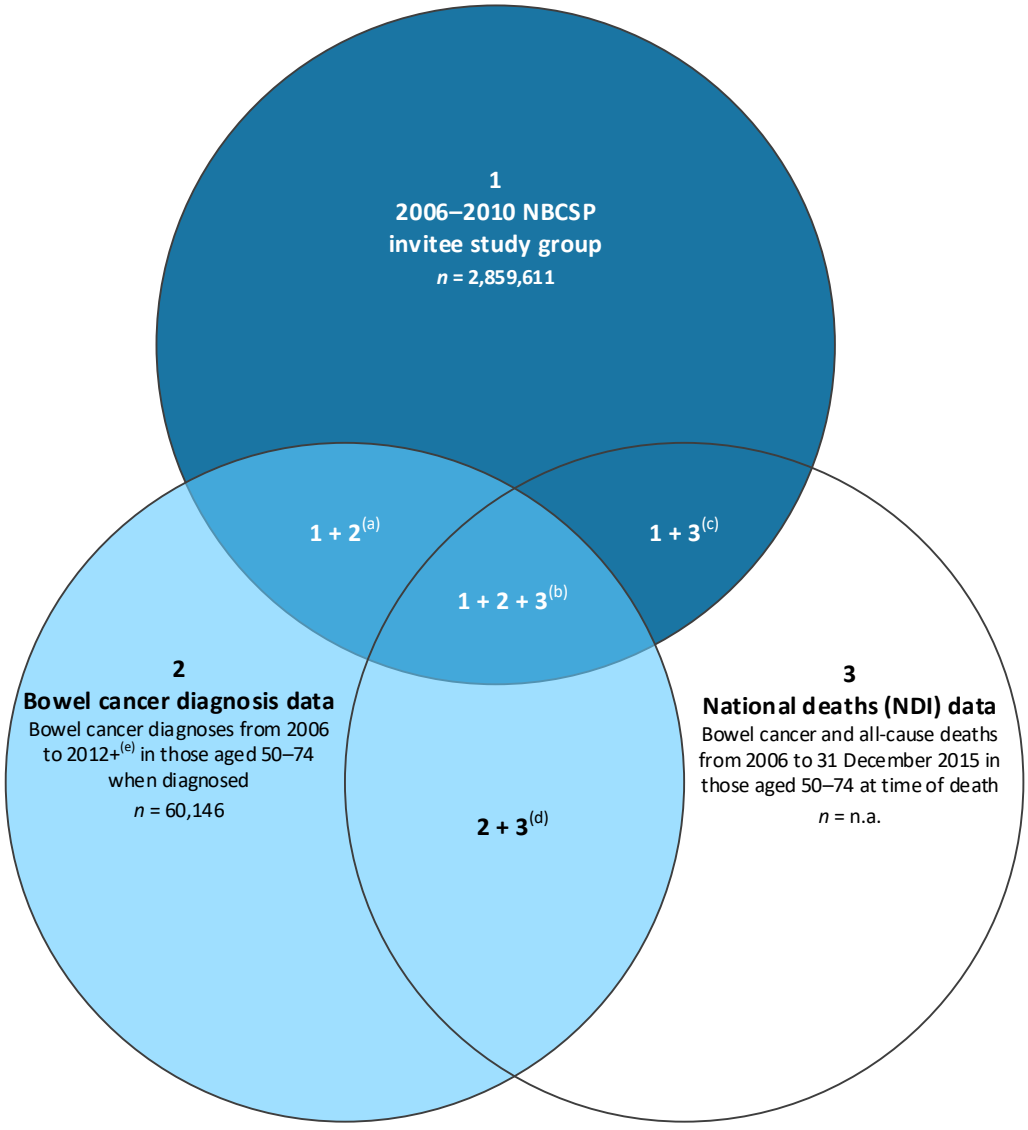
Figure 2.2: Data flow in this project

The linkage process involved creating record pairs by matching records from one data set with records from another data set, 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 recognised when interpreting the results.

Linkage of the three data sources

The linkage across the three project data sources is depicted in Figure 2.3.



(a) Those in the 2006–2010 NBCSP invitee study group with a bowel cancer diagnosis, but no bowel cancer death link (*n* = 16,784).

(b) Those in the 2006–2010 NBCSP invitee study group with a bowel cancer diagnosis and bowel cancer death link (*n* = 4,683). There were 2,301 other matches to non-bowel cancer deaths.

(c) Those in the 2006–2010 NBCSP invitee study group with 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* = 1,683). There were 110,261 matches to non-bowel cancer deaths.

(d) Bowel cancers diagnosed 2006–2012+(e) in those aged 50–74 who also had a bowel cancer death link (*n* = 9,582). There were 3,104 matches to non-bowel cancer deaths.

(e) The end-point of bowel cancer diagnosis data differed by jurisdiction, ranging from 2012 to 2015.

Figure 2.3: Linkage outcomes across the three project data sources

For the ‘NBCSP invitee study group to bowel cancer diagnosis’ data linkage, 23,768 presumed correct bowel cancer diagnosis matches to invitees were made. However, 8,314 were then excluded from the analyses due to diagnoses before invitation (5,820), or more than 2 years after a negative screen (2,494).

The linkages using the NDI data set resulted in 15,948 presumed correct bowel cancer death matches—6,366 to NBCSP invitees, and 9,582 to non-invitees (see footnotes (b), (c) and (d) in Figure 2.3). However, 3,302 were then excluded from analyses as they were deaths in those diagnosed before invitation (1,619) or a bowel cancer death in those with no bowel cancer diagnosis (1,683, due to NDI data being more recent than the diagnosis data).

Regarding all-cause deaths, there were 130,697 presumed correct matches—118,011 to NBCSP invitees, and 12,686 to non-invitees. Of these, 113,991 matches to NBCSP invitees were excluded from analyses (111,944 were in those invited but without a bowel cancer diagnosis, and 2,047 were all-cause deaths in those diagnosed before invitation.

After linkage across the three data sets, it was possible to summarise the bowel cancer diagnoses into four subgroups (with bowel cancer and all-cause death information included where appropriate): screen-detected cancers, interval cancers, non-responder cancers and never-invited cancers. These are now described more fully.

2006–2010 NBCSP invitee study group: These three subgroups are contained within the ‘1 + 2’ and ‘1 + 2 + 3’ intersections in Figure 2.3:

1. Screen-detected cancers

These were bowel cancers diagnosed in individuals following NBCSP invitation and subsequent positive iFOBT. This subgroup included those who were invited to participate when they turned one of the target ages in 2006–2010. 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 used because that is the recommended rescreening interval (CCA & ACN 2005; CCACCGWP 2017).

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 2.3.

4. Never-invited cancers

These were bowel cancers diagnosed in individuals aged 50–74 who were not invited to participate in the NBCSP in 2006–2010. As can be seen in Figure 2.3, 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, a 50th, 55th or 65th) in that time. As jurisdictions included bowel cancer diagnosis data later than 2010 (Figure 2.1), and only NBCSP invitees from 2006 to 2010 were linked to these diagnosis data, individuals aged 50, 55 or 65 at a time of diagnosis *after* 2010 may be due to invitation and participation in the NBCSP from 2011 onwards. These 6,765 individuals diagnosed 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 comprised those reaching their 50th, 55th or 65th birthday in 2006–2010, a higher proportion of diagnoses in this group were at those ages, or within a year or two afterwards. Further, as mentioned earlier, later diagnoses in the never-invited group who were at a screening target age when diagnosed were excluded. These effects gave a different age structure for the NBCSP invitee group compared with the never-invited group (Table 2.1). Differences in age at diagnosis between groups were adjusted for in relevant analyses.

Table 2.1: Age-at-diagnosis differences for 2006–2010 NBCSP invitee and never-invited groups

	Age at diagnosis (years)									
	50	51–54	55	56–64	65	66–69	70–74			
Group	Proportion of diagnoses (%)							Mean	Median	Total number
NBCSP invitee	2.7	7.6	8.9	28.8	13.4	27.5	11.1	62.2	65	15,454
Never-invited	0.9	5.3	0.6	35.5	1.1	14.5	42.2	66.2	68	36,378
Total										**51,832**

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 four jurisdictions were found to have suitable cancer staging data for the study time period—New South Wales, Victoria, Tasmania and the Australian Capital Territory. These jurisdictions provided about 60% 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, those aged 50–54, 55–59, 60–64, 65–69 and 70–74), which, while incorporating the NBCSP target ages, also included ages up to 74.

Statistical analyses

Each project objective could be considered a separate analysis, as each used a different subgroup of the overall linked data set, as well as different methods. They are therefore discussed individually here.

Objective 1 data and methods

Describe differences in bowel cancer and all-cause mortality between 2006–2010 bowel cancer diagnoses in those invited to screen and those aged 50–74 who were not invited into the NBCSP.

Those diagnosed with bowel cancer were followed up until 31 December 2015 (the latest date that cause of death information was available in the NDI data set when data linkage was undertaken). Bowel cancers that linked to participants within the 2006–2010 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 of cancers was compared with bowel cancers in those aged 50–74 at the time of diagnosis that did not link to a 2006–2010 NBCSP invitee—the 'never-invited' bowel cancer study group. This first comparison was considered an intention-to-screen analysis but comparisons between mortality outcomes for the NBCSP subgroups were also made.

Time from diagnosis to death due to bowel cancer (ICD-10: C18.0–C20.9, plus C26.0 recorded as the underlying cause of death) was the first 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 2015). Therefore, the groups compared in the intention-to-screen analysis were:

- NBCSP invitees who had been diagnosed with bowel cancer (3,064 bowel cancer deaths and 12,390 with follow-up ended). This group was further divided into screen-detected, interval and non-responder subgroups in a secondary mortality analysis
- those aged 50–74 when diagnosed with bowel cancer who had not been a 2006–2010 NBCSP invitee (9,582 bowel cancer deaths and 26,796 with follow-up ended).

An 'all cause of death' comparison was also made to investigate if there were differences between the two groups in relation to deaths from any cause. There were:

- NBCSP invitees who had been diagnosed with bowel cancer (4,020 all-cause deaths and 11,434 with follow-up ended). This group was further divided into screen-detected, interval and non-responder subgroups in a secondary mortality analysis
- those aged 50–74 when diagnosed with bowel cancer who had not been a 2006–2010 NBCSP invitee (12,686 all-cause deaths and 23,692 with follow-up ended).

Hazard ratios were calculated in this objective. They are generated from 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 indicates the strength of the

association and can help decide whether the characteristic of interest could be a cause for an event (for example, death from bowel cancer after a bowel cancer diagnosis). Factors such as individual screening or testing behaviours might affect the survival analyses (see the following subsection 'A note on lead-time bias').

Ninety-five per cent (95%) confidence intervals are also presented to indicate the statistical precision and significance. The result is interpreted as having a statistically significant impact (that is, not due to chance) if the interval does not cross the value of 1 (Kalbfleisch & Prentice 1980).

A note on lead-time bias

Cancer survival is based on the time between cancer diagnosis and death; it is therefore sensitive to anything that affects the timing of either diagnosis or death. 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 having an impact on 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 (de Vries et al. 2010; Duffy et al. 2008; Gigerenzer et al. 2008). Asymptomatic cancers that can be diagnosed 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 to evaluate 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 began (in 2006) for its impact to affect longer term mortality and survival rates, especially as biennial screening was not in place until 2019.

Therefore, to factor in lead-time bias in this study, further 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 in those whose bowel cancer was detected after a 2006–2010 invitation to screen in the NBCSP, compared with those aged 50–74 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 four jurisdictions supplying staging data that could be combined into a summary stage system (New South Wales, Victoria, Tasmania and the Australian Capital Territory). There were small differences in the years of cancer diagnosis data available from the four jurisdictions for this report. New South Wales had bowel cancer diagnoses from 2006 to the end of 2012 available, Tasmania and the Australian Capital Territory had diagnoses up until the end of 2014, and Victoria up until the end of 2015. (See 'Jurisdictional cancer registry data', Appendix A, for more information.)

