Research Article

Cancer Epidemiology, Biomarkers & Prevention

Benefits, Harms, and Cost-Effectiveness of Potential Age Extensions to the National Bowel Cancer Screening Program in Australia

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Abstract

Background: The Australian National Bowel Cancer Screening Program (NBCSP) is rolling out 2-yearly immunochemical fecal occult blood test screening in people aged 50 to 74 years. This study aimed to evaluate the benefits, harms, and cost-effectiveness of extending the NBCSP to younger and/or older ages.

Methods: A comprehensive validated microsimulation model, Policy1-Bowel, was used to simulate the fully rolled-out NBCSP and alternative strategies assuming screening starts at 40 or 45 years and/or ceases at 79 or 84 years given three scenarios: (i) perfect adherence (100%), (ii) high adherence (60%), and (ii) low adherence (40%, as currently achieved).

Results: The current NBCSP will reduce colorectal cancer incidence (mortality) by 23% to 51% (36% to 74%) compared with no screening (range reflects participation); extending screening to younger or older ages would result in additional reductions of 2 to 6 (2 to 9) or 1 to 3 (3 to 7) percentage points, respectively. With an indicative willingness-to-pay threshold of A$50,000/life-year saved (LYS), only screening from 50 to 74 years [incremental cost-effective ratio (ICER): A$2,984–5,981/LYS) or from 45 to 74 years (ICER: A$17,053–29,512/LYS) remained cost-effective in all participation scenarios. The number-needed-to-colonoscope to prevent a death over the lifetime of a cohort in the current NBCSP is 35 to 49. Starting screening at 45 years would increase colonoscopy demand for program-related colonoscopies by 3% to 14% and be associated with 55 to 170 additional colonoscopies per additional death prevented.

Conclusions: Starting screening at 45 years could be cost-effective, but it would increase colonoscopy demand and would be associated with a less favorable incremental benefits-to-harms trade-off than screening from 50 to 74 years.

Impact: The study underpins recently updated Australian colorectal cancer management guidelines that recommend that the NBCSP continues to offer bowel screening from 50 to 74 years. *Cancer Epidemiol Biomarkers Prev; 27(12); 1450–61. ©2018 AACR.*

Introduction

The National Bowel Cancer Screening Program (NBCSP) in Australia was initiated in 2006 and has been rolling out via the inclusion of new age cohorts over time (1). From 2020 onward, the fully rolled-out program will offer 2-yearly immunochemical fecal occult blood testing (iFOBT; also known as fecal immunochemical test or FIT) for people aged 50 to 74 years. Consistent with the current NBCSP recommendations, an evaluation conducted by the U.S. Preventive Services Task Force (USPSTF) in 2008 considered the optimal age to begin and to stop colorectal cancer screening, and recommended that screening should be conducted from age 50 to 75 years (2). The same screening age range was also recommended in an updated 2016 USPSTF evaluation, which found that lowering the screening start age from 50 to 45 years would yield a relatively small gain in terms of life-years but would require a large increase in the number of colonoscopies required (3).

Some commentators in the Australian context have called for an earlier age of starting screening, with a recent report suggesting that biennial iFOBT screening from 40 to 70 years is cost-effective when compared with no screening (4). However, because 2-yearly iFOBT screening is already established in Australia, the relevant policy questions relate to the incremental

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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impact and cost-effectiveness of potential age extensions to the program (either to younger or older ages). Furthermore, a systematic evaluation of the trade-off of benefits to harms of screening at different ages has not been performed. The aim of the current study is, therefore, to evaluate the incremental health benefits, harms, costs, and resource utilization of extending the age of screening to people in their 40s and to people in their late 70s and early 80s, and to compare this with the current program involving screening in those aged 50 to 74 years. This evaluation was performed to support the 2017 review of the *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*, auspiced by Cancer Council Australia (CCA; ref. 5).

Materials and Methods

Policy1-Bowel model

A microsimulation model, Policy1-Bowel, was used for the evaluation. Model design, and calibration and validation results for the Australian NBCSP have been previously described (6, 7). In brief, the Policy1-Bowel model, adapted from the Dutch Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model, simulates the development of three types of lesions—conventional adenomas, hyperplastic polyps, and sessile serrated adenomas (7, 8). The model assumed that ∼85% of colorectal cancers develop from conventional adenoma via the conventional adenoma–carcinoma pathway, and 15% of colorectal cancers arise from sessile serrated adenomas via the serrated pathway. The location, shape, size, degree of dysplasia, and architecture of adenoma and the location and size of sessile serrated adenomas and hyperplastic polyps are modeled. Supplementary Fig. S1 shows the model's natural history pathways. A single age cohort consisting of 10 million males and 10 million females was simulated for each strategy evaluated. The simulation begins from age 20 and continues on an annual time-step until the individual dies or becomes 90 years old (in the base case; 100 years in supplementary analysis), whichever occurs first. Patients with cancer in the model are assumed to have a probability of dying from colorectal cancer for a period of 5 years after diagnosis; this varies by cancer stage, time since cancer diagnosis, and whether cancer was diagnosed via screening or was symptomatically detected. All simulated individuals also have a probability of dying from other causes, which is informed by all-cause mortality data (excluding colorectal cancer mortality) in the Australian population (9, 10).

iFOBT screening, follow-up colonoscopy, and surveillance colonoscopy management pathways

The comparator strategy for the analysis was the current NBCSP, biennial iFOBT screening at 50 to 74 years. Eight alternative age-extended strategies assuming screening started from 40 or 45 years and/or stopped at 79 or 84 years (i.e., 40–74, 40–79, 40–84, 45–74, 45–79, 45–84, 50–79, and 50–84 years) were evaluated. The detailed modeled management pathways for screening, diagnostic assessment, and surveillance are provided in Supplementary Fig. S2 and Supplementary Table 1. Colonoscopy surveillance to follow-up individuals with a previous positive iFOBT result was assumed to stop at 75 years for the comparator strategy (current program; based on existing guideline recommendations; refs. 11, 12), but to continue to 80 and 85 years for strategies assuming screening continued to 79 or 84 years, respectively.