This analysis had a main intention-to-screen component, with further analyses between the NBCSP invitee subgroups. For the intention-to-screen analysis, the 9,132 participants within the 2006–2010 NBCSP invitee study group diagnosed with bowel cancer from those jurisdictions 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 20,738 people aged 50–74 at the time of bowel cancer diagnosis who did not receive a 2006–2010 NBCSP invitation—the 'never-invited' bowel cancer group.

As a second analysis, the NBCSP invitee group was further divided into screen-detected (2,478) and non-responder (6,270) subgroups, for comparison.

Logistic regression involves calculating the probability of the event's occurring for varying levels of characteristics in a study population. It is 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 indicate the statistical precision and significance of the result.

Odds ratios compare the odds of a specified event's 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 a reduced risk for those with the characteristic.

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 4,242 people in the screen-detected subgroup, and 646 in the interval cancer subgroup.

However, for some of the characteristics under investigation, their total counts were lower (see Table 3.1). This was because not all cases had valid socioeconomic status, remoteness, morphology and summary stage data available.

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

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

Objective 4 data and methods

Describe the positive predictive value and negative predictive value of the screening test.

This objective necessarily involved using data only for members of the 2006–2010 NBCSP invitee study group who participated (that is, the screen-detected and interval cancer subgroups). As the recommended iFOBT rescreening interval for bowel cancer is 2 years (CCA & ACN 2005; CCACCGWP 2017), this time period was used as a cut-off for screen-detected cancer diagnoses. 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, or if, a 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 data for the 2006–2010 NBCSP invitee study group to bowel cancer diagnosis data found that 15,454 cases of bowel cancer were diagnosed in individuals invited to participate in the NBCSP (Table 3.1). Of these, 4,242 (27%) were screen-detected (see Box 3.1), 646 (4%) were interval cancers and the remaining 10,566 (68%) were diagnosed in individuals who were invited but did not participate. There were an extra 5,820 diagnoses made before a person's invitation, and 2,494 bowel cancers were diagnosed in the interval group more than 2 years after their last screening test; as discussed in the Methods section in Chapter 2, these diagnoses were excluded from further analysis.

Box 3.1: 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 1,119 bowel cancers confirmed in the 2006–2010 invitee study group following positive screening tests. After linkage to the bowel cancer diagnosis data set in this project, a total of 4,242 bowel cancer diagnoses followed a positive screening test in this group. Therefore, the linkage identified 3,123 additional bowel cancer diagnoses in this group that had not been previously attributed to NBCSP participation.

Among individuals aged 50–74 who had not been invited to participate (the never-invited group), 36,378 cancer cases were diagnosed.

After the exclusions mentioned, the total number of bowel cancers in the study was 51,832.

Table 3.1: Characteristics of those in the study groups who were diagnosed with bowel cancer

	2006–2010 NBCSP invitees											
	Screen-detected		Interval		Non-responder		*Total*		Never-invited		Total	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	***No.***	***%***	**No.**	**%**	**No.**	**%**
Sex												
Male	2,573	60.7	324	50.2	6,439	60.9	*9,336*	*60.4*	21,590	59.3	30,926	59.7
Female	1,669	39.3	322	49.8	4,127	39.1	*6,118*	*39.6*	14,788	40.7	20,906	40.3
Age at diagnosis[(a)]												
50–54	402	9.5	64	9.9	1,124	10.6	*1,590*	*10.3*	2,237	6.1	3,827	7.4
55–59	1,242	29.3	177	27.4	2,924	27.7	*4,343*	*28.1*	3,729	10.2	8,072	15.6
60–64	337	7.9	33	5.1	1,113	10.5	*1,483*	*9.6*	9,380	25.8	10,863	21.0
65–69	1,991	46.9	365	56.5	3,970	37.6	*6,326*	*40.9*	5,667	15.6	11,993	23.1
70–74	270	6.4	7	1.1	1,435	13.6	*1,712*	*11.1*	15,365	42.2	17,077	32.9
Socioeconomic status[(b)]												
1 (most disadvantaged)	927	22.1	129	20.3	2,337	22.4	*3,393*	*22.2*	8,537	23.6	11,930	23.2
2	893	21.3	135	21.2	2,195	21.0	*3,223*	*21.1*	8,217	22.7	11,440	22.2
3	840	20.0	133	20.9	2,151	20.6	*3,124*	*20.4*	7,300	20.1	10,424	20.2
4	818	19.5	111	17.4	2,050	19.6	*2,979*	*19.5*	6,293	17.4	9,272	18.0
5 (least disadvantaged)	717	17.1	129	20.3	1,715	16.4	*2,561*	*16.8*	5,897	16.3	8,458	16.4
Remoteness area[(b)]												
Major cities	2,605	62.1	414	65.0	6,924	66.3	*9,943*	*65.1*	22,988	63.4	32,931	63.9
Inner regional	998	23.8	163	25.6	2,213	21.2	*3,374*	*22.1*	8,466	23.4	11,840	23.0
Outer regional	555	13.2	62	9.7	1,169	11.2	*1,786*	*11.7*	4,132	11.4	5,918	11.5
Remote	62	1.5	5	0.8	186	1.8	*253*	*1.7*	505	1.4	758	1.5
Very remote	21	0.5	2	0.3	73	0.7	*97*	*0.6*	178	0.5	275	0.5

(continued)

Table 3.1 (continued): Characteristics of those in the study groups who were diagnosed with bowel cancer

	2006–2010 NBCSP invitees											
	Screen-detected		Interval		Non-responder		*Total*		Never-invited		Total	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	***No.***	***%***	**No.**	**%**	**No.**	**%**
Cancer site[(c)]												
Right-sided colon	1,070	25.2	307	47.5	3,268	30.9	*4,645*	*30.1*	12,193	33.5	16,838	32.5
Left-sided colon	1,947	45.9	158	24.5	3,698	35.0	*5,803*	*37.6*	12,753	35.1	18,556	35.8
Rectum	1,090	25.7	156	24.1	3,304	31.3	*4,550*	*29.4*	10,278	28.3	14,828	28.6
Colon, n.o.s.	135	3.2	25	3.9	296	2.8	*456*	*3.0*	1,154	3.2	1,610	3.1
Summary stage[(d)]												
Localised	1,098	44.3	125	32.6	1,520	24.2	*2,743*	*30.0*	5,786	27.9	8,529	28.6
Regionalised	987	39.8	145	37.8	2,839	45.3	*3,971*	*43.5*	9,272	44.7	13,243	44.3
Distant	184	7.4	60	15.6	1,315	21.0	*1,559*	*17.1*	3,931	19.0	5,490	18.4
Unknown	209	8.4	54	14.1	596	9.5	*859*	*9.4*	1,749	8.4	2,608	8.7
Morphology[(b)(e)]												
Adenocarcinomas	4,046	97.0	571	88.4	9,939	94.1	*14,556*	*94.6*	34,294	94.3	48,850	94.4
Other types	127	3.0	75	11.6	627	5.9	*829*	*5.4*	2,084	5.7	2,913	5.6
Total	**4,242**		**646**		**10,566**		**15,454**		**36,378**		**51,832**	

n.o.s. = not otherwise specified.

(a) The 2006–2010 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

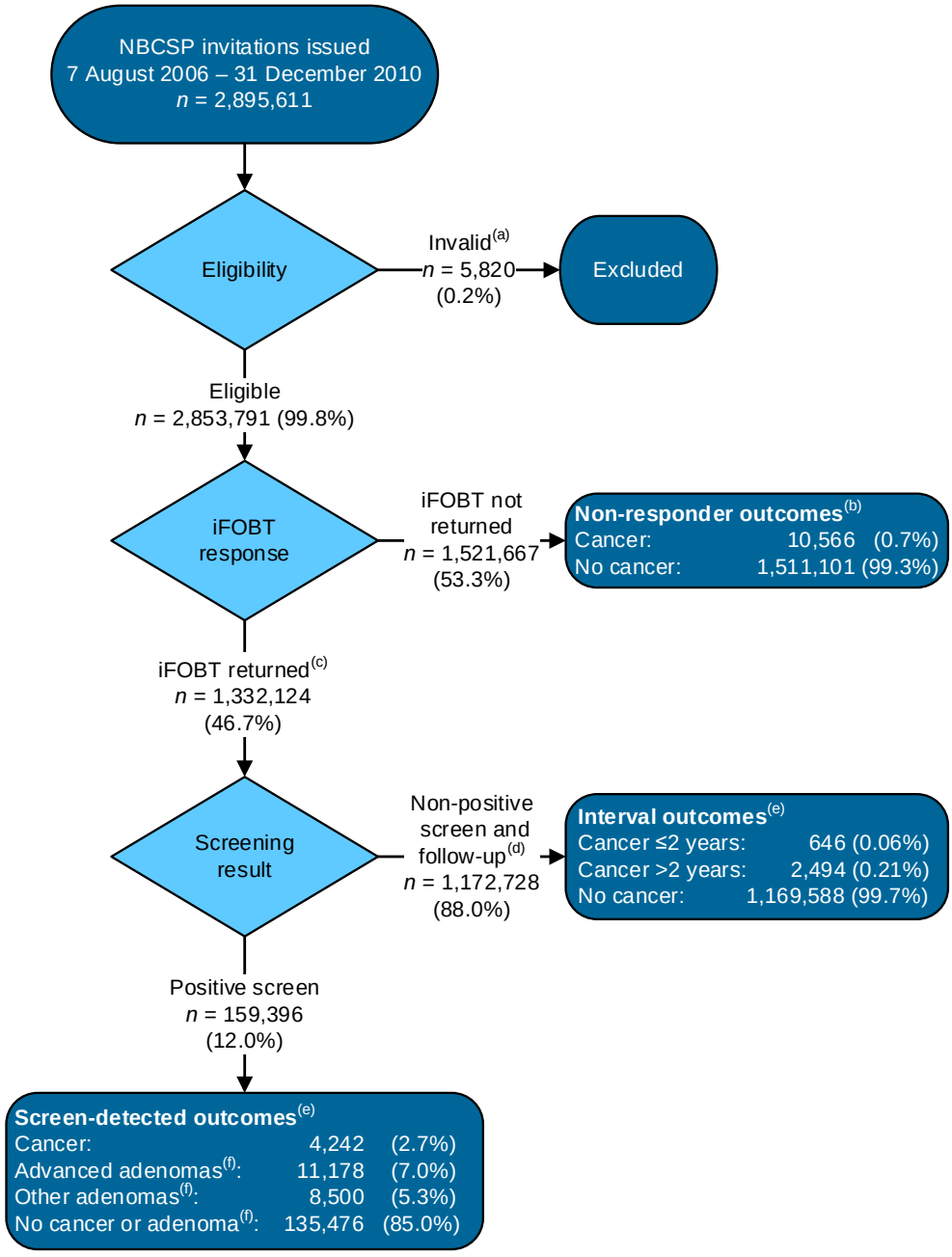
(b) Those with missing data for this characteristic were excluded. Therefore, the sum of numbers in this characteristic does not equal the total (308, 111 and 69 diagnoses were missing socioeconomic status, remoteness area, and morphology data, respectively).

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

(d) Only summary stage data for New South Wales, Victoria, Tasmania and the Australian Capital Territory were used. Therefore, the sum of numbers in this characteristic does not equal the total (21,962 diagnoses from the other jurisdictions were missing summary stage data).