Screening participation and other adherence assumptions

All strategies were evaluated considering three scenarios with different screening adherence assumptions. Scenario 1 assumed perfect adherence to recommendations for screening (i.e., 100% participation), colonoscopy follow-up, and surveillance. Although not achievable in practice, this analysis allows a direct comparison of the outcomes and costs of screening approaches independent of the differing (and uncertain) adherence assumptions for each strategy. Strategies were also evaluated assuming more realistic assumptions for adherence. Scenario 2 assumed "high" adherence—an overall ∼60% screening participation among people aged 50 to 74 years who were invited to participate in screening, considering different screening participation rates for people who have never taken part in screening before and people who have completed at least one round of screening previously (Table 1). The ∼60% potentially feasible participation assumption is based on the 54% to 57% 2-year participation rate achieved in the National Cervical Cancer Screening Program and the breast cancer screening program, BreastScreen, in Australia (13, 14). Scenario 3 assumed "low" adherence—an overall ∼40% screening participation in 50 to 74 years, derived from the recently observed 41% NBCSP participation rate (Table 1; ref. 15). In the imperfect adherence scenarios, favorable assumptions were made with respect to the benefits of starting screening earlier or finishing later because we assumed this would not decrease participation in the currently targeted age groups, which is unlikely to be the case in practice. We also assumed that people starting screening in their 40s would have equivalent participation to those in their 50s, which may not be the case. This is a favorable assumption for strategies that assumed a wider screening age range as it resulted in a higher proportion of individuals being screened at least once in their lifetime (see Supplementary Figs. S3 and S4). In Scenarios 2 and 3, compliance to follow-up colonoscopy after a positive iFOBT result was assumed to be 71% (as observed; ref. 15); compliance to subsequent surveillance colonoscopy recommendations to follow-up individuals, who have had at least one adenoma or sessile serrated adenoma removed in the previous colonoscopy examination was assumed to be 80% (as per the assumption used in previous studies; refs. 6, 7, 16).

Cost and test characteristics assumptions

A health services perspective was taken for the analysis. Overhead costs related to administration (other than the costs of sending test kits) and promotion of the screening program, and individual's out-of-pocket costs were not included. Costs considered were the costs associated with sending the home-based iFOBT kits used in the current program, laboratory analysis of the completed iFOBT samples, general practitioner visits for follow-up of positive iFOBT results, colonoscopy procedures with/without adverse events (and polypectomy if required), and colorectal cancer treatment. The modeled test characteristics of iFOBT and colonoscopy were informed by review of the international literature and calibrated to the outcomes observed in the NBCSP (7). The assumptions for costs and for the test characteristics of iFOBT and colonoscopy and the associated data sources are provided in Table 1.

Modeled analysis

The modeled output for each strategy includes age-specific colorectal cancer incidence and mortality rates, costs, life-years, and the number of screening and diagnostic tests that occurred

Table 1. Key model parameters assumptions and data sources

Key model parameters	Baseline	Sensitivity analysis		References
		Minimum	Maximum	
Cost				
Postage (one-way)	A$2	N/A	N/A	Assumption (6, 7)
Test kit sent	A$8	A$6	A$10	Assumption (6, 7)
Test kit received and analyzed in the lab	A$20	A$18	A$22	Assumption (6, 7)
GP consultation for FOBT positive result	A$37.05	N/A	N/A	MBS item 23 (24)
Colonoscopy, with/without polypectomy (without complication)[a]	A$1,800	A$1,440	A$2,500	Assumption (6, 7)
Colonoscopy with/without polypectomy (with complication)	$14,838.91	N/A	N/A	Inflated cost of DRG-AG item G48A (25)
Stage 1 cancer treatment[b,c]	A$36,914	A$29,558	A$40,606	Inflated value from Pignone et al. 2011 (26)
Stage 2 cancer treatment[b,c]	A$56,589	A$57,511	A$62,248	
Stage 3 cancer treatment[b,c]	A$88,700	A$44,422	A$97,570	
Stage 4 cancer treatment[b,c]	A$73,402	A$10,798	A$80,742	
iFOBT test characteristics (per person)[d]				
Specificity	94.8%	95.6%	94.1%	Obtained via calibrating to iFOBT positivity rates observed in NBCSP and colonoscopy outcomes among positive iFOBT (7)
Sensitivity for conventional adenoma of any size	15.2%	13.1%	17.4%	
Sensitivity for conventional adenoma >5 mm	30.2%	26.0%	34.3%	
Sensitivity for conventional adenoma >10 mm	41.5%	41.5%	47.1%	
Sensitivity for CRC	58.6%	50.7%	66.2%	
Colonoscopy test detection rate (per lesion)				
Conventional adenoma 1–5 mm	79%	71.0%	86.9%	Van Rijn et al. 2006 (27)
Conventional adenoma 6–9 mm	85%	76.5%	93.5%	
Conventional adenoma >10 mm	92%	82.5%	100.0%	
SSA (any size)	78%	71.0%	86.9%	
CRC (any stage)	95%	85.5%	100.0%	
Colonoscopy completion rate	100% to the end of cecum	N/A	N/A	Assumption (6, 7)
Colonoscopy adverse event probability				
Nonfatal adverse event	0.27%	0.15%	0.35%	AIHW 2015 (1)
Death	0%	N/A	0.01%	AIHW 2015 (1), Jentschura et al. 1994 (28)
Screening initiation rate[e]				
First invitation	Scenario 1: 100%; Scenario 2: 57.0% Scenario 3: 29.0%	N/A	N/A	Rates modeled for scenarios 1 and 2 were assumptions; rate modeled for scenario 3 was based on current observed rate (15).
Second invitation[f]	Scenario 1: 100%; Scenario 2: 28.5% Scenario 3: 14.5%	N/A	N/A	
Subsequent invitation[f]	Scenario 1: 100%; Scenario 2: 14.3% Scenario 3: 7.3%	N/A	N/A	Assumption
Rescreening probability[e,g]	Scenario 1: 100%; Scenario 2 and 3: 75%	N/A	N/A	AIHW 2015 (1)
Colonoscopy compliance rate				
Follow-up colonoscopy[g,h]	71%	N/A	N/A	AIHW 2015 (1)
Surveillance colonoscopy[h]	80%	N/A	N/A	Assumption (6, 7)

(Continued on the following page)

Table 1. Key model parameters assumptions and data sources (Cont'd)

Key model parameters	Baseline	Sensitivity analysis		References
		Minimum	Maximum	
5-year survival rate in patient detected with colorectal cancer due to symptoms shown				
Stage 1 cancer	86.9%	N/A	N/A	Morris et al. 2007 (29)
Stage 2 cancer	73.0%	N/A	N/A	
Stage 3 cancer	42.4%	N/A	N/A	
Stage 4 cancer	9.5%	N/A	N/A	
Relative 5-year survival of screen-detected cancer versus symptomatically detected cancer				
Stage 1 cancer	1.1	1	N/A	Parente et al. 2015, Gill et al. 2014, Pande et al. 2013 (30–32)
Stage 2 cancer	1.2	1	N/A	
Stage 3 cancer	1.4	1	N/A	
Stage 4 cancer	2.3	1	N/A	
Precancer natural history assumption	Baseline assumptions	Less aggressive precancer natural history assumptions	More aggressive precancer natural history assumptions	Lew et al. 2018 (6)

Abbreviations: CRC, colorectal cancer; AIHW, Australian Institute of Health and Welfare; N/A, not applicable; SSA, sessile serrated adenoma.

[a]The modeled $1,800 cost of a single colonoscopy examination was assumed to include the cost of the colonoscopy procedure as well as the cost of sedation, histopathology, and other item(s) related to the colonoscopy examination.

[b]Value inflated based on consumer price index of health in 2010–11 (96.4) and in June 2014 (115.2; refs. 33, 34).

[c]The baseline cost assumption is consistent with the latest estimates of an Australian study by Ananda et al. (2016), which found the treatment cost was A$34,337–34,952 for stage 1 colorectal cancer, $43,776–45,108 for stage 2 cancer, $86,317–89,596 for stage 3 cancer, and $71,156–81,403 for stage 4 cancer (35).

[d]The NBCSP used *Magstream HemSp* with a rabbit serum buffer, manufactured by Fujirebio Inc., as the screening test in 2006–2017 (36). The Program followed the manufacturer's recommendations to use 20 ng Hb/mL buffer (equivalent to 20 μg Hb/g feces) as the cutoff for test positivity and to collect two fecal samples from participants.

[e]Different screening participation rates were assumed for people who have never participated in screening before and people who have participated in at least once in the previous screening round(s) in scenarios 2 and 3. Screening initiation rates refer to screening participation rate for individuals who have never participated in the screening program before. Rescreening probabilities refer to the screening participation rate for individuals who have participated at least once in the previous screening rounds.

[f]For those who refused the first screening invitation, the initiation rate for the second invitation round was assumed to be half of the rate modeled for the first round. This assumption was made based on data observed in the NBCSP (15). The screening initiation rate in the subsequent invitation rounds was assumed to be half of the rate of the second round initiation.

[g]Age- and sex-specific rates modeled based on data observed in the National Bowel Cancer Screening Program in 2015 (15).

[h]Follow-up colonoscopy refer to diagnostic colonoscopy assessments to provide follow-up a positive iFOBT result. Surveillance colonoscopy refer to colonoscopy assessments to provide surveillance for people with previous abnormal findings (detection of at least one adenoma and/or SSA) at colonoscopy.

over the lifetime of a single cohort. The 2001 standard Australian population was used to calculate the age-standardized cancer incidence and mortality rates. For the current analysis, the discounted lifetime costs and life-years were calculated by accruing the predicted cost and life-years from age 20 to 90 years (or 100 years in supplementary analysis) and discounting at a rate of 5% per annum from age 40 years (17). We used the same perspective (i.e., health services perspective), discount rate and willingness-to-pay (WTP) threshold [i.e., $50,000/life-year saved (LYS)] as per a prior Medical Services Advisory Committee evaluation of the National Cervical Screening Program in Australia (18). Cost-effectiveness ratios (CER) in comparison with no screening were calculated for all strategies, and incremental cost-effectiveness ratios (ICER) were calculated for each dominating strategy (i.e., the strategy with the lowest cost compared with strategies with similar or lower effectiveness) in the cost-effectiveness analysis. The number of iFOBT kit returns and colonoscopy examinations were estimated over the lifetime of 100,000 persons alive at 40 years. The average lifetime number of iFOBTs completed was estimated per person alive at 40 years. The benefit-and-harm balance was estimated using the number needed-to-colonoscope (NNC) and the incremental number-needed-to-colonoscopy (INNC) per colorectal cancer death prevented. An NNC was calculated by dividing the number of colonoscopies by deaths prevented in the lifetime of 100,000 persons alive at 40 years for each strategy, compared with no screening or the current program. An INNC was derived by dividing the additional number of colonoscopies (AC) by the additional number of colorectal cancer deaths prevented (CDP) from the next most beneficial dominating strategy (i.e., a strategy for which no other strategy of similar or less effectiveness had a better benefits-to-harms ratio) in the benefit-to-harm analysis.

One-way sensitivity analysis was performed for scenario 1 for key parameters, including costs (for iFOBT, colonoscopy, and cancer treatment), iFOBT test characteristics, colonoscopy lesion-specific detection rates, precancerous natural history assumptions, and cancer survival assumptions (Table 1). A probabilistic sensitivity analysis with 200 sets of alternative natural history assumptions has been previously performed to evaluate the impact of uncertainties associated with natural history assumptions on the estimated cost-effectiveness of the current program (i.e., 2-yearly iFOBT screening at 50–74 years); the cost-effectiveness ratio findings varied by ±$2,500/LYS from the baseline CERs −$2,693–3048/LYS, i.e., the current program was found to be highly cost-effective in all scenarios in probabilistic sensitivity analysis (7). In the current study, all strategies were evaluated with the most and the least aggressive natural history assumptions in one-way sensitivity analyses to assess the impact of uncertainties associated with natural history assumptions on the ICER findings. Because the current evaluation considered stopping screening at older ages, a supplementary analysis was also performed to assess the impact of the simulation stop age on the predicted health and cost-effectiveness outcomes by repeating the base-case simulations with the simulation stopping at the age

of 100 years. All costs are presented in 2015 Australian dollars ($A1 = USD 0.7706, June 20, 2015).

Results

Health outcomes

Compared with no screening, we found that 2-yearly iFOBT screening at 50 to 74 years (the current program once fully rolled out) is predicted to reduce overall age-standardized colorectal cancer incidence and mortality rates by 51% and 74%, respectively, in scenario 1 (perfect adherence), by 32% and 51%, respectively, in scenario 2 ("high adherence"), and by 23% and 36%, respectively, in scenario 3 ("low adherence"; Table 2). Compared with the current program, lowering the screening start age to 40 (or 45) years would result in an additional reduction of 5 to 6 (2 to 3) percentage points (range reflecting adherence assumptions) in cancer incidence and 6 to 9 (2 to 4) percentage points in cancer mortality rates; extending the screening cessation age to 79 (or 84) years would result in an additional reduction of 1 to 2 (2 to 3) and 3 to 5 (5 to 7) percentage points, respectively; extending screening to both younger and older ages would result in an additional reduction of ∼8 and 12 to 15 percentage points, respectively (Table 2).

Cost-effectiveness

The estimated life-years, lifetime cost, and CER compared with no screening for each strategy are provided in Supplementary Table 2. When compared with no screening, the CER for 2-yearly iFOBT screening was less than the indicative WTP of $50,000 per LYS in Australia for all screening age ranges considered. However, in the incremental cost-effectiveness analysis (relevant to the current policy question since the rollout for the NBCSP is already well under way), only screening at 50 to 74 years (i.e., the current program; ICER: A$2,984–5,981/LYS, with the range reflecting adherence assumptions) and screening at 45 to 74 years (ICER: A$17,053–29,512/LYS) were found to be cost-effective in all adherence scenarios given the indicative WTP threshold. Screening from 50 to 79 years, 45 to 79 years, and 40 to 74 years was found to be cost-effective when assuming nonperfect screening adherence in scenario 2 and/or scenario 3 (Fig. 1), but not in the perfect compliance situation of scenario 1. No strategy that assumed screening continued until 84 years was cost-effective in any adherence scenario (Fig. 1).

Resource utilization

Compared with the current program, the estimated relative increase in NBCSP-related iFOBT tests and colonoscopies were ranged from 42% to 52% (17% to 23%) and 18% to 36% (3% to 14%), respectively, if the screening start age was lowered to 40 (or 45) years, with the range reflecting adherence assumptions (Fig. 2); the corresponding increases were 14% to 16% (30% to 36%) and 9% to 24% (27% to 53%), respectively, if the screening cessation age was extended to 79 (or 84) years, and 66% to 91% and 72% to 109%, respectively, if the screening age range was widened to 40 to 84 years (Fig. 2). The average lifetime numbers of iFOBTs completed per person are shown in Table 3.