(e) Morphology groupings based on International Agency for Research on Cancer (IARC) international rules for multiple primary cancers, using International Classification of Diseases for Oncology, Third edition (ICD-O-3) (IARC 2004). See Appendix A for further information.

Figure 3.1 presents cancer and adenoma (pre-cancerous lesion) outcomes for the three subgroups (that is, screen-detected, interval and non-responders) of the 2006–2010 NBCSP invitee group only, based on their progression through the NBCSP screening pathway.



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

(b) Bowel cancer diagnoses in those who did not screen by 2016 (non-responders), using available cancer registry data (Figure 2.1).

(c) Includes all screen results up until 2016.

(d) Includes both negative and inconclusive screening results.

(e) Bowel cancer diagnoses, using available cancer registry data (Figure 2.1), by length of time between screen and diagnosis. Positive rescreens to 2016 are included but diagnosis data ends at 2016 so cancer diagnosis data may be incomplete.

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

Figure 3.1: Cancer and adenoma outcomes for the 2006–2010 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 3.1).

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

Bowel cancer differences

Cancer type

Adenocarcinomas (the malignant evolution of previously benign adenomas) represented over 94% of bowel cancers diagnosed for each subgroup, except for interval cancers, where they accounted for 88% (Table 3.1).

Cancer site

The specific site of cancers within the bowel is of interest as it is known to affect mortality risk: left-sided cancers have a lower mortality rate than right-sided 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 (46%) than in other subgroups (25%–35%), and the proportion of right-sided cancers was higher in the interval subgroup (48%) than in other subgroups (25%–34%) (Table 3.1). The proportions across the bowel cancer sites were generally 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 38% in those aged 69–74 (Table 3.2). Conversely, left-sided and rectal cancer proportions decreased with age.

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

Table 3.2: Bowel cancer site[(a)] by age group and sex

	Right-sided	Left-sided	Rectum	Colon, n.o.s.	Total	Right-sided	Left-sided	Rectum	Colon, n.o.s.
	No.					%			
Age group at diagnosis[(b)]									
50–54	943	1,447	1,344	93	3,827	24.6	37.8	35.1	2.4
55–59	2,086	3,078	2,671	237	8,072	25.8	38.1	33.1	2.9
60–64	3,186	3,929	3,447	301	10,863	29.3	36.2	31.7	2.8
65–69	4,066	4,317	3,216	394	11,993	33.9	36.0	26.8	3.3
70–74	6,557	5,785	4,150	585	17,077	38.4	33.9	24.3	3.4
Sex									
Men	8,509	11,552	9,913	952	30,926	27.5	37.4	32.1	3.1
Women	8,329	7,004	4,915	658	20,906	39.8	33.5	23.5	3.2
Total	**16,838**	**18,556**	**14,828**	**1,610**	**51,832**	**32.5**	**35.8**	**28.6**	**3.1**

n.o.s. = not otherwise specified.

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

(b) The 2006–2010 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

Summary stage

Of the 29,870 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; this difference was statistically significant ($\chi^2 = 31.4$, $P < 0.001$) (Table 3.1). This is investigated further in the 'Objective 2' section of Chapter 4.

Cancer site versus cancer stage

The relationship between cancer site and cancer stage was also examined (Table 3.3).

Table 3.3: 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.**					**%**			
					2006–2010 NBCSP invitee group				
Right-sided	731	1,373	503	157	2,764	26.4	49.7	18.2	5.7
Left-sided	1,029	1,481	548	266	3,324	31.0	44.6	16.5	8.0
Rectum	939	1,057	377	386	2,759	34.0	38.3	13.7	14.0
Colon, n.o.s.	44	60	131	50	285	15.4	21.1	46.0	17.5
All sites	*2,743*	*3,971*	*1,559*	*859*	*9,132*	*30.0*	*43.5*	*17.1*	*9.4*
					Never-invited group				
Right-sided	1,743	3,515	1,306	369	6,933	25.1	50.7	18.8	5.3
Left-sided	1,968	3,245	1,373	453	7,039	28.0	46.1	19.5	6.4
Rectum	1,948	2,386	957	783	6,074	32.1	39.3	15.8	12.9
Colon, n.o.s.	127	126	295	144	692	18.4	18.2	42.6	20.8
All sites	*5,786*	*9,272*	*3,931*	*1,749*	*20,738*	*27.9*	*44.7*	*19.0*	*8.4*
					All study groups				
Right-sided	2,474	4,888	1,809	526	9,697	25.5	50.4	18.7	5.4
Left-sided	2,997	4,726	1,921	719	10,363	28.9	45.6	18.5	6.9
Rectum	2,887	3,443	1,334	1,169	8,833	32.7	39.0	15.1	13.2
Colon, n.o.s.	171	186	426	194	977	17.5	19.0	43.6	19.9
All sites	**8,529**	**13,243**	**5,490**	**2,608**	**29,870**	**28.6**	**44.3**	**18.4**	**8.7**

n.o.s. = 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 (17%), compared with the never-invited group (19%).

4 Results

Objective 1

The first objective was to describe any differences in bowel cancer and all-cause mortality between 2006–2010 bowel cancer diagnoses in those invited to screen and those aged 50–74 who were not invited into the NBCSP.

Rationale	There would be great value in knowing if there were differences in bowel cancer and all-cause mortality (after a bowel cancer diagnosis) between those invited to screen in 2006–2010 and those aged 50–74 who were not invited into the NBCSP.
Data used in meeting this objective	In meeting this objective, the following three types of data sources were used: the NBCSP invitee study group, bowel cancer diagnosis data, and national deaths data. Time from diagnosis to death due to bowel cancer was the main 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 2015, which was the latest date deaths information were available in the NDI data set). All-cause mortality was also analysed, where time from diagnosis to death from any cause was measured. See the Methods section in Chapter 2 for more information.
Analyses	This objective included an intention-to-screen bowel cancer and all-cause mortality analyses, 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, which show how much higher the probability of death's occurring in one group is than in another 'reference' group.
Guide to interpretation	Re-analysis with more years of outcome data may help mitigate potential lead-time bias issues.

Key findings

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

- of the 15,454 people in the NBCSP invitee group with a bowel cancer diagnosis
  - 3,064 (19.8%) had died of bowel cancer before 2016
  - 4,020 (26.0%) had died from any cause by the same date
- of the 36,378 never-invited people with a bowel cancer diagnosis
  - 9,582 (26.3%) had died of bowel cancer before 2016
  - 12,686 (34.9%) had died from any cause by the same date.

- Using proportional hazards regression, the risk of death from bowel cancer was 28% 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 (13% higher risk in the never-invited group). Lastly, the risk of death from any cause was a statistically significant 7% higher for 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 2 and 3 times the risk of death, respectively) relative to the screen-detected group—after adjusting for age group at diagnosis, and cancer site and type. After correcting for potential lead-time bias, the risk was 50% higher for the interval subgroup and over 2 times the risk in the non-responder group
- the risk of death from any cause was 69% higher for non-responders when compared with the screen-detected group. This increase in risk was mainly due to the difference in bowel cancer mortality, as the risk of death from other causes than bowel cancer was not significantly different between the two groups. Lastly, there was not a statistically significant difference between the interval and screen-detected groups for all-cause mortality risk.

Of all bowel cancers diagnosed there was a higher risk of bowel cancer death in:

- men; people with the most socioeconomic disadvantage; people outside *Major cities*; and people with more-advanced summary stage cancers, right-sided or 'colon, not otherwise specified' cancers, or non-adenocarcinoma cancers.

Results

Intention-to-screen bowel cancer mortality analysis

The first comparison of bowel cancer mortality outcomes was between people in the NBCSP invitee group and the never-invited group, in an intention-to-screen bowel cancer mortality analysis. Of the 36,378 never-invited people with a bowel cancer diagnosis, 9,582 (26.3%) had died of bowel cancer by 31 December 2015 (Table 4.1). Of the 15,454 people in the NBCSP invitee group with a bowel cancer diagnosis, 3,064 (19.8%) had died of bowel cancer by the same date. The mean follow-up time to bowel cancer death for all diagnoses was 21.3 months (range 0–117.8 months, standard deviation 19.0 months).

Table 4.1: Cumulative bowel cancer deaths, by study group

			Bowel cancer deaths					
			Years since diagnosis					
Study group		Bowel cancer diagnoses	1	2	3	4	5	at 31/12/2015
NBCSP invitee	No.	15,454	1,192	1,936	2,449	2,753	2,922	3,064
	Proportion (%)		7.7	12.5	15.8	17.8	18.9	19.8
Never-invited	No.	36,378	3,809	6,302	7,802	8,641	9,105	9,582
	Proportion (%)		10.5	17.3	21.4	23.8	25.0	26.3

Note: Proportions indicate the percentage of those diagnosed with a bowel cancer who have died from bowel cancer by a particular time point from their diagnosis. See Table B1 for these data stratified by age group.

Intention-to-screen survival plots for bowel cancer mortality

The general logrank test statistic of $\chi^2 = 107.4$ with 1 degree of freedom ($P < 0.0001$) 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 4.1).

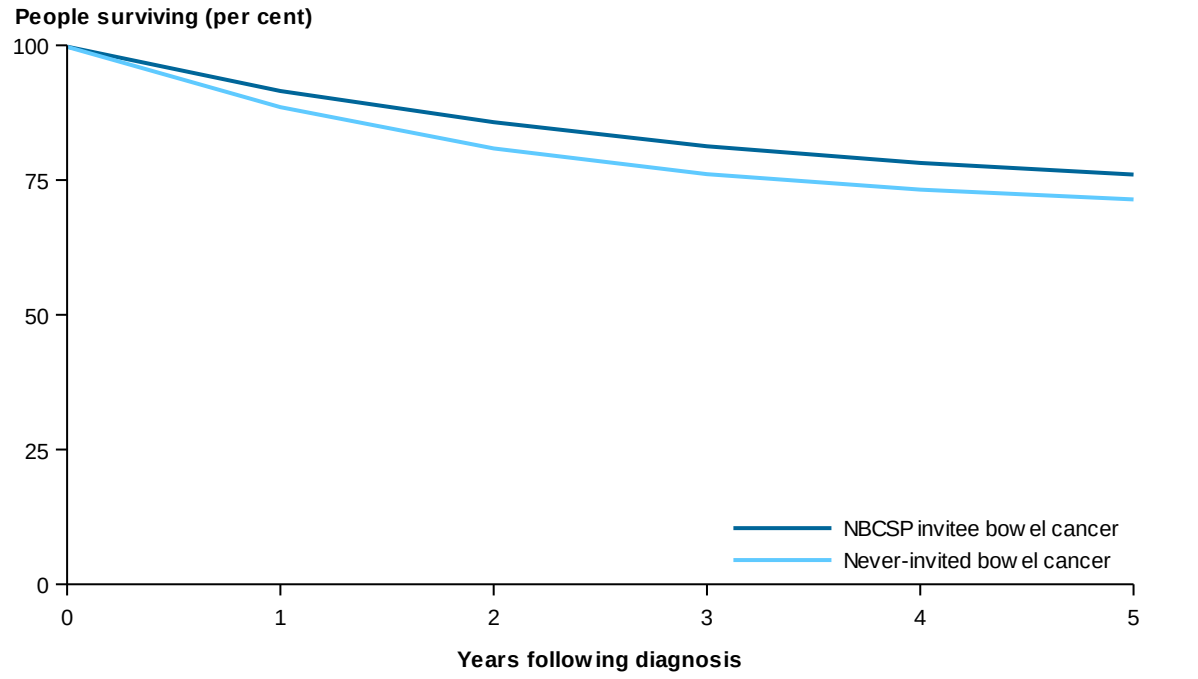


Figure 4.1: Bowel cancer mortality survival plots for the NBCSP invitee and never-invited groups

Intention-to-screen hazard ratios for bowel cancer mortality

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 4.2.