Number-needed-to-colonoscope

The estimated NNC of each strategy to prevent one colorectal cancer case or death compared with the current program is shown in Table 3. The "benefits–harms frontier" (i.e., a representation of strategies with the most favorable balance between benefits and

Table 2. Model-estimated age-standardized rate of colorectal cancer incidence and colorectal cancer mortality per 100,000 persons for base-case analysis

	Scenario 1 (perfect adherence)				Scenario 2 ("high" adherence)				Scenario 3 ("low" adherence)			
	CRC incidence		CRC mortality		CRC incidence		CRC mortality		CRC incidence		CRC mortality	
Screening age range	ASR[a]	% Red. compared with NS	ASR[a]	% Red. compared with NS	ASR[a]	% Red. compared with NS	ASR[a]	% Red. compared with NS	ASR[a]	% Red. compared with NS	ASR[a]	% Red. compared with NS
NS	62.7	–	23.0	–	62.7	–	23.0	–	62.7	–	23.0	–
50–74 (current program)	30.6	51%	6.1	74%	42.5	32%	11.3	51%	48.3	23%	14.7	36%
40–74	27.8	56%	4.6	80%	39.1	38%	9.5	59%	44.7	29%	12.6	45%
40–79	26.3	58%	3.7	84%	38.0	39%	8.5	63%	43.5	31%	11.7	49%
40–84	25.7	59%	3.3	86%	37.4	40%	8.0	65%	43.1	31%	11.2	51%
45–74	29.4	53%	5.5	76%	40.9	35%	10.5	54%	46.7	25%	13.8	40%
45–79	27.2	57%	4.2	82%	39.1	38%	9.1	60%	45.1	28%	12.5	46%
45–84	26.8	57%	4.0	83%	38.6	38%	8.7	62%	44.8	29%	12.2	47%
50–79	29.6	53%	5.3	77%	41.0	34%	10.2	56%	47.3	24%	13.8	40%
50–84	28.9	54%	4.8	79%	40.6	35%	9.7	58%	46.9	25%	13.3	42%

Abbreviations: ASR, age-standardized rate; CP, current program; CRC, colorectal cancer; NS, no screening; Red, reduction.
[a]Per 100,000 individuals, assuming 2001 Australian Standard Population across all ages.

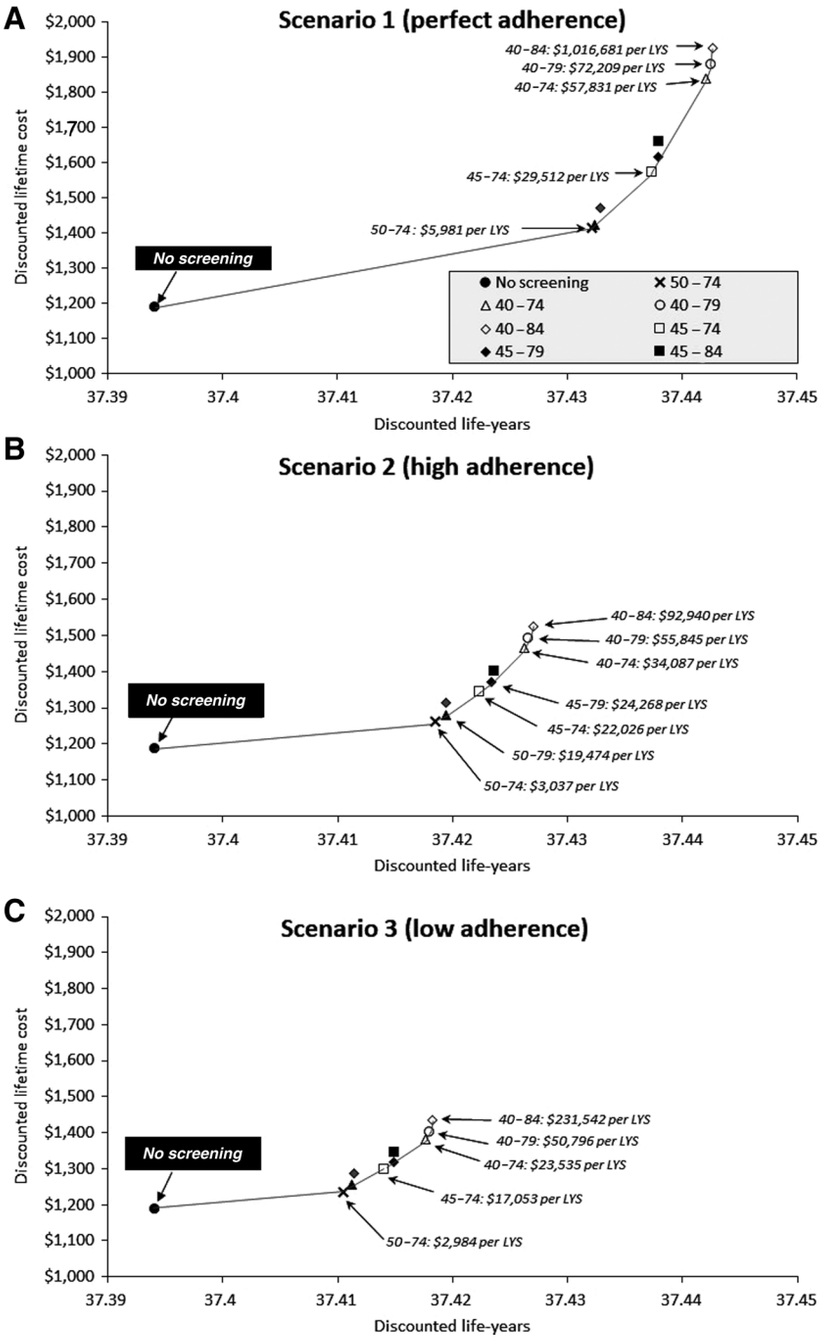

Figure 1.
Cost-effectiveness planes for alternative adherence assumptions for base-case analysis. Scenario 1 assumed perfect adherence; scenario 2 assumes high (but more realistic) adherence; and scenario 3 assumes lower adherence. Text and numbers shown in the chart indicate the strategies identified on the cost-effectiveness frontier and the ICER associated with that strategy.

harms compared with strategies with similar effectiveness/benefits) and the INNC of the "dominating" strategies are shown in Fig. 3. The current program (i.e., screening at 50–74 years) was always the first strategy on the frontier (associated with an NNC of 49, 36, and 35 per cancer death prevented in scenarios 1, 2 and 3 when compared with no screening) but the other dominating strategies varied between the three participation/adherence scenarios. The INNC increased noticeably along the benefits–harms frontier due to the relatively smaller increase in the number of colorectal cancer deaths prevented compared with the increase in the number of colonoscopies required for each strategy on the frontier.

Sensitivity analyses

Detailed outcomes of the one-way sensitivity analyses are provided in Supplementary Tables 3 to 21. Similar to base-case findings, screening at 50 to 74 years (i.e., current practice) was always the first strategy identified on the cost-effectiveness frontier in all analyses (ICER: A$3,765–13,791/LYS). Screening at 45 to 74 years was found to be cost-effective in most cases (ICERs of

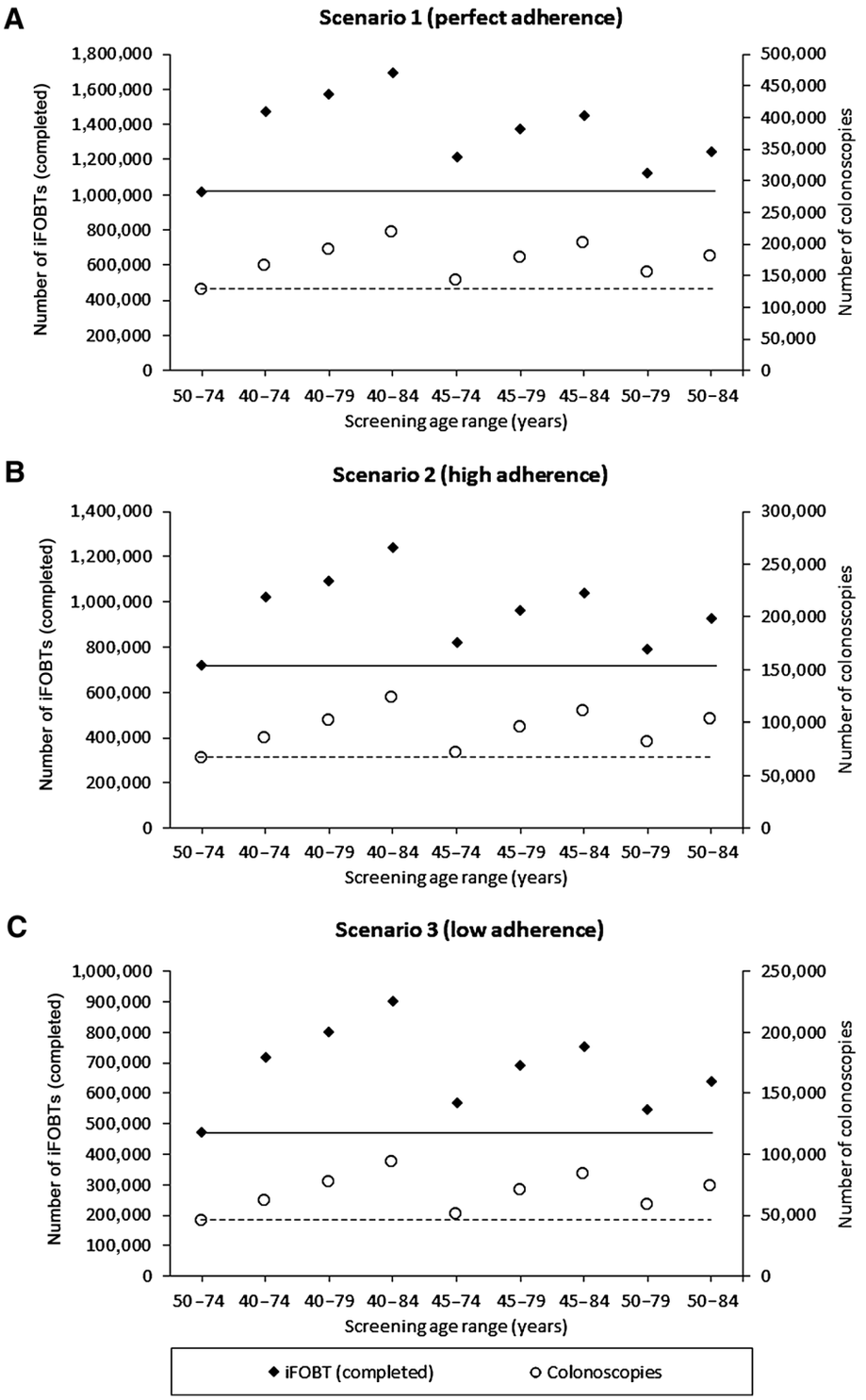

Figure 2.
Model-estimated number of iFOBT (completed) and colonoscopies in the lifetime of 100,000 persons alive at 40 years for base-case analysis. The black solid line in the chart indicates the estimated number of completed iFOBTs associated with the current program (2-yearly iFOBT screening at 50–74 years); the black dashed line indicates the estimated number of colonoscopies associated with the current program.

$11,760–43,929/LYS in the analyses when this strategy was found to be cost-effective), except when a lower nonfatal colonoscopy adverse event rate was assumed (it was extended dominated by screening at 45–79 years in this case) or a less aggressive natural history was assumed (ICER: 58,208/LYS). Screening at 50 to 79 years was found to be cost-effective (ICER: $10,690–36,383/LYS) in more than half of the analyses; it was extended dominated by the strategy assuming screening at 45 to 74 years otherwise.

A 2014 review has suggested that colorectal cancer rates in Australia are rising in the population under 50 years (19). In sensitivity analysis, a scenario assuming a more aggressive natural history was assessed. This scenario is associated with a cancer

Table 3. Model-estimated lifetime of colorectal cancer incidence, colorectal cancer mortality, and colonoscopy per 100,000 persons, and number-needed-to-colonoscope to prevent one colorectal cancer case/death for all strategies for base-case analysis

Screening age range	Lifetime number of iFOBTs completed per person[a]	Lifetime no. of CRC cases per 100,000 persons[a]	Lifetime no. of CRC deaths per 100,000 persons[a]	Lifetime no. of COLs per 100,000 persons[a,b]	NNC to prevent one CRC case[c]	NNC to prevent one CRC death[c]
Scenario 1 (perfect adherence)						
NS	N/A	7,660	2,880	N/A	N/A	N/A
50–74 (CP)	10.4	3,214	621	110,505	N/A	N/A
40–74	15.5	3,013	511	130,334	99	180
40–79	16.7	2,761	383	147,536	82	156
40–84	18.2	2,745	331	167,160	121	195
45–74	12.8	3,199	601	113,940	233	170
45–79	14.6	2,844	416	136,087	69	125
45–84	15.6	2,828	381	152,854	110	176
50–79	12.0	3,043	507	120,750	60	89
50–84	13.5	3,018	452	140,228	152	176
Scenario 2 ("higher" adherence)						
NS	N/A	7,660	2,880	N/A	N/A	N/A
50–74 (CP)	7.3	4,810	1,296	57,452	N/A	N/A
40–74	10.3	4,441	1,106	72,351	40	78
40–79	11.3	4,232	968	84,658	47	83
40–84	12.5	4,235	899	98,828	72	104
45–74	8.5	4,672	1,228	63,130	41	84
45–79	10.0	4,359	1,021	78,516	47	77
45–84	10.8	4,350	973	90,702	72	103
50–79	8.3	4,578	1,144	69,477	52	79
50–84	9.4	4,589	1,083	83,486	117	122
Scenario 3 ("lower" adherence)						
NS	N/A	7,660	2,880	N/A	N/A	N/A
50–74 (CP)	4.9	5,644	1,755	39,724	N/A	N/A
40–74	7.4	5,182	1,498	53,914	31	55
40–79	8.3	4,981	1,371	64,466	37	65
40–84	9.3	4,999	1,314	76,968	58	85
45–74	5.9	5,461	1,654	45,228	30	55
45–79	7.2	5,182	1,468	58,091	40	64
45–84	7.8	5,191	1,429	68,523	64	88
50–79	5.7	5,462	1,625	49,423	53	75
50–84	6.7	5,482	1,566	61,082	131	113