Table 4.2: Crude bowel cancer mortality hazard ratios for intention to screen[a]

Variable	Crude HR*	95% CI*	*P* value
Study group			
NBCSP invitee	1.0	. .	. .
Never-invited	1.24	1.19–1.29	<0.0001
Sex			
Men	1.0	. .	. .
Women	0.88	0.84–0.91	<0.0001
Age group at diagnosis[b]			
50–54	1.0	. .	. .
55–59	0.96	0.89–1.04	0.31
60–64	1.13	1.05–1.21	0.001
65–69	1.03	0.96–1.11	0.42
70–74	1.02	0.95–1.09	0.66
Socioeconomic status			
1 (most disadvantaged)	1.0	. .	. .
2	0.97	0.92–1.02	0.25
3	0.90	0.85–0.95	<0.0001
4	0.86	0.81–0.90	<0.0001
5 (least disadvantaged)	0.79	0.74–0.83	<0.0001
Unknown quintile	1.05	0.84–1.30	0.68
Remoteness area			
Major cities	1.0	. .	. .
Inner regional	1.11	1.06–1.16	<0.0001
Outer regional	1.11	1.05–1.17	0.0004
Remote and Very remote	1.21	1.06–1.37	0.004
Unknown remoteness area	1.25	0.89–1.75	0.19
Cancer site[c]			
Left-sided colon	1.0	. .	. .
Right-sided colon	1.13	1.08–1.17	<0.0001
Rectum	1.02	0.98–1.07	0.31
Colon, not otherwise specified	2.76	2.55–2.99	<0.0001
Summary stage[d]			
Localised	1.0	. .	. .
Regionalised	4.37	3.93–4.85	<0.0001
Distant	32.52	29.32–36.02	<0.0001
Unknown	6.81	6.01–7.71	<0.0001
Morphology[e]			
Adenocarcinomas	1.0	. .	. .
Other histological types	1.69	1.58–1.81	<0.0001

* HR = hazard ratio; CI = confidence interval.

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

(b) The 2006–2010 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, Victoria, 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 1.24, 95% CI: 1.19–1.29). Regression was then performed against several other explanatory variables to look for potential confounding variables.

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

Women had a lower risk of bowel cancer death (hazard ratio 0.88, 95% CI: 0.84–0.91). People with either right-sided (hazard ratio 1.13, 95% CI: 1.08–1.17) or 'colon, not otherwise specified' bowel cancers (hazard ratio 2.76, 95% CI: 2.55–2.99) 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 1.69, 95% CI: 1.58–1.81) compared with adenocarcinomas, and individuals with bowel cancers of more advanced summary stage—that is, regionalised and distant cancers (hazard ratio of 4.37 and 32.52, 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.

After adjusting for the statistically significant effects of sex, age group at diagnosis, remoteness area, socioeconomic group and bowel cancer site and type, the adjusted hazard ratio for the never-invited group was 1.28 (95% CI: 1.22–1.34) when compared with the invitee group. That is, after a bowel cancer diagnosis, the risk of death from bowel cancer by 31 December 2015 was 28% 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 (Brenner et al. 2011; Duffy et al. 2008) 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 1.13, 95% CI: 1.08–1.19).

Intention-to-screen all-cause cancer mortality analysis

All-cause mortality outcomes between people in the NBCSP invitee and the never-invited groups were then analysed. Of the 36,378 never-invited people with a bowel cancer diagnosis, 12,686 (34.9%) had died from any cause by 31 December 2015 (Table 4.3). Of the 15,454 people in the NBCSP invitee group with a bowel cancer diagnosis, 4,020 (26.0%) had died from any cause by the same date. The mean follow-up time to death for all diagnoses was 22.9 months (range 0–117.8 months, standard deviation 21.1 months).

Table 4.3: Cumulative all-cause deaths, by study group

			All deaths					
			Years since diagnosis					
Study group		Bowel cancer diagnoses	1	2	3	4	5	at 31/12/2015
NBCSP invitee	No.	15,454	1,535	2,455	3,088	3,508	3,757	4,020
	Proportion (%)		9.9	15.9	20.0	22.7	24.3	26.0
Never-invited	No.	36,378	4,927	8,014	9,950	11,118	11,808	12,686
	Proportion (%)		13.5	22.0	27.4	30.6	32.5	34.9

Note: Proportions indicate the percentage of those diagnosed with a bowel cancer who have died from any cause by a particular time point from their diagnosis. See Table B2 for these data stratified by age group.

Intention-to-screen hazard ratios for all-cause mortality

Investigation of explanatory variables using regression found the same variables were suitable for the all-cause mortality model as those used in the bowel cancer mortality analysis. That is, the unadjusted all-cause mortality hazard ratios for sex, age group, socioeconomic group, remoteness area, cancer site and morphology all had statistically significant differences.

After adjusting for these effects, the all-cause mortality analyses resulted in a hazard ratio of 1.07 (95% CI: 1.03–1.12), including lead-time adjustment for those who died from bowel cancer. This meant that the never-invited group had a 7% higher risk of death from any cause. When investigating the mortality risk from non-bowel cancer deaths only, there was not a statistically significant difference between these groups (hazard ratio 1.04, 95% CI: 0.96–1.13).

NBCSP invitee subgroup bowel cancer mortality analysis

The second comparison of bowel cancer mortality outcomes was between people in the NBCSP invitee subgroups (Table 4.4). Of the 4,242 NBCSP invitees with a screen-detected bowel cancer diagnosis, 407 (9.6%) had died of bowel cancer before 2016. By the same time, 142 (22.0%) of the 646 NBCSP invitees with an interval bowel cancer diagnosis had died of bowel cancer, as had 2,515 (23.8%) of the 10,566 non-responders with a bowel cancer diagnosis. The mean follow-up time to bowel cancer death for all NBCSP invitee diagnoses was 21.6 months (range 0–98.8 months, standard deviation 18.6 months).

Table 4.4: Cumulative bowel cancer deaths, by study subgroup

			Bowel cancer deaths					
			Years since diagnosis					
Study subgroup		Diagnoses	1	2	3	4	5	at 30/12/2015
Screen-detected	No.	4,242	90	180	259	314	360	407
	Proportion (%)		2.1	4.2	6.1	7.4	8.5	9.6
Interval	No.	646	42	82	109	126	136	142
	Proportion (%)		6.5	12.7	16.9	19.5	21.1	22.0
Non-responder	No.	10,566	1,060	1,674	2,081	2,313	2,426	2,515
	Proportion (%)		10.0	15.8	19.7	21.9	23.0	23.8
Never-invited	No.	36,378	3,809	6,302	7,802	8,641	9,105	9,582
	Proportion (%)		10.5	17.3	21.4	23.8	25.0	26.3

Note: Proportions indicate the percentage of those diagnosed with a bowel cancer who have died from bowel cancer by a particular time point from their diagnosis. See Table B1 for these data stratified by age group.

NBCSP invitee subgroup survival plots for bowel cancer mortality

The general logrank test statistic of $\chi^2 = 553.9$ with 2 degrees of freedom ($P < 0.0001$) showed a strong effect of subgroup (screen-detected, interval and non-responder) on risk of bowel cancer mortality. The survival curves (Figure 4.2) 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 4.2 for comparison.)

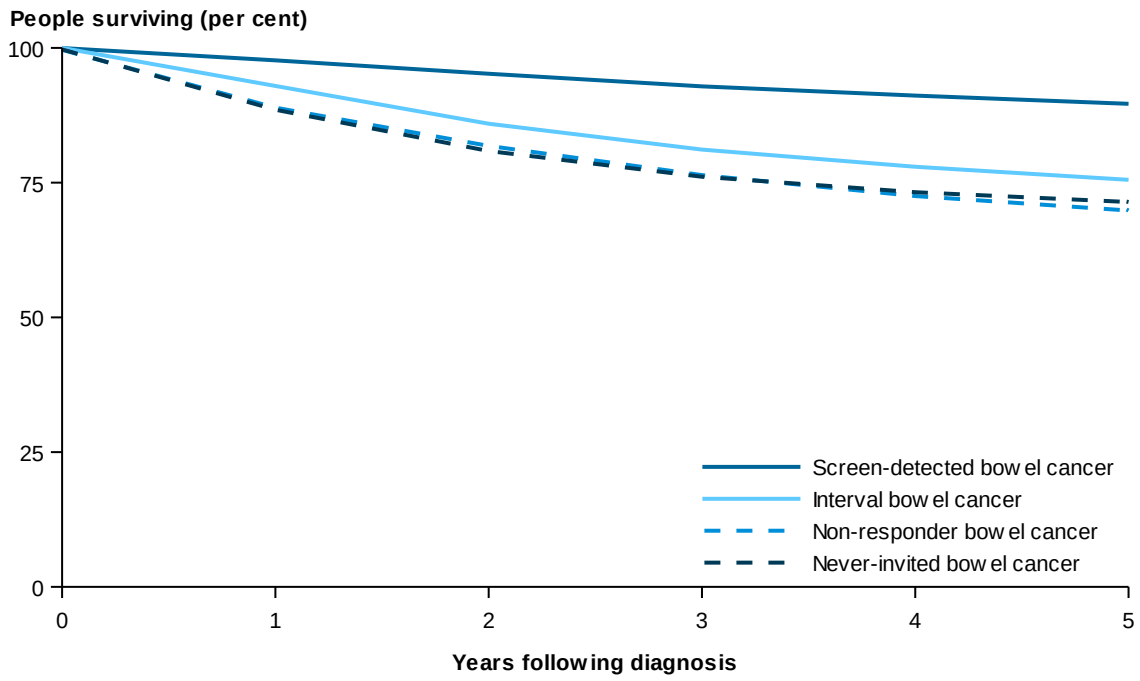


Figure 4.2: Bowel cancer mortality survival plots for the NBCSP invitee subgroups, and the never-invited group

NBCSP invitee subgroup hazard ratios for bowel cancer mortality

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 of the following variables: 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 4.5.

Table 4.5: Crude bowel cancer mortality hazard ratios for NBCSP invitees only[(a)]

Variable	Crude HR*	95% CI*	*P* value
NBCSP invitee subgroup			
Screen-detected	1.0	. .	. .
Interval	2.49	2.06–3.02	<0.0001
Non-responder	3.31	2.98–3.68	<0.0001
Sex			
Men	1.0	. .	. .
Women	0.89	0.83–0.96	0.002
Age group at diagnosis[(b)]			
50–54	1.0	. .	. .
55–59	1.26	1.10–1.44	0.001
60–64	1.36	1.13–1.63	0.001
65–69	1.32	1.16–1.50	<0.0001
70–74	1.77	1.50–2.09	<0.0001
Socioeconomic status			
1 (most disadvantaged)	1.0	. .	. .
2	1.0	0.90–1.11	0.95
3	0.92	0.83–1.03	0.13
4	0.90	0.81–1.00	0.06
5 (least disadvantaged)	0.79	0.70–0.89	<0.0001
Unknown quintile	1.18	0.86–1.62	0.30
Remoteness area			
Major cities	1.0	. .	. .
Inner regional	1.05	0.96–1.14	0.27
Outer regional	0.97	0.86–1.09	0.57
Remote and Very remote	1.16	0.91–1.48	0.24
Unknown remoteness area	0.00	0.00–0.00	0.90
Cancer site[(c)]			
Left-sided colon	1.0	. .	. .
Right-sided colon	1.29	1.19–1.41	<0.0001
Rectum	1.15	1.05–1.25	0.003
Colon, not otherwise specified	2.86	2.43–3.36	<0.0001
Summary stage[(d)]			
Localised	1.0	. .	. .
Regionalised	4.87	3.91–6.06	<0.0001
Distant	39.41	31.81–48.82	<0.0001
Unknown	7.73	6.01–9.93	<0.0001
Morphology[(e)]			
Adenocarcinomas	1.0	. .	. .
Other histological types	1.67	1.46–1.91	<0.0001

* HR = hazard ratio; CI = confidence interval.

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

(b) The 2006–2010 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, Victoria, 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 3.31, 95% CI: 2.98–3.68) and interval cancer subgroup (hazard ratio 2.49, 95% CI: 2.06–3.02) was significantly increased. Regression was then performed against several other explanatory variables, to look for potential confounding variables.

There were differences in the unadjusted mortality hazard ratios across age-at-diagnosis and socioeconomic groups (Table 4.5). Other statistically significant crude hazard ratio outcomes included cancer site and type, sex, and summary stage of cancer.

Women had a lower risk of bowel cancer death (hazard ratio 0.89, 95% CI: 0.83–0.96). Invitees with right-sided (hazard ratio 1.29, 95% CI: 1.19–1.41), rectum (hazard ratio 1.15, 95% CI: 1.05–1.25) and 'colon, not otherwise specified' bowel cancers (hazard ratio 2.86, 95% CI: 2.43–3.36) 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 1.67, 95% CI: 1.46–1.91) compared with adenocarcinomas, and invitees with bowel cancers of more advanced summary stage; that is, regionalised and distant cancers (hazard ratio of 4.87 and 39.41, 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. The 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 sex, age group at diagnosis, socioeconomic group and bowel cancer site and type, the adjusted bowel cancer mortality hazard ratio was 2.43 (95% CI: 2.00–2.94) for people in the interval subgroup and 3.38, (95% CI: 3.04–3.76) 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 2 and 3 times the risk, respectively), and these differences were statistically significant.

After correcting for potential lead-time bias in screen-detected cancers, the mortality risks for people with interval cancers (hazard ratio 1.49, 95% CI: 1.23–1.81) and for people in the non-responder subgroup (hazard ratio 2.05, 95% CI: 1.84–2.28) were still significantly higher.

NBCSP invitee subgroup all-cause mortality analysis

The final comparison of mortality outcomes was between people in the NBCSP invitee subgroups who had died from any cause (Table 4.6). Of the 4,242 NBCSP invitees with a screen-detected bowel cancer diagnosis, 618 (14.6%) had died from any cause before 2016. By the same time, 178 (27.6%) of the 646 NBCSP invitees with an interval bowel cancer diagnosis had died from any cause, as had 3,224 (30.5%) of the 10,566 non-responders with a bowel cancer diagnosis. The mean follow-up time to death for all NBCSP invitee diagnoses was 22.9 months (range 0–101.9 months, standard deviation 20.3 months).

Table 4.6: Cumulative all-cause deaths, by study subgroup

			All deaths					
			Years since diagnosis					
Study subgroup		Diagnoses	1	2	3	4	5	at 30/12/2015
Screen-detected	No.	4,242	127	247	349	440	515	618
	Proportion (%)		3.0	5.8	8.2	10.4	12.1	14.6
Interval	No.	646	52	99	132	155	168	178
	Proportion (%)		8.0	15.3	20.4	24.0	26.0	27.6
Non-responder	No.	10,566	1,356	2,109	2,607	2,913	3,074	3,224
	Proportion (%)		12.8	20.0	24.7	27.6	29.1	30.5
Never-invited	No.	36,378	4,927	8,014	9,950	11,118	11,808	12,686
	Proportion (%)		13.5	22.0	27.4	30.6	32.5	34.9

Note: Proportions indicate the percentage of those diagnosed with a bowel cancer who have died from any cause by a particular time point from their diagnosis. See Table B2 for these data stratified by age group.

NBCSP invitee subgroup hazard ratios for all-cause mortality

Investigation of explanatory variables using regression found the same variables were suitable for the all-cause mortality model as those used in the bowel cancer mortality analysis of the NBCSP invitee subgroup. That is, the unadjusted all-cause mortality hazard ratios for sex, age group, socioeconomic group, cancer site and morphology all had statistically significant differences.

After adjusting for these effects, including lead-time bias in screen-detected cancers, the all-cause mortality analyses showed that there was no longer a statistically significant difference in the hazard ratio between those in the interval cancer subgroup and those in the screen-detected subgroup (hazard ratio 1.18, 95% CI: 0.99–1.39). But the all-cause mortality risk for people in the non-responder subgroup was still significantly higher (hazard ratio 1.69, 95% CI: 1.55–1.85). To investigate further, the non-bowel-cancer deaths were compared for those in the screen-detected and non-responder groups; there was no statistically significant difference in non-bowel-cancer mortality risk for non-responders when compared with those in the screen-detected group (hazard ratio 1.09, 95% CI: 0.93–1.28).

Objective 2

The second objective was to describe differences in summary stage between those whose bowel cancer was diagnosed after a 2006–2010 NBCSP invitation, and those aged 50–74 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 for this objective were based on the subset of people diagnosed with bowel cancer from the four jurisdictions supplying staging data that could be combined into a summary stage system. (See the 'Jurisdictional cancer registry data' 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: least advanced (localised summary stage), regionalised, and 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 four 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 30% for NBCSP invitees compared with 28% 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 1.12 for more advanced (worse prognosis) bowel cancers. This means that the people diagnosed with bowel cancer in the never-invited group had 12% higher odds of its being at a more-advanced summary stage than for diagnoses in the NBCSP invitee group. This indicates slight down-staging of cancer (related to better prognosis) for NBCSP invitees compared with the never-invited group, even including the non-responders who were later diagnosed with bowel cancer.

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

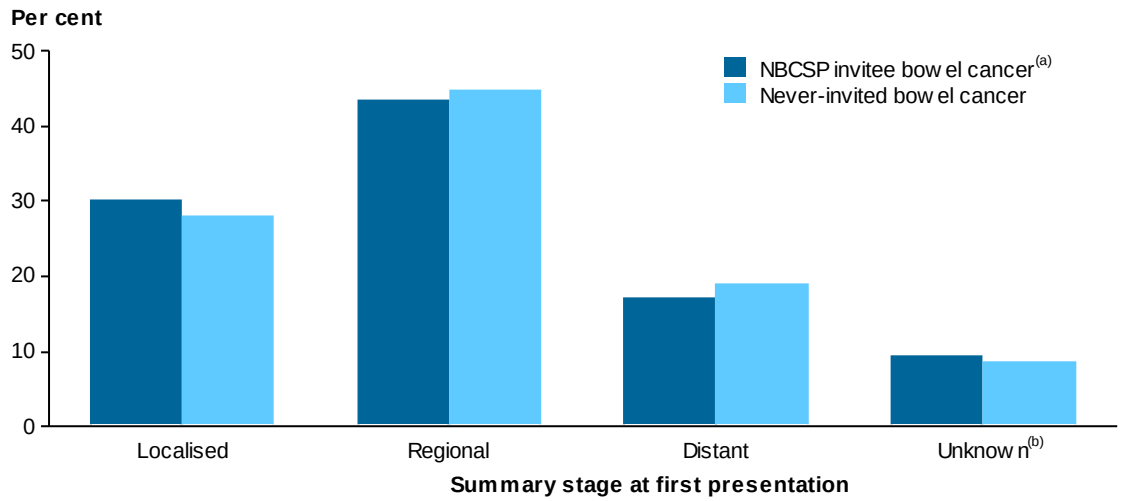
- there were larger statistically significant differences in the cancer summary stage profile. In the screen-detected subgroup, the percentage of people with bowel cancers in the localised (least advanced) stage was 44%, compared with 24% in the non-responder subgroup
- after adjusting for differences in age groups between the subgroups, people in the non-responder subgroup had 171% higher odds of having a more-advanced (worse prognosis) bowel cancer than 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 4.3).



(a) Includes bowel cancer in people invited into the NBCSP in 2006–2010 (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, Victoria, Tasmania and the Australian Capital Territory were used. See Appendix A for further information.

Figure 4.3: Summary stage of bowel cancer diagnosed in individuals invited to the NBCSP and those not invited, 2006–2010

The proportion of people diagnosed with a localised (least advanced) bowel cancer was 30.0% for NBCSP invitees compared with 27.9% for those who were never invited to participate in the NBCSP between 2006 and 2010. Similarly, the proportion of people diagnosed with a distant (most advanced) bowel cancer was 17.1% for NBCSP invitees compared with 19.0% 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 ($\chi^2 = 24.0$, $P < 0.0001$).

To ensure that 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.

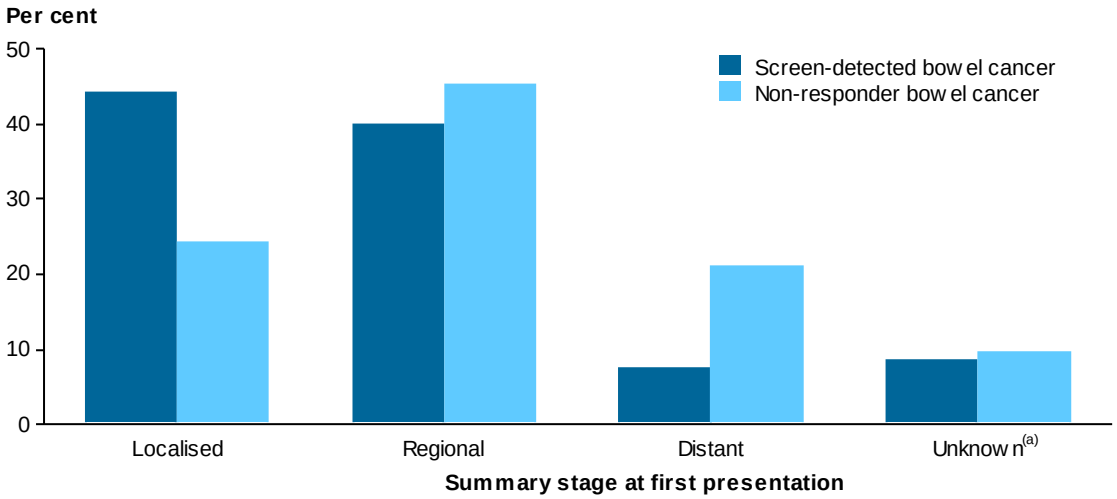
Using multivariable logistic regression, earlier summary stage was clearly associated with the NBCSP invitees when compared with the never-invited group ($\chi^2 = 23.9$, $P < 0.0001$). Age group at diagnosis was also associated with summary stage ($\chi^2 = 75.0$, $P < 0.0001$). There was no association between sex and summary stage.

After adjusting for age group at diagnosis, the odds for more-advanced summary stage for NBCSP non-invitees was 1.12 (95% CI: 1.06–1.18). In other words, bowel cancers diagnosed in the never-invited group had 12% higher odds of being more advanced than the odds for those diagnosed in the NBCSP invitee group. This indicates slight down-staging of bowel cancers—related to better prognosis—for the NBCSP invitee cohort (which includes those who did not participate) 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 a statistically significant difference in summary stage profile between these two groups ($\chi^2 = 33.9$, $P < 0.0001$), with non-responders having a worse summary stage profile than those diagnosed without being invited. Therefore, the statistically significant difference observed in the intention-to-screen analysis (between the NBCSP invitees and the never-invited group) was due to better summary stage diagnoses in the screen-detected and interval subgroups, not the non-responder subgroup (Table 3.1).

NBCSP invitee subgroup summary stage analysis

The summary stage profiles of NBCSP invitees diagnosed following a positive iFOBT (screen-detected subgroup) were compared with those who were invited but did not participate (non-responder subgroup) (Figure 4.4).



(a) Cancer stage was not known.