Abbreviations: CP, current program; CRC, colorectal cancer; N/A, not applicable; NNC, number-needed-to-colonoscopy; NS, no screening.
[a]Estimated in the lifetime of a person (or 100,000 persons) alive at 40 years.
[b]Included colonoscopies performed to follow-up positive iFOBT result and provided surveillance.
[c]Compared with current program.

incidence rate of 9.0 per 100,000 persons in 30 to 34 years, 22.2 in 35 to 39 years, 39.3 in 40 to 44 years, and 59.7 in 45 to 49 years, equivalent to a 1.8, 2.0, 2.2, 2.2-fold, respectively, increase from the base-case cancer incidence rates. When assuming no screening, this scenario is predicted to be associated with an age-standardized bowel cancer incidence rate of 75.1 per 100,000 persons for all ages (a 1.2-fold increase from the base-case age-standardized cancer incidence rate). Under these extreme assumptions, screening at 50 to 74 years (ICER: A$3,765/LYS) followed by screening at 45 to 74 years (ICER: A$11,760/LYS) and screening at 40 to 74 years (ICER: A$21,854/LYS) were found to be cost-effective in the incremental cost-effectiveness analysis (Supplementary Table 20).

Supplementary analyses

Detailed outcomes of the supplementary analyses for an extended simulation to age 100 years are provided in Supplementary Tables 22 and 23 and Supplementary Fig. S5. The estimated health outcomes for each strategy were consistent with the base-case findings, but (as expected) extending the simulation increased the cost-effectiveness of older ages of stopping screening; screening at 50 to 79 years (ICER: $4,062–9,050/LYS, with the range reflecting adherence assumptions) and 45 to 79 years (ICER: $15,266–33,681/LYS) were found to be cost-effective in all screening adherence scenarios. Screening at 50 to 74 years (i.e., the current program) was found to be cost-effective and was the first scenario on the cost-effectiveness frontier when assuming imperfect screening adherence (i.e., scenarios 2 and 3); it was "extended dominated" by a strategy assuming screening at 50 to 79 years when perfect adherence was assumed (i.e., scenario 1).

Discussion

We have performed, for the first time, a detailed evaluation of the benefits, harms, and cost-effectiveness of extending the NBCSP in Australia to younger and/or older ages. We found that, compared with the current program (i.e., screening at 50–74 years), colorectal cancer mortality could be further reduced by 2 to 9 percentage points (with range dependent on screening participation and follow-up adherence) if the screening start age was lowered to 40 or 45 years, and by 3 to 7 percentage points if the screening cessation age was extended to 79 or 84 years. However, these strategies would be associated with a substantial increase in the number of program-related colonoscopies required (3% to 36% increase if the screening start age was lowered, and 9% to 53% increase if the screening cessation age was extended). Only the current program and screening at 45 to 74 years were found to

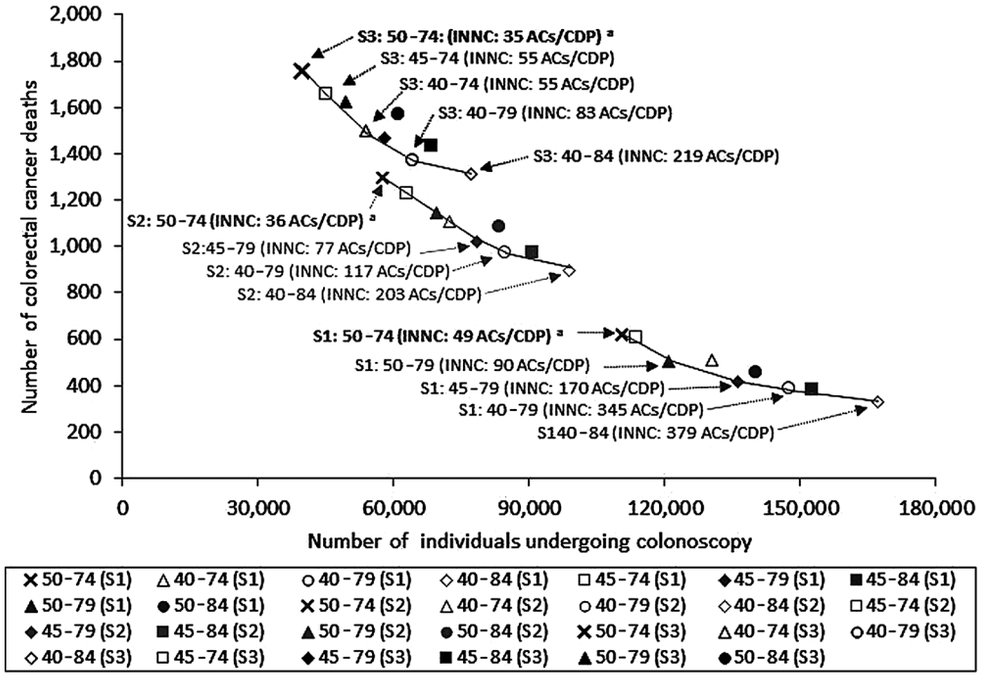

Figure 3.

Comparison of number of colorectal cancer deaths versus number of colonoscopies in the lifetime of 100,000 persons alive at 40 years for the base-case analysis. The text and numbers shown in the chart indicate the strategies identified on the "benefit–harm frontier" and the incremental number-needed-to-colonoscope per additional death prevented compared with the next less effective strategy on the "frontier." AC, additional colonoscopy; CDP, cancer death prevented; INNC, incremental number-needed-to-colonoscope per additional death prevented; S1, scenario 1; S2, scenario 2; S3, scenario 3. [a]Compared with no screening, which was predicted to be associated with 2,881 colorectal cancer deaths and zero colonoscopies in the lifetime of 100,000 persons alive at 40 years.

be cost-effective under all screening adherence assumptions in the base case analysis, but starting screening at 45 years would increase program-related colonoscopy demand by 3% to 14% and be associated with 55 to 170 additional colonoscopies per additional deaths prevented over the lifetime of a cohort compared with the current program. This should be compared with the situation for the current program, which was predicted to be associated with an NNC of 35 to 49 colonoscopies per death prevented when compared with no screening.

A strength of the study was that we used a comprehensive and calibrated model of colorectal cancer natural history that incorporated two biological pathways of colorectal cancer development—the adenoma–carcinoma pathway and the serrated pathway. The model evaluation incorporated the observed screening behavior in the NBCSP, and model-predicted iFOBT screening-related outcomes have been previously calibrated and validated to the data observed in the NBCSP (7). One limitation of the study relates to our assumptions about screening adherence and compliance to colonoscopy referral. The modeled compliance rate to colonoscopy follow-up after a positive iFOBT (~71%) was based on the current rate reported in Australia. However, this is likely to be an underestimate of the actual compliance rate due to underreporting of attendance in the context of nonmandatory reporting of colonoscopy to the NBCSP register (15). The modeled screening participation in 40- to 49-year-olds and 75- to 84-year-olds was, by necessity, based on assumptions. We made favorable assumptions with respect to screening participation over a lifetime if screening started earlier or ended later because we assumed that age-extended strategies would be associated with a higher proportion of individuals being screened at least once (or a few times) in a lifetime compared with the current program (see Supplementary Figs. S2 and S3). This, by itself, is expected to increase the overall effectiveness of screening for scenarios where nonperfect adherence is assumed; in our findings, we did consequently observe that the relative cost-effectiveness ratio and benefit-to-harm balance of some of the extended-age strategies compared with the current program were increased in lower adherence scenarios compared with the perfect adherence scenario. For example, we found that screening from 50 to 79, 45 to 79, or 40 to 74 years could potentially be cost-effective in some participation scenarios but not in the perfect adherence scenario. However, there are considerable uncertainties about whether these benefits to overall lifetime participation would actually be observed in practice. Extending the age range of screening could in the worst case have no impact on the number of people screened at least once in a lifetime, instead resulting only in already well-screened individuals having more tests in a lifetime. Therefore, more evidence on the impact of extending the screening age range on overall participation is an important area of future research. Furthermore, it should be borne in mind that increasing the number of individuals screened at least once in a lifetime can also be done by increasing participation in the currently targeted age group, and the results of this evaluation found that screening in the current age group is associated with a better balance of benefits to harms. For all the above reasons, we also assessed outcomes and cost-effectiveness of the alternative strategies in the

context of theoretical, perfect adherence to both screening and colonoscopy referral. Although this is highly unlikely to be achievable in practice, this perfect adherence scenario does give a clearer measure of the benefits of the age extensions *per se* (as opposed to the uncertain and indirect effects of the age extensions on the overall uptake of screening over a lifetime for individuals in the population).

This study used the estimated colorectal cancer incidence and mortality rates and life-years as the main effectiveness outcomes and we did not consider quality-adjusted-life-years (QALY). Therefore, one limitation is that the health-related quality-of-life effects associated with completing iFOBT screening, attending colonoscopy examination, adverse events due to colonoscopy, and cancer diagnosis and treatment were not represented in the effectiveness findings; on the other hand, setting-specific bowel cancer screening-related quality-of-life data in the Australian context are not available, and the assessment of disutility and QALYs is fraught with uncertainty. Previous analyses of screening programs in Australia have also used life-years as the primary measure for similar reasons (18).

The sensitivity of the incremental cost-effectiveness findings was examined through extensive one-way sensitivity analyses. In a supplementary analysis where we continued the simulation to age 100 years, we found that screening to age 79 years did become cost-effective in all participation scenarios, including perfect participation. Screening at 50 to 79 years and 45 to 79 years were found to be the only two cost-effective strategies under all screening adherence assumptions in this extended simulation. However, again the uncertainties in this finding are considerable because, although the Policy1-Bowel model has undergone extensive calibration and validation, most of the observed data used for calibration (for example, prevalence of adenoma) were available only up to age 74 years (7). Furthermore, the routinely reported colorectal cancer incidence and mortality data in Australia group all people aged 85 or older together (20). Age expectancy at the age of 90 years is less than 5 years for Australian men and women, resulting in a high competing risk of death from causes other than bowel cancer in people aged 90 years or older (20). Due to the considerable uncertainties inherent in simulating outcomes to very old ages, we prioritize the findings of the base-case analysis in which the simulation was terminated at 90 years.

We were not able in the current analysis to explicitly consider the role of comorbidities in the decision on whether screening is appropriate, nor were we able to consider issues around the provision of colonoscopy in screen-positive elderly individuals; this may not be clinically appropriate in very frail people, and it is known that the colonoscopy complication rates increase in the elderly (21). However, in relation to the potential for extending screening to older ages, we plan more detailed future work which explicitly considers the role of comorbidity and/or life expectancy assessment before offering screening to older age groups (similar to recent recommendations for offering PSA testing to fully informed men with a life expectancy of at least 7 years; ref. 22).

In general terms, our analysis indicates that given the current evidence base, at this stage the only robust finding for a potentially cost-effective age extension to the current NBCSP would be lowering the screening start age to 45 years. However, this strategy would be associated with a considerable increase in the number of program-related colonoscopies needed to follow-up abnormal screening results compared with the current program, and the incremental benefit-to-harm balance for starting screening earlier was substantially less favorable than starting at 50 years. Our findings that lowering the screening start age from 50 to 45 years would be associated with a significant increase in the number of program-related colonoscopies but a relatively smaller gain in population-level screening effectiveness (i.e., additional colorectal cancer deaths prevented) is consistent with the findings of the 2016 US Preventive Task Force Evaluation (3). However, it should be noted that analyses of trends in colorectal cancer rates in Australia and the USA have suggested that rates are increasing in people in their 40s (19, 23). Although we have taken existing trends into account in this analysis and performed related sensitivity analysis, it is possible that if future further increases over time in this age group are confirmed in Australia, the balance of benefits to harms of screening in this age group could improve. This is an area for future research in terms of detailed analysis of trends in Australia and might warrant more research into the clinical effectiveness, the cost-effectiveness, and the balance of benefits to harms of screening in people in their forties if the incidence rate in this age group continues to increase over time.

The current study was performed to underpin and inform the recently revised *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer* in Australia (5). Taking into account all of the above factors, the expert Working Party who provided oversight to the process of guidelines review recommended that the age range for organized population screening continues to be 50 to 74 years; starting screening at age 45 is not recommended for population screening, although this modeling indicated that it may be cost-effective, because there is a much less favorable ratio of benefits to harms than for 50 to 74 years (5). Based on the findings reported here, however, the guidelines also recommend that for people aged 45 to 49 years who request screening after being fully informed of the benefits and harms of testing, general practitioners could offer an immunochemical fecal occult blood test every 2 years during the lead-up to the first routine invitation by the NBCSP at age 50 years (5).

Conclusion

Extending screening to older ages is not likely to be cost-effective and thus may not be an appropriate use of resources; further work is required to assess whether more targeted screening in elderly people without significant comorbidities might be appropriate. Starting screening at 45 years would potentially be cost-effective, but would substantially increase the number of program-related colonoscopies, and screening people in their 40s would be associated with a less favorable benefit-to-harm balance, with an NNC of 55 to 170 for each additional death prevented compared with the current program. Although we did not formally evaluate the impact of interventions to increase screening participation here, our findings suggest that resources may be more optimally invested in increasing adherence in the existing NBCSP target age group rather than in extending the age range.