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

Figure 4.4: 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 44.3% compared with 24.2% in the non-responder subgroup. Further, the proportion of distant (most advanced) cancers was 7.4% in the screen-detected subgroup compared with 21.0% in the non-responder subgroup. After excluding the 'Unknown' summary stage diagnoses, the differences in summary stage profiles between the two groups were highly statistically significant ($\chi^2 = 438.8$, $P < 0.0001$).

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 ($\chi^2 = 427.3$, $P < 0.0001$). Age group at diagnosis was also associated with summary stage ($\chi^2 = 17.3$, $P = 0.002$). There was no association between sex and summary stage ($\chi^2 = 1.1$, $P = 0.29$).

The final odds ratio for later summary stage for the non-responders was 2.71 (95% CI: 2.46–2.98). This means that bowel cancers diagnosed in the non-responder subgroup had 171% 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 3.1), and, until data linkages such as those carried out for the previous report (AIHW 2014) and 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	Bowel cancer data from the screen-detected and interval cancer subgroups was used for this objective. (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 (48% versus 25%), which were related to a higher risk of death (see 'Objective 1')
- interval cancers had a different summary stage profile (a lower proportion were localised and a higher proportion were distant)
- the ratio of interval cancer diagnoses between men and women was approximately equal whereas more screen-detected cancers were found in men than women (61% versus 39%)
- interval cancers were significantly more likely to be non-adenocarcinoma cancer types (12% 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 iFOBT who were later found to have bowel cancer (the interval cancer subgroup) were analysed and compared with the screen-detected subgroup (Table 4.7).

For this analysis, there were 646 individuals in the interval cancer subgroup and 4,242 individuals in the screen-detected subgroup.

Table 4.7: Characteristics of individuals diagnosed with bowel cancer in the screen-detected and interval cancer subgroups

	Screen-detected		Interval[a]		
Characteristic	**No.**	**%**	**No.**	**%**	***P* value**
Sex					
Men	2,573	60.7	324	50.2	
Women	1,669	39.3	322	49.8	<0.0001
Age at diagnosis[b]					
50–54	402	9.5	64	9.9	
55–59	1,242	29.3	177	27.4	
60–64	337	7.9	33	5.1	
65–69	1,991	47.0	365	56.5	
70–74	270	6.4	7	1.1	<0.0001
Socioeconomic status[c]					
1 (most disadvantaged)	927	21.9	129	20.0	
2	893	21.1	135	20.9	
3	840	19.8	133	20.6	
4	818	19.3	111	17.2	
5 (least disadvantaged)	717	16.9	129	20.0	0.32
Remoteness[c]					
Major cities	2,605	61.4	414	64.1	
Inner regional	998	23.5	163	25.3	
Outer regional	555	13.1	62	9.6	
Remote	62	1.5	5	0.8	
Very remote	21	0.5	2	0.3	0.06
Site[d]					
Right-sided colon	1,070	25.2	307	47.5	
Left-sided colon	1,947	45.9	158	24.5	
Colon, not otherwise	135	3.2	25	3.9	
Rectum	1,090	25.7	156	24.1	<0.0001
Summary stage[e]					
Localised	1,098	44.3	125	32.6	
Regionalised	987	39.8	145	37.8	
Distant	184	7.4	60	15.6	
Unknown	209	8.4	54	14.1	<0.0001
Morphology[c][f]					
Adenocarcinomas	4,046	97.0	571	88.4	
Other histological types	127	3.0	75	11.6	<0.0001
Total	**4,242**		**646**		

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

(b) The 2006–2010 NBCSP invitees were those turning 50 (from July 2008), 55 or 65.

(c) Those with missing data for this characteristic were excluded. Therefore, the sum of numbers for 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, Victoria, Tasmania and the Australian Capital Territory were used. Therefore, the sum of numbers for this characteristic does not equal the total.

(f) Morphology groupings are 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 ($\chi^2 = 160.1$, $P < 0.0001$), with the screen-detected subgroup having a higher proportion of left-sided cancers (46%) and a lower proportion of right-sided cancers (25%) than the interval subgroup (25% and 48%, 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 3.1), of all groups, the highest proportion of left-sided cancers was in the screen-detected group.

There was a statistically significant difference in the proportions of male and female diagnoses across the two subgroups ($\chi^2 = 25.6$, $P < 0.0001$). The sex split in the interval cancer subgroup was close to equal, whereas there were more men than women with screen-detected cancers.

There were also differences in the 5-year age groups at diagnosis between the two sub-cohorts ($\chi^2 = 45.0$, $P < 0.0001$), which may be related to those in the interval cancer subgroup being diagnosed within 2 years of a screening target age, while screen-detected cancers can be diagnosed at a later time after a positive screening test.

There was a significant difference in the summary stage profile between the two subgroups ($\chi^2 = 48.8$, $P < 0.0001$). Screen-detected cancers were more likely to be localised and less likely to be distant.

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 ($\chi^2 = 102.2$, $P < 0.0001$). The interval cancer subgroup had a higher proportion of non-adenocarcinoma cancer types (12% versus 3%).

There were no statistically significant differences in socioeconomic status quintiles or remoteness area between individuals in the screen-detected and interval subgroups.

Objective 4

Objective 4 was to describe the positive predictive value and negative predictive value of the screening test.

Rationale	The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of the NBCSP screening test are of interest to evaluate if the test is maximising true positive results for cancer and minimising false positive results.
Data used in meeting this objective	Meeting this objective necessarily involved using only data from members of the 2006–2010 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 for 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 appeared only since the previous screen. Therefore, these statistics are likely to change 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; CCACCGWP 2017). If participants who did not have 2 years of follow-up available were also included, it would potentially bias the statistics, as some participants with fewer 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 iFOBT. Note that the screening test used at the time of this study was replaced in January 2018, so these results will not apply to tests after this time.

Key findings

- The PPV and NPV 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 2006–2010 NBCSP invitee group who participated, 85% of those who were diagnosed with a bowel cancer within 2 years had received a positive screening test, and 92% 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 iFOBT screening studies.

Results

Of those in the 2006–2010 NBCSP invitee group who participated, the sensitivity of the iFOBT was 85% and the specificity was 92% (Table 4.8). That is, 85% of all who screened and were later diagnosed with a bowel cancer had a positive screening test, and 92% of those who were not diagnosed with bowel cancer within 2 years of their screening test had a negative screening result. The PPV and NPV 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 4.8: Performance of iFOBT for diagnosing bowel cancer, 2006–2010 NBCSP invitees

	Actual cancer outcome[(a)]		
Screening result	**Cancer diagnosed**	**Cancer not diagnosed**	**Total**
Positive iFOBT	3,194	86,524	**89,718**
	(3.6% PPV)		
Negative iFOBT	558	995,922	**996,480**
	(0.06% false negatives)	(99.9% NPV)	
Total	**3,752**	**1,082,446**	**1,086,198**
	(85.1% sensitivity)	(92.0% 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 linked bowel screening records of people invited into the NBCSP in 2006–2010 with population-based data sets of bowel cancer diagnoses and national deaths information. These linkages allowed 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 enable examination of the mortality impact of the NBCSP overall.

Bowel cancer and all-cause mortality rates were lower in the NBCSP invitee study group

Bowel cancer mortality

The results showed 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 by 31 December 2015 after a diagnosis was 28% higher in the never-invited group, compared with NBCSP invitees. Even after correcting for potential lead-time bias, this risk was still a statistically significant 13% 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 than for the screen-detected subgroup.

These results were consistent with the findings in the previous report (AIHW 2014), but the size of differences between cohorts varied in the two reports. However, as the two reports used different invitee cohorts, with differences such as in the spread of diagnosis ages (see Table 2.1) and different follow-up periods, some differences between the findings in the two reports were expected.

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

All-cause mortality

All-cause mortality was also analysed. This analysis showed that after a bowel cancer diagnosis there was a statistically significant 7% higher risk of death from any cause in the never-invited group when compared with those invited (regardless of participation). This included adjusting for lead-time bias in those who died from bowel cancer, but not in those who died from other causes.

Analysis of all causes of death after a bowel cancer diagnosis *excluding* bowel cancer death did not find a significant difference in risk between invitees and those never invited. Therefore, the significant all-cause mortality difference was mainly due to the different risks of bowel cancer death between the two groups.

Within the NBCSP invitee group specifically, the risk of death from any cause was considerably higher for the non-responder subgroup than for the screen-detected subgroup, even though the risk of non-bowel-cancer death was the same. This also pointed to the difference in bowel cancer mortality risk causing the significant change in all-cause risk.

The other mortality finding of interest was that the main contributor to 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, differences were observed 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 12% 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 171% 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).

Unlike our previous study (AIHW 2014), further analysis showed a statistically significant difference between the summary stage profile of cancers diagnosed in the non-responder subgroup and the never-invited subgroup. Cancers diagnosed in those invited who did not respond had a worse summary stage profile than bowel cancers in the never-invited group. Reasons for this are unknown. But this further highlighted that better summary stage outcomes for all 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 associated with participation in the NBCSP rather 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 one of the main objectives 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 for Objective 1.

These findings were based on bowel cancer summary staging data from four of the eight Australian jurisdictions (that is, New South Wales, Victoria, 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 four.

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 men than women, even though more women than men participate in screening (see the *NBCSP monitoring report 2018*—AIHW 2018), 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; Cole et al. 2013; Morris et al. 2012; Steele et al. 2012).

Site of bowel cancer affects prognosis

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

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

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 three main differences between screen-detected and never-invited bowel cancers (cancer site, type, and summary stage), the characteristic with the greatest effect on mortality risk was summary stage. This may help to 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 (646), 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 (88% compared with 97%). It was not possible to determine if these interval cancers existed at the time of screening (but were not detected), or they 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 three groups would be thought to have cancers found at a similar symptomatic time in their progression.

Interval cancers were therefore detected at an earlier summary stage than the other symptomatic diagnoses yet had differences from screen-detected cancers. As for the previous study, these factors together mean that further 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 et al. 2004; Iacopetta 2002; Sawhney et al. 2006) or differences in family history of bowel cancer (Samadder et al. 2014). This would require further data not included in this study.

Screening test performance

In this project, the PPV and NPV of the screening test for bowel cancer were 3.6% and 99.9%, respectively. A similar PPV was reported by Shin and colleagues (2013). As well, the high sensitivity (85%) and specificity (92%) of the iFOBT 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. It should be noted that the screening test used at the time of this study was replaced in January 2018, so these results will not apply to NBCSP screening tests after this time.

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 that:

- 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. Though, it is recommended that those with a positive iFOBT are placed on a 'within 30 days' elective procedure waiting list if they are having a public health system colonoscopy. So, it is possible they may receive a colonoscopy more quickly than symptomatic patients
- cancer summary stage data were extracted and interpreted from histology and other clinical 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 (14% for the interval group, 8%–9% for others).

Project limitations

This project had several limitations:

- Data on cancer summary stage were restricted to those jurisdictions where staging data were considered to be of sufficient completeness for reporting—New South Wales, Victoria, Tasmania and the Australian Capital Territory. Therefore only 29,870 records were included in analyses involving bowel cancer summary stage (a further 21,962 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.
- While this study had more follow-up time for analysis than the previous study (AIHW 2014), a later re-analysis with 10 years of outcome data would help to mitigate the potential issues of lead-time and length-time biases.
- 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, or other chronic illness) would help clarify the differences in this subgroup.
- Details of the screening (for example, alternative iFOBT testing) or colonoscopy history of the never-invited study group would allow improved focus on asymptomatic cancers in this group.
- As NBCSP form return for adenoma diagnoses is not considered complete (see Box 3.1 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 PPV and NPV, and 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. However, as only people of specific ages were invited to participate in the NBCSP during 2006–2010 and other people of similar ages were not invited to participate during this period, there are not expected to be substantial differences between those invited and those not invited to screen.