Disclosure of Potential Conflicts of Interest

KC is co-PI of unrelated investigator-initiated trial of cervical screening in Australia ('Compass') conducted by the Victorian Cytology Service, which has received a funding contribution from Roche Molecular Systems and Ventana Inc., USA. No potential conflicts of interest were disclosed.

Disclaimer

The funder had no role in study design, data collection, or data analysis. The funder was an observer at meetings of advisory committees (i.e., meetings of the Cancer Council Australia Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer Working Party). J.-B. Lew, M. Caruana, and K. Canfell had access to raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

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References

1. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program: monitoring report 2013–14. Cancer series No. 94. Cat. no. CAN 94. Canberra: AIHW; 2015.
2. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, van BM, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149.
3. Knudsen AB, Zauber AG, Rutter CM, Naber SK, Doria-Rose VP, Pabiniak C, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595–609.
4. Bolin TD, Korman MG, Nicholson F, Pezzullo L, Engelman J, Collings K, et al. Cost-effectiveness of screening for bowel cancer. Med J Aust 2016; 204:11–2.
5. Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. Sydney: Cancer Council Australia; 2017.
6. Lew JB, St John DJB, Macrae FA, Emery JD, Ee HC, Jenkins MA, et al. Evaluation of the benefits, harms and cost-effectiveness of potential alternatives to iFOBT testing for colorectal cancer screening in Australia. Int J Cancer 2018;143:269–82.
7. Lew JB, St John DJ, Xu XM, Greuter MJE, Caruana M, Cenin DR, et al. Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study. Lancet Public Health 2017;2:e331–40.
8. Greuter MJ, Xu XM, Lew JB, Dekker E, Kuipers EJ, Canfell K, et al. Modeling the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA). Risk Anal 2014;34:889–910.
9. Australian Institute of Health and Welfare (AIHW). GRIM (General Record of Incidence of Mortality) books 2013: All causes combined. Canberra: AIHW; 2015.
10. Australian Institute of Health and Welfare (AIHW). Australian Cancer Incidence and Mortality (ACIM) books: Bowel cancer. Canberra: AIHW; 2014.
11. Cancer Council Australia Colonoscopy Surveillance Working Party. Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease. Cancer Council Australia, Sydney. 2011.
12. Barclay K. Cancer Council Australia Surveillance Colonoscopy Guidelines Working Party. Algorithm for Colonoscopic Surveillance Intervals – Adenomas. 2013. http://www.gastroservices.com.au/pdf/algorithm-for-colonoscopic-surveillance-intervals-adenomas.pdf (accessed 28-12-2016).
13. Australian Institute of Health and Welfare (AIHW). Cervical screening in Australia 2014–2015. Cancer series no. 105. Cat. no. CAN 104. Canberra: AIHW; 2017.
14. Australian Institute of Health and Welfare (AIHW). BreastScreen Australia monitoring report 2013–2014.Cancer series no. 100. Cat. no. CAN 99. Canberra: AIHW; 2017.
15. Australian Institute of Health and Welfare (AIHW). National Bowel Cancer Screening Program: monitoring report 2018. Cat. no. CAN 112. Canberra: AIHW; 2018.
16. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. Med J Aust 2014;201:456–61.
17. Australian Government Department of Health. The Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines. 2016. https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf (accessed 18-4-2018).
18. Lew JB, Simms KT, Smith MA, Hall M, Kang YJ, Xu XM, et al. Primary HPV testing versus cytology-based cervical screening in women in Australia vaccinated for HPV and unvaccinated: effectiveness and economic assessment for the National Cervical Screening Program. Lancet Public Health 2017;2:e96–107.
19. Young JP, Win AK, Rosty C, Flight I, Roder D, Young GP, et al. Rising incidence of early-onset colorectal cancer in Australia over two decades: report and review. J Gastroenterol Hepatol 2015;30:6–13.
20. Australian Institute of Health and Welfare. Australian Cancer Incidence and Mortality (ACIM) books: Colorectal cancer (also called bowel cancer). Canberra: AIHW; 2017.
21. Day LW, Kwon A, Inadomi JM, Walter LC, Somsouk M. Adverse events in older patients undergoing colonoscopy: a systematic review and meta-analysis. Gastrointest Endosc 2011;74:885–96.
22. Prostate Cancer Foundation of Australia and Cancer Council Australia PSA Testing Guidelines Expert Advisory Panel. Clinical practice guidelines PSA Testing and Early Management of Test-Detected Prostate Cancer. Sydney: Cancer Council Australia; 2016.
23. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. J Natl Cancer Inst 2017;109. doi: 10.1093/jnci/djw322.
24. Australian Government Department of Health. Medicare Benefits Schedule Book (Operating from 01 January 2014). Canberra: Australia Government Department of Health; 2013.
25. Independent Hospital Pricing Authority. National Hospital Cost Data Collection Australia Public Hospitals Cost Report 2011–2012, Round 16. New South Wales: IHPA; 2014.

26. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John DJ. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. Med J Aust 2011;194:180–5.
27. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343–50.
28. Jentschura D, Raute M, Winter J, Henkel T, Kraus M, Manegold BC. Complications in endoscopy of the lower gastrointestinal tract. Therapy and prognosis. Surg Endosc 1994;8:672–6.
29. Morris M, Iacopetta B, Platell C. Comparing survival outcomes for patients with colorectal cancer treated in public and private hospitals. Med J Aust 2007;186:296–300.
30. Parente F, Vailati C, Boemo C, Bonoldi E, Ardizzoia A, Ilardo A, et al. Improved 5-year survival of patients with immunochemical faecal blood test-screen-detected colorectal cancer versus non-screening cancers in northern Italy. Dig Liver Dis 2015;47:68–72.
31. Gill MD, Bramble MG, Hull MA, Mills SJ, Morris E, Bradburn DM, et al. Screen-detected colorectal cancers are associated with an improved outcome compared with stage-matched interval cancers. Br J Cancer 2014; 111:2076–81.
32. Pande R, Froggatt P, Baragwanath P, Harmston C. Survival outcome of patients with screening versus symptomatically detected colorectal cancers. Colorectal Dis 2013;15:74–9.
33. Australian Bureau of Statistics. Consumer Price Index: March Quarter 2013. Canberra, Australia: Australian Bureau of Statistics; 2013.
34. Australian Bureau of Statistics. Consumer Price Index: March Quarter 2015. Canberra, Australia: Australian Bureau of Statistics; 2015.
35. Ananda S, Kosmider S, Tran B, Field K, Jones I, Skinner I, et al. The rapidly escalating cost of treating colorectal cancer in Australia. Asia-Pac J Clin Oncol 2016;12:33–40.
36. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pac J Clin Oncol 2016;12:7–9.