Future directions of this work

To allow mortality reductions due to the program to be fully apparent, 10 years of follow-up data would be optimal. This study had access to only 5 years of follow-up data, at most (some jurisdictions had less). However, the findings of this report indicate that there are better bowel cancer outcomes for those invited into the NBCSP, particularly for those who participate. As discussed, the statistically significant mortality results support those predicted by the earlier randomised trials of iFOBT screening.

By 2019, the full rollout of biennial screening will be in place. This will make similar analyses with a cohort from later periods more difficult, as the never-invited population aged 50–74 will become extremely small. Further, continuing to use an invited cohort from the earlier program years (such as 2006–2010) will have its own issues, due to their later re-invitations needing to be considered, and ensuring newer invitees after this period are properly excluded to make sure that they are not mistakenly assumed to be part of the never-invited population.

Therefore, future data linkages—such as those undertaken in this report—would need their methodology to be adjusted to ensure that they help to optimally monitor the effect of the NBCSP on Australian bowel cancer morbidity and mortality outcomes.

Appendix A: Additional data source details

NBCSP data

This section provides further detail on the National Bowel Cancer Screening Program data set used in this project.

NBCSP target population

The NBCSP has been phased in gradually. Table A1 outlines the start dates of each phase, and the target age groups.

Table A1: 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[(b)]	50, 55 and 65
2[(a)]	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) Ongoing NBCSP funding began.

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

Note: The eligible population for all Phase 2 and Phase 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 (except 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 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.

Completion of NBCSP forms by practitioners is not mandatory. There is also the possibility of inconsistent reporting, including limited information on participant outcomes. These inconsistencies are noted in the AIHW's NBCSP annual monitoring reports to indicate data reliability. In this project, the linkage of the 2006–2010 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 iFOBT kit in December 2008, which was found to be unreliable (AIHW 2012), may have lowered the positivity rate in this study group; however, this effect would have been minimal, as less than 5% of iFOBT kits were affected. Those people invited

in December 2008 who were affected by this issue were given the opportunity to re-test in 2009.

The 2006–2010 NBCSP invitees are counted only once in the reporting period, even if they had more than one abnormality detected per invitation round. Results confirmed by histopathology 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 adenoma confirmed by histopathology that shows villous change and/or high-grade dysplasia and/or a 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 to be advanced.

A person with multiple adenomas was 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: C18.0–C18.4) were considered to be right-sided cancers. Left-sided cancers were those diagnosed at the splenic flexure and in the descending colon, sigmoid colon and the recto-sigmoid junction (ICD-10: C18.5–C19). The category ‘colon, not otherwise specified’ included tumours overlapping two sites in the colon (C18.8) or with no site specified (C18.9). Cancers of the rectum were those classified as ICD-10: C20.8–C20.9. 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 the extent or spread of cancer at the time of diagnosis. Such information is important for several reasons, including determining an individual’s

prognosis, assisting in the planning and evaluation of treatment, and contributing to cancer monitoring and research.

For the years analysed, stage of bowel cancer at diagnosis was not routinely collected by all jurisdictional cancer registries, meaning there was not complete national stage data. For this project, all jurisdictions were investigated for cancer staging data; however, only four had applicable data for the study time period. Therefore, staging analyses in this report used data from only four of the eight Australian jurisdictions. These four jurisdictions—New South Wales, Victoria, Tasmania and the Australian Capital Territory—provided about 60% 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 several different staging systems used for different cancers, and in different regions and countries, but also there are 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, New South Wales and Australian Capital Territory bowel cancer diagnoses included ‘Summary stage at first presentation’ information, which was supplied in four categories (Table A2).

Summary stage at first presentation system

In this staging system, tumours are allocated to one of three categories, as well as to an ‘Unknown’ category (Table A2).

Table A2: Summary stage at first presentation system[(a)]

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 not enough evidence is 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.

(a) The most serious extent of cancer spread reported within 4 months of the initial diagnosis was used.

Source: Tracey et al. 2006.

Victorian staging data

Victorian bowel cancer diagnoses included 'extent of disease' staging data with five options (Table A3).

Table A3: Victorian cancer registry bowel cancer staging system

Stage	Description
Localised	Localised to the tissue of origin.
Regional	Spread of cancer cells to regional lymph nodes and/or beyond tissue of origin.
Distant metastases	Cancer cells that have broken away from the primary tumour. Includes non-regional lymph nodes.
Other	Not applicable. Morphology codes for which bowel cancer staging is not applicable. These were excluded.
Unknown	Unknown stage. Includes in situ, uncertain behaviour tumours which are not staged.

Source: Victorian Cancer Registry (V Thursfield 2017, pers. comm., 30 October).

For this report, the 'Other' group (which was not applicable to bowel cancers) was excluded.

Tasmanian staging data

Tasmanian bowel cancer diagnoses included staging data with six options (Table A4).

Table A4: 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 haematopoietic cancers. These were excluded.
Unknown	These are cases for which not enough evidence is available to adequately assign a stage.

Source: Tasmanian Cancer Registry (M Dalton 2012, pers. comm., 8 March; B Stokes 2014, pers. comm., 14 March).

As New South Wales and the Australian Capital Territory do for data on summary stage at first presentation, 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 A2 to allow the data to be compatible with the summary staging data for New South Wales, Victoria and the Australian Capital Territory.

To simplify text in this report, 'summary stage at first presentation' has been called 'summary stage'.

Cancer behaviour and grade

Bowel cancer diagnoses data from jurisdictional cancer registries generally contain information only 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 be categorised further 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 IARC (Table A5) (IARC 2004).

Table A5: 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 (n.o.s.)	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	9590–9591, 9596, 9650–9667, 9670–9719, 9727–9729, 9731–9734, 9740–9742, 9750–9758, 9760–9769, 9800–9801, 9805, 9820, 9823–9837, 9840, 9860–9931, 9940, 9945–9946, 9948, 9950, 9960–9964, 9970, 9975, 9980–9987, 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.

Classification of population groups

Cancer data were analysed by remoteness and socioeconomic status. Remoteness was classified into areas according to the 2006 Australian Bureau of Statistics (ABS) Australian Standard Geographical Classification (ABS 2006), while socioeconomic status quintiles were classified using the 2006 ABS Index of Relative Socioeconomic Disadvantage.

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 already stated, geographical location was classified according to the ABS Australian Standard Geographical Classification Remoteness Structure, which groups geographical areas into six remoteness categories, using the Accessibility/Remoteness Index for Australia. This index 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 score on this index 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 (at time of invitation for invitees and at time of diagnosis for never-invited people) were mapped to the 2006 Remoteness Structure, classified to five 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, except 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 four Socioeconomic Indexes for Areas developed by the ABS (ABS 2008) and is based on factors such as average household income, education levels and unemployment rates. The IRSD is not a person-based measure; rather, it 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 to socioeconomic groups (quintiles) according to the IRSD of their residential postcode at the time of invitation. Never-invited people were assigned based on postcode at time of diagnosis. Socioeconomic groups (based on IRSD rankings) were calculated with a 2006 Census postal area correspondence (previously called a concordance) using a population-based method at the Australia-wide level.

The first socioeconomic group (labelled '1') corresponds to geographical areas containing the 20% of the population with the most disadvantage according to the IRSD, and the fifth group (labelled '5') corresponds to the 20% of the population with the 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. For those with a bowel cancer diagnosis who are known to be alive at time *t*:

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

For those with a bowel cancer diagnosis and a bowel cancer death at time *t*:

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

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 transition rates from Brenner and colleagues (2011), as shown in Table A6, were used for *λ*.

Table A6: Asymptomatic to symptomatic transition rates for bowel cancer

Sex	Age group at diagnosis	Transition rate (λ) per 100 diagnoses, per year
Men	50–59	18.1
	60–64	19.2
	65–69	21.3
	70–74	20.6
Women	50–59	21.3
	60–64	22.5
	65–69	21.9
	70–74	20.8

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

Appendix B: Additional data tables

Table B1: Cumulative bowel cancer deaths, by age group and study group

Study subgroup		Diagnoses	Bowel cancer deaths					
			Years since diagnosis					
			1	2	3	4	5	at 30/12/2015
			Aged 50–54 at diagnosis					
Screen-detected	No.	402	6	11	18	24	30	34
	Proportion (%)		1.5	2.7	4.5	6.0	7.5	8.5
Interval	No.	64	4	6	8	8	8	8
	Proportion (%)		6.3	9.4	12.5	12.5	12.5	12.5
Non-responder	No.	1,124	77	146	190	216	227	233
	Proportion (%)		6.9	13.0	16.9	19.2	20.2	20.7
NBCSP invitee	*No.*	*1,590*	*87*	*163*	*216*	*248*	*265*	*275*
	Proportion (%)		*5.5*	*10.3*	*13.6*	*15.6*	*16.7*	*17.3*
Never-invited	No.	2,237	269	453	572	625	659	697
	Proportion (%)		12.0	20.3	25.6	27.9	29.5	31.2
			Aged 55–59 at diagnosis					
Screen-detected	No.	1,242	18	45	61	78	92	114
	Proportion (%)		1.4	3.6	4.9	6.3	7.4	9.2
Interval	No.	177	4	20	31	36	40	40
	Proportion (%)		2.3	11.3	17.5	20.3	22.6	22.6
Non-responder	No.	2,924	263	450	585	672	718	752
	Proportion (%)		9.0	15.4	20.0	23.0	24.6	25.7
NBCSP invitee	*No.*	*4,343*	*285*	*515*	*677*	*786*	*850*	*906*
	Proportion (%)		*6.6*	*11.9*	*15.6*	*18.1*	*19.6*	*20.9*
Never-invited	No.	3,729	310	580	759	872	954	1,080
	Proportion (%)		8.3	15.6	20.4	23.4	25.6	29.0
			Aged 60–64 at diagnosis					
Screen-detected	No.	337	3	8	10	11	11	12
	Proportion (%)		0.9	2.4	3.0	3.3	3.3	3.6
Interval	No.	33	2	2	2	2	2	2
	Proportion (%)		6.1	6.1	6.1	6.1	6.1	6.1
Non-responder	No.	1,113	105	149	175	182	183	183
	Proportion (%)		9.4	13.4	15.7	16.4	16.4	16.4
NBCSP invitee	*No.*	*1,483*	*110*	*159*	*187*	*195*	*196*	*197*
	Proportion (%)		*7.4*	*10.7*	*12.6*	*13.1*	*13.2*	*13.3*
Never-invited	No.	9,380	959	1,633	2,054	2,297	2,424	2,536
	Proportion (%)		10.2	17.4	21.9	24.5	25.8	27.0

(continued)

Table B1 (continued): Cumulative bowel cancer deaths, by age group and study group

Study subgroup		Diagnoses	Bowel cancer deaths					
			Years since diagnosis					
			1	2	3	4	5	at 30/12/2015
			Aged 65–69 at diagnosis					
Screen-detected	No.	1,991	47	95	144	173	199	219
	Proportion (%)		2.4	4.8	7.2	8.7	10.0	11.0
Interval	No.	365	30	52	66	78	84	90
	Proportion (%)		8.2	14.2	18.1	21.4	23.0	24.7
Non-responder	No.	3,970	457	708	883	987	1,042	1,091
	Proportion (%)		11.5	17.8	22.2	24.9	26.2	27.5
NBCSP invitee	*No.*	*6,326*	*534*	*855*	*1,093*	*1,238*	*1,325*	*1,400*
	Proportion (%)		*8.4*	*13.5*	*17.3*	*19.6*	*20.9*	*22.1*
Never-invited	No.	5,667	576	987	1,226	1,359	1,474	1,629
	Proportion (%)		10.2	17.4	21.6	24.0	26.0	28.7
			Aged 70–74 at diagnosis					
Screen-detected	No.	270	16	21	26	28	28	28
	Proportion (%)		5.9	7.8	9.6	10.4	10.4	10.4
Interval	No.	7	2	2	2	2	2	2
	Proportion (%)		28.6	28.6	28.6	28.6	28.6	28.6
Non-responder	No.	1,435	158	221	248	256	256	256
	Proportion (%)		11.0	15.4	17.3	17.8	17.8	17.8
NBCSP invitee	*No.*	*1,712*	*176*	*244*	*276*	*286*	*286*	*286*
	Proportion (%)		*10.3*	*14.3*	*16.1*	*16.7*	*16.7*	*16.7*
Never-invited	No.	15,365	1,695	2,649	3,191	3,488	3,594	3,640
	Proportion (%)		11.0	17.2	20.8	22.7	23.4	23.7
			All ages					
Screen-detected	**No.**	**4,242**	**90**	**180**	**259**	**314**	**360**	**407**
	Proportion (%)		**2.1**	**4.2**	**6.1**	**7.4**	**8.5**	**9.6**
Interval	**No.**	**646**	**42**	**82**	**109**	**126**	**136**	**142**
	Proportion (%)		**6.5**	**12.7**	**16.9**	**19.5**	**21.1**	**22.0**
Non-responder	**No.**	**10,566**	**1,060**	**1,674**	**2,081**	**2,313**	**2,426**	**2,515**
	Proportion (%)		**10.0**	**15.8**	**19.7**	**21.9**	**23.0**	**23.8**
NBCSP invitee	***No.***	***15,454***	***1,192***	***1,936***	***2,449***	***2,753***	***2,922***	***3,064***
	Proportion (%)		***7.7***	***12.5***	***15.8***	***17.8***	***18.9***	***19.8***
Never-invited	**No.**	**36,378**	**3,809**	**6,302**	**7,802**	**8,641**	**9,105**	**9,582**
	Proportion (%)		**10.5**	**17.3**	**21.4**	**23.8**	**25.0**	**26.3**

Note: Proportions indicate the percentage of those diagnosed with a bowel cancer who have died from bowel cancer by a particular time point from their diagnosis.

Table B2: Cumulative all-cause deaths, by age group and study group

Study subgroup		Diagnoses	All deaths: Years since diagnosis 1	2	3	4	5	All deaths at 30/12/2015
			Aged 50–54 at diagnosis					
Screen-detected	No.	402	6	16	23	30	37	42
	Proportion (%)		1.5	4.0	5.7	7.5	9.2	10.4
Interval	No.	64	4	6	9	9	9	9
	Proportion (%)		6.3	9.4	14.1	14.1	14.1	14.1
Non-responder	No.	1,124	88	163	215	247	259	265
	Proportion (%)		7.8	14.5	19.1	22.0	23.0	23.6
NBCSP invitee	*No.*	*1,590*	*98*	*185*	*247*	*286*	*305*	*316*
	Proportion (%)		*6.2*	*11.6*	*15.5*	*18.0*	*19.2*	*19.9*
Never-invited	No.	2,237	308	518	649	711	756	804
	Proportion (%)		13.8	23.2	29.0	31.8	33.8	35.9
			Aged 55–59 at diagnosis					
Screen-detected	No.	1,242	25	60	79	103	124	150
	Proportion (%)		2.0	4.8	6.4	8.3	10.0	12.1
Interval	No.	177	6	23	37	42	46	47
	Proportion (%)		3.4	13.0	20.9	23.7	26.0	26.6
Non-responder	No.	2,924	323	541	693	800	855	907
	Proportion (%)		11.0	18.5	23.7	27.4	29.2	31.0
NBCSP invitee	*No.*	*4,343*	*354*	*624*	*809*	*945*	*1,025*	*1,104*
	Proportion (%)		*8.2*	*14.4*	*18.6*	*21.8*	*23.6*	*25.4*
Never-invited	No.	3,729	376	685	889	1,022	1,123	1,325
	Proportion (%)		10.1	18.4	23.8	27.4	30.1	35.5
			Aged 60–64 at diagnosis					
Screen-detected	No.	337	4	11	13	14	14	16
	Proportion (%)		1.2	3.3	3.9	4.2	4.2	4.7
Interval	No.	33	3	3	3	3	3	3
	Proportion (%)		9.1	9.1	9.1	9.1	9.1	9.1
Non-responder	No.	1,113	131	183	214	223	225	228
	Proportion (%)		11.8	16.4	19.2	20.0	20.2	20.5
NBCSP invitee	*No.*	*1,483*	*138*	*197*	*230*	*240*	*242*	*247*
	Proportion (%)		*9.3*	*13.3*	*15.5*	*16.2*	*16.3*	*16.7*
Never-invited	No.	9,380	1,193	1,977	2,475	2,788	2,964	3,132
	Proportion (%)		12.7	21.1	26.4	29.7	31.6	33.4

(continued)

Table B2 (continued): Cumulative all-cause deaths, by age group and study group

Study subgroup		Diagnoses	All deaths: Years since diagnosis 1	2	3	4	5	at 30/12/2015
			Aged 65–69 at diagnosis					
Screen-detected	No.	1,991	73	136	203	260	307	377
	Proportion (%)		3.7	6.8	10.2	13.1	15.4	18.9
Interval	No.	365	37	65	81	99	108	117
	Proportion (%)		10.1	17.8	22.2	27.1	29.6	32.1
Non-responder	No.	3,970	598	917	1,145	1,294	1,385	1,474
	Proportion (%)		15.1	23.1	28.8	32.6	34.9	37.1
NBCSP invitee	*No.*	*6,326*	*708*	*1,118*	*1,429*	*1,653*	*1,800*	*1,968*
	Proportion (%)		*11.2*	*17.7*	*22.6*	*26.1*	*28.5*	*31.1*
Never-invited	No.	5,667	773	1,281	1,601	1,813	1,984	2,343
	Proportion (%)		13.6	22.6	28.3	32.0	35.0	41.3
			Aged 70–74 at diagnosis					
Screen-detected	No.	270	19	24	31	33	33	33
	Proportion (%)		7.0	8.9	11.5	12.2	12.2	12.2
Interval	No.	7	2	2	2	2	2	2
	Proportion (%)		28.6	28.6	28.6	28.6	28.6	28.6
Non-responder	No.	1,435	216	305	340	349	350	350
	Proportion (%)		15.1	21.3	23.7	24.3	24.4	24.4
NBCSP invitee	*No.*	*1,712*	*237*	*331*	*373*	*384*	*385*	*385*
	Proportion (%)		*13.8*	*19.3*	*21.8*	*22.4*	*22.5*	*22.5*
Never-invited	No.	15,365	2,277	3,553	4,336	4,784	4,981	5,082
	Proportion (%)		14.8	23.1	28.2	31.1	32.4	33.1
					All ages			
Screen-detected	**No.**	**4,242**	**127**	**247**	**349**	**440**	**515**	**618**
	Proportion (%)		**3.0**	**5.8**	**8.2**	**10.4**	**12.1**	**14.6**
Interval	**No.**	**646**	**52**	**99**	**132**	**155**	**168**	**178**
	Proportion (%)		**8.0**	**15.3**	**20.4**	**24.0**	**26.0**	**27.6**
Non-responder	**No.**	**10,566**	**1,356**	**2,109**	**2,607**	**2,913**	**3,074**	**3,224**
	Proportion (%)		**12.8**	**20.0**	**24.7**	**27.6**	**29.1**	**30.5**
NBCSP invitee	***No.***	***15,454***	***1,535***	***2,455***	***3,088***	***3,508***	***3,757***	***4,020***
	Proportion (%)		***9.9***	***15.9***	***20.0***	***22.7***	***24.3***	***26.0***
Never-invited	**No.**	**36,378**	**4,927**	**8,014**	**9,950**	**11,118**	**11,808**	**12,686**
	Proportion (%)		**13.5**	**22.0**	**27.4**	**30.6**	**32.5**	**34.9**

Note: Proportions indicate the percentage of those diagnosed with a bowel cancer who have died from bowel cancer by a particular time point from their diagnosis.

Glossary

adenocarcinoma: The malignant progression of a benign **adenoma**.

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.

asymptomatic: Describes the situation where 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: Cancer, also called malignancy, is 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 2016).

colon: (also called large intestine). Lower part of the digestive system that reabsorbs water, salt and some nutrients from digested food, forming faeces that are later passed out of the body. In this report, the bowel consist of the colon and rectum.

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

down-staging: Said to occur about cancers diagnosed in a group of people exposed to a particular treatment if they are, on average, at a less-advanced stage than cancers diagnosed in a similar group of people not exposed to the treatment. 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: Comprises people registered as an Australian citizen or migrant in the Medicare enrolment file, or registered with a Department of Veterans' Affairs gold card, who 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 **iFOBT** 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. The **iFOBT** tests detect blood-in-stool (blood in the faeces), which may be caused by a number of conditions. A false positive finding for bowel cancer may still mean the existence of other non-bowel cancer conditions, or pre-cancerous polyps or **adenomas**.

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

iFOBT: Immunochemical faecal occult blood test—specific type of FOBT test that requires no dietary or medicinal changes before the test. FOBTs are 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 iFOBTs into one of three groups:

1. correctly completed
2. incorrectly completed
3. unsatisfactory.

Participants are provided with specific instructions on how to complete the iFOBT. 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 taken more than 2 weeks apart, or a kit that has taken more than 1 month in transit to arrive). Participants with iFOBTs that are not correctly completed are asked to complete another iFOBT.

iFOBT result: The iFOBT 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).

incidence: The number of new cases (of an illness or event, and so on) occurring during a given period. Compare with **prevalence** (AIHW 2016).

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. 2002:901).

interval cancer: Defined in this report 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: 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 earlier diagnosis may make no difference to the outcome of the disease (that is, the date of death). The earlier diagnosis could therefore artificially increase (bias) survival time from that if the cancer were 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 test with a negative screening result, or a result that is inconclusive or unsatisfactory (and the participant did not successfully re-test).

non-responder: A person who was 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 agreed to participate in the National Bowel Cancer Screening Program by returning a completed **iFOBT** kit and participant details form.

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

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

positivity rate: The number of positive **iFOBT** results as a percentage of the total number of valid iFOBT 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 2016).

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 test** result require further assessment and diagnosis to determine whether or not they have the disease or risk marker being screened for.

sensitivity: A measure of how good a screening test is in identifying people with **bowel cancer**.

socioeconomic status: A measure of socioeconomic status in which small areas of Australia are classified on a continuum from disadvantaged to affluent. See Appendix A for details.

specificity: A measure of how good a screening test is in correctly identifying those who 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 A1.

tumour: See **neoplasm**.

underlying cause of death: The 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 2016).

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

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Related publications

The following AIHW publications may be of interest:

- AIHW 2018. National Bowel Cancer Screening Program: monitoring report 2018. Cat. no. CAN 112. Canberra: AIHW.
- AIHW 2017. Cancer in Australia 2017. Cancer series no. 101. Cat. no. CAN 100. Canberra: AIHW.
- AIHW 2014. Analysis of bowel cancer outcomes for the National Bowel Cancer Screening Program. Cat. no. CAN 87. Canberra: AIHW.

This report compares mortality outcomes and cancer characteristics for two populations: those invited to screen in the National Bowel Cancer Screening Program in 2006–2010, and those of a similar age who were not invited in that time period.

Of the bowel cancer diagnoses, non-invitees had a 13% higher risk of dying from bowel cancer than invitees, and cancers in non-invitees were more likely to be more advanced.

